With the Author's Compliments

Three Lectures

ON THE

PATHOLOGY AND TREATMENT

OF

DIABETES MELLITUS

VIEWED BY

THE LIGHT OF PRESENT-DAY KNOWLEDGE

Delivered before the Royal College of Physicians of London

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PATHOLOGY AND TREATMENT OF DIABETES MELLITUS

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LECTURE I.

Delivered on Nov. 17th.

Mr. President, Colleagues, and Gentlemen,—A faulty metabolism of carbohydrate stands at the foundation of the elimination of sugar that occurs in connexion with diabetes. When carbohydrate food is properly metabolised, it is placed in a position to be applied to utilisation and becomes lost sight of in the system. Not so in diabetes. Here the carbohydrate food fails to pass out of the condition of carbohydrate and filters off from the body with the urine in the form of sugar. To obtain a knowledge of where the fault lies, and what it consists of, it is requisite that we should have a knowledge of what transpires in connexion with the normal disposal of carbohydrate. This matter falls in the domain of physiology, and to physiology we have therefore in the first instance to look, for the groundwork to proceed upon. Such is the position in which physiology stands in relation to the subject to be dealt with, and unless we are here led in a right way, we cannot expect to be placed upon right ground for dealing with the problem before us.

By observation and methodically arranged experimental work, we obtain a knowledge of facts, and by the application of our reasoning power to these facts, we deduce from them governing laws or principles of action. As an outcome of the completion of this

INDUCTIVE METHOD

of procedure, the recognised facts no longer remain as isolated items of consideration, but fall into a correlated series, mutually linked together and fitting in with and supporting the deduction that has been formulated.

With the discovery of a law of action, an insight is given which constitutes a source of power by enabling us, through the agency of a designed modification of the conditions, to bring about a desired result. For instance, whilst nothing was known in the case of fevers, and such-like diseases, about the connecting microbe link standing at their foundation, we could only deal with them in an empirical way, and remained powerless to exert any intrinsic control over them. As soon, however, as their dependence upon the presence of a bacterial organism was discovered, a basis was supplied for a systematic extension of knowledge, which, spreading out in various directions, has vastly increased our power in the exercise of our medical art.

Diabetes constitutes the result of an erroneous procedure connected with the application of carbohydrate to the purposes of life. It falls within the province of physiology to reveal to us the nature of the procedure normally taking place, and necessarily we must possess this knowledge before we can stand in a position to comprehend the nature of the error that is productive of the disease. The art of medicine, therefore, which is concerned in rectifying the effects of the error, appeals to physiology for a rational basis upon which to work, and for the attainment of working success, everything hinges upon the soundness or otherwise of the teaching supplied.

At first the disease was only known through the bodily symptoms produced, and it remained, till what may be spoken of as a not far remote date, for sugar to be recognised as an eliminated principle in the urine. Without any guiding conception as to the nature of the disease, it afterwards became empirically found out that

FOOD CONSTITUTED AN INFLUENCING FACTOR

in connexion with treatment. In 1848 our countryman, Dr. Prout, said "the first and chief point to be attended to in the treatment of diabetes is diet." Bouchardat of Paris in 1841 introduced gluten bread and gave cases to show the beneficial effect of its employment in the place of ordinary bread. At this epoch, a great move was made by the announcement in 1848 of Bernard's glycogenic doctrine, which formed the starting point for the active and wide-spread prosecution of the varied researches which have brought us to the position in which we now stand.

Without the knowledge of why or wherefore, experience, as I have said, had begun to suggest that dieting attended with a restriction of carbohydrate food, produced a beneficial effect as a measure of treatment in diabetes. To this the glycogenic doctrine gave no support, seeing that it implied the passage of the food carbohydrate through the circulation to the tissues in the form of sugar and the production of sugar by the liver when carbohydrate was not supplied from without. Thus it was considered to be an essential condition of life that sugar as a force-producing agent should be constantly flowing through the circulation for the purpose of utilisation by the tissues, and the mode of experimenting then adopted, and relied upon, sustained this view. I need not here enter into the consideration of the fallacious character of the evidence upon which the glycogenic doctrine was built. I have shown in my recent work on "Carbohydrate Metabolism and Diabetes" that the propositions originally formulated can be indisputably asserted to be no longer tenable.

It has been said that, at the time of the promulgation of the glycogenic doctrine, experience had commenced to point to the benefit derivable from the restriction of carbohydrate food in the treatment of diabetes. Reasoning based upon this doctrine now stepped in to exert a neutralising effect. See, for instance, the line of argument adopted by M. Rigodin and quoted in the first edition of my work "On the Nature and Treatment of Diabetes." Because the experimental work of the period had shown, as it was thought, that the presence of sugar in the economy was indispensable to life, M. Rigodin considered it rational to allow a diet in which sugar-forming substances entered largely upon the ground that patients suffering from the disease were losing large quantities of sugar.

The same kind of mischievous idea, as it may be truly styled, is found to have place in certain quarters even at the present time—viz., amongst those who take falsely grounded physiological views as their standpoint instead of the teaching derived from the facts revealed by the actual effect of food on persons suffering from the disease.

In support of this assertion let me refer to the recently published work

OF PROFESSOR VON NOORDEN

on diabetes mellitus. At page 81 of the English translation by Dr. Boardman Reed, 1906, the following words are to be found:—"Secondary over-production of sugar, on the other hand, plays an important part in diabetes. The cells (of the body) are everlastingly hungry for sugar, although they are immersed in a medium which contains an abnormally large amount of it. They cannot avail themselves of this sugar for reasons that have been already discussed. Consequently they are continually signalling for the mobilisation of fresh quantities. Where the carbohydrates of the food and the stored-up glycogen can no longer supply the demand, as is the case in all severe forms of diabetes, then proteid, and, as a last resource, fat are called upon to yield sugar. Thus groups of atoms are claimed for this purpose which are usually of service for other purposes. This process may be designated a secondary over-production of sugar."

Here, verily, is an illustration of the kind of dilemma that the glycogenic doctrine may give rise to. It is assumed under it that sugar in a free form has to be constantly flowing into the system to meet a demand existing for it. It is further assumed that, accompanying this flow, there is a concordant removal of the sugar as it is passing through the systemic capillaries, and that diabetes is the result of an error at this point, leading to a non-consumption of the sugar. Notwithstanding, in the state of things portrayed, the system is over-burdened with sugar and gravely disordered from its presence, it is paradoxically contended that more is wanted, and that the want should be met by the supply of carbohydrate from without, and if not met in this way, that protein and fat are called upon to yield it.

At present, I will not pursue this matter further, but will leave it till other questions have been considered, and a more fitting position has been reached for speaking of the manner in which the application of carbohydrate to the purposes of life takes place.

For the proper comprehension of the nature of diabetes, it is necessary, as I have previously said, to have a right comprehension of the manner in which carbohydrate becomes physiologically disposed of within the system. Unless we stand upon sound ground here, we cannot rationally cope, in the practice of medicine, with the erroneous state existing in diabetes.

All are agreed that one destination of carbohydrate is in the production of fat. This, however, does not fall within the subject matter before us and therefore does not call for consideration to be here given to it. The point to be dealt with is the mechanism associated with the passage of carbohydrate from its seat of absorption in the walls of the alimentary canal to that of utilisation in the tissues.

Local absorption by the walls of the alimentary canal and utilisation in the tissues obviously imply that

THE CIRCULATORY SYSTEM HAS TO BE TRAVERSED.

In what way does this occur? The character of the respiratory quotient suffices to show that carbohydrate is used up as such in the tissues to which it must, therefore, of necessity be transported from the seat of absorption. It next follows that, in the mode of transport that takes place, there must be nothing to stand in conflict with the maintenance of what is observed, in respect to other conditions, to constitute the normal state. The point plainly put is,—Does the carbohydrate pass through the circulation in the form of free sugar, or does it, on absorption, become immediately placed in combination with other matter, and, in this locked-up state, become transported to the seat of utilisation? Let us examine the question that has been here put forward and see how the two propositions stand in the presence of the evidence that is respectively adducible in connexion with them.

First, let attention be given to the view that the carbohydrate of our food is conveyed in the form of free sugar through the circulation to the tissues. This view is comprised in the glycogenic doctrine, which also includes the production of sugar by the liver for furnishing a supply of sugar to the blood when the supply of carbohydrate from the food is in default. When the doctrine in question was first propounded, the liver was regarded, unlike the other organs of the body, as being loaded with sugar, and the blood issuing from it as containing sugar to a conspicuous extent larger in amount than was to be met with elsewhere. In addition to this, the blood contained in the systemic veins was represented as containing notably less sugar than was present in the blood of the arterial system—a fallacious assumption upon which was based a coincident destruction of sugar during the transit of the blood through the systemic capillaries.

All this is now put on one side, and even the French school no longer contends for that which was in former times confidingly accepted. Notwithstanding, however, that the experimental ground has so vastly changed, a lingering disposition exists to retain the idea that carbohydrate follows the course assumed under the glycogenic doctrine, and passes in the form of free sugar through the circulatory system from the seat of absorption to that of utilisation in the tissues, such passage of free sugar, either from the food or the liver, being regarded as a necessary condition of life.

Now the passage of sugar to the tissues means associated passage to the kidney, and this means proportionate outflow with the urine. In proportion as sugar is present in the blood so it may be confidently said is it present in the urine. Impermeability of the kidney to sugar used to be spoken of. It is a pure fiction, invented to escape from the difficulty arising from not finding sugar in the urine as an outcome of the imaginary flow of sugar into the circulation from the food and the liver. Up to a certain point, sugar, it was said, might be present in the circulation without showing itself in the urine, whilst when present beyond the particular point, an escape occurred and thus accounted for the state existing in diabetes.

Nothing could be more devoid of substantiality than such a proposition. However unwilling persons have been to admit that

NORMAL URINE CONTAINS SUGAR,

the fact of its presence must now, after upwards of 50 years of hard contention, be looked upon as fully established. The negative reaction given with Fehling's solution has constituted the source of the fallacious impression, but it has now been made clear that principles are present in the urine which have the effect of interfering to a certain extent with copper sub-oxide precipitation and thus concealing limited amounts of sugar. All this is now fully recognised, and sugar has been incontestably shown by other means to be present in normal urine.

The nature, indeed, of things is such that, in proportion as sugar is present in the blood, so it may be looked for to be present in the urine. Sugar belongs to the class of small molecular bodies, and we know that these, whether of a drug, saline, or other nature, flow off in association with the water of the urine from the blood circulating through the kidney. It is inconceivable that sugar could exist in the blood without passing off with the water of the urine; and experience shows, in cases of glycosuria, that the kidney is exceedingly sensitive to sugar, the urine being instantaneously influenced by any alteration of the amount of sugar in the blood.

In a paper on the effect of the intravenous injection of sugar on the urine, contained in Vol. XXIV., 1899, of the *Journal of Physiology*, I have given a number of prefatory observations on the condition of healthy urine in relation to sugar, and it is seen that much variation in the amount present exists. In some, the amount was considerably beyond that which, under preconceived notions, would be considered credible. Doubt, however, upon the point of validity, or about the figures being in the main part due to carbohydrate is removed by determinations having in each case been made before and after hydrolysis, and by the results that were thence obtained. With the other cupric oxide reducing principles in the urine, no increase of reducing power is by the hydrolysing process brought about, and therefore all the rise that took place, and in some instances it was considerable, must have been attributable to the presence of carbohydrate.

The amount of sugar ordinarily present in the blood stands at about 1 per 1000, and as the urinary water flows off, it is accompanied with a relative proportion of the sugar and other small molecular bodies present in the blood. According to the state of blood plasma, so, in this respect, may be expected to be the state of the urinary flow from it taking place through the tuft belonging to the Malpighian body. The larger

the larger will be the amount flowing off with the urine. With 4 grammes per kilogramme of dextrose intravenously injected, 47 per 1000 of sugar was found, in one of the experiments mentioned in the paper above referred to, in the urine collected within less than one and a half minutes from the commencement of the injection. The sugar literally runs off through the kidney like running through a filter.

There is good ground for inferring that the same line of action occurs with small quantities as with large, and that the urine coming, for instance, other circumstances being equal, from blood containing 1·5 per 1000 of sugar will contain proportionately more sugar than that coming from blood containing 1 per 1000. The fluctuation of sugar within certain limits in normal blood will thus account for the fluctuation that is observable in normal urine.

Activity of kidney will, of course, constitute an influencing factor. If the circumstances should be such as to lead to a low output of urine, the output of sugar will be low in proportion. If urinary water does not escape, there cannot be an outflow of sugar.

The percentage relation of sugar in the urine will also be influenced by the degree of concentration the output from the Malpighian tuft attains in transit through the uriniferous tubules. Hence degree of concentration, which is denoted by the specific gravity, constitutes an item that demands consideration. Indeed, through concentration, the sugar belonging to healthy urine may be relatively raised sufficiently to give rise to the production of a perceptible reduction with Fehling's solution, and it is known that medical practitioners have to be upon their guard not to interpret it in a wrong way and put it down as an indication of disease.

The point that I desire should be clearly understood is that the urine, alike for small quantities and for large, affords an indication of the state of the blood with reference to sugar, and that if, from any circumstance, there is an entry of free sugar into the circulation, it becomes at once proportionately apparent through the medium of the urine.

In the healthy state, the carbohydrate taken into the stomach does not reveal itself either in the blood or in the urine. There may be—say 200 or 300, or there may be 600 or 700 grammes taken, and the condition as regards both blood and urine remains unaltered, although as small a quantity as 1-4000th of the weight of the animal intravenously injected, in a pronounced manner affects them.

In diabetes, on the other hand, the carbohydrate reaching the stomach is followed with the same result as on being intravenously injected. This constitutes

THE ESSENTIAL DIFFERENCE BETWEEN HEALTH AND DIABETES.

In the latter, the carbohydrate taken as food shows itself in the blood and urine, just as it does when introduced in a direct manner into the circulation.

Cases of diabetes present themselves in which a certain amount of carbohydrate can be ingested without producing any discernible effect. Taken within the specific amount, it follows the course that it does in health and becomes subsequently lost to view. Taken, however, beyond the special amount, the result observed is the production of glycosuria corresponding to the extent to which the carbohydrate has surpassed the extreme amount from which no glycosuria follows. Up to a sharply defined point, the carbohydrate taken in these cases behaves as it does in the healthy subject, and fails to be subsequently recognisable, whilst that which is taken in excess of the defined point flows off in the form of sugar with the urine just as it does in a bad case of diabetes, and just as it would do if introduced by injection in a direct manner into the circulation.

Here, then, carbohydrate within a certain limit comports itself as it does under normal conditions, and beyond the limit, takes the course that is followed in diabetes. An intervening line exists between the normal and the abnormal states, and it is interesting and instructive to give attention to the facts observable in connexion with the transition from the one to the other. To watch the condition closely, the circumstances should be such as to permit of the transition point being discernible. Cases vary much as to where the boundary line denoting

THE TOLERATION POINT OF CARBOHYDRATE

lies. The tolerating power may be little, or it may be considerable. In either case, the result is the same on overstepping the boundary line existing, and in the phenomenon, an explanation is seen of the *modus operandi* of the diet testing resorted to by the physician for the supply of diagnostic information in connexion with diabetes. For the sake of illustration, I will cite the following two examples, which show how quickly the change is wrought, and how marked is the effect that may be produced by a limited amount of carbohydrate.

The subject of a mild form of glycosuria—that is, a person who could partake to a fair extent of carbohydrate without passing sugar, partook at breakfast, which was finished at 10 A.M., of fish, some toast, a tablespoonful of raspberry jam, and a cup of tea with one piece of sugar in it. The time of his visit to me was 10.15 A.M. At 10.20, he passed some urine, which gave no reaction with Fehling's solution. Thinking, however, that sugar would be likely to show itself, I purposely prolonged the consultation and obtained urine again at 10.40. This was found to contain 32·8 per 1000 of sugar. It was, probably, to the sugar taken, and not the starchy matter, that the high figures were due, sugar being ready for immediate absorption whilst starch has to undergo a preparatory conversion into sugar. With reference to the figures, it has also to be taken into account that urine having been passed at 10.20, that which was obtained at 10.40 represented secretion unmixed with urine secreted before the food was taken. The urine of 10.20 would partly consist of this latter, and probably if it had not been present to dilute the other, a certain amount of show of reaction would have been obtained.

In the other case, the patient, 53 years of age at the present time, has been the subject of diabetes for seven years. During the last four years, full restriction from carbohydrate food has been necessary to keep the urine free from sugar. The patient resides in Ireland, and for business purposes comes to London about twice a year, upon which occasions it is usual for him to fall under my notice. I observe from my notes that on Sept. 27th, 1904, night and morning specimens were brought for examination and were found to be free from sugar. Curiosity had led the patient to take a little toast at breakfast to see if it would affect the urine, and I find it noted that urine passed a short time afterwards gave a slight reaction with Fehling's solution.

Having started with the trial of the effect of toast in the manner mentioned, he continued to carry it on at his subsequent visits, and I will give the precise results that have been observed. April 11th, 1905, no sugar was found in the night and morning specimen of urine brought for examination, whilst two hours after breakfast, at which a single piece of toast was taken, the urine contained 10·9 per

1000 of sugar. Oct. 9th, 1906, the night and morning specimens brought gave no reaction of sugar. Breakfast had been taken at eight, and included the test piece of toast. Some urine was passed at 8.30 and 9.30 and was brought mixed together. It gave a trace of sugar reaction. Urine was again passed at 10.30 during the visit, and this was found to contain 19·2 per 1000 of sugar. March 13th, 1907, the night and morning specimens gave no reaction of sugar. Breakfast with the toast as before was taken at 9.15. The urine collected at 10.10 contained a trace of sugar, and that passed at 11, 10·9 per 1000. Oct. 8th, 1907, the patient breakfasted in a like manner to previously at 8.15. The night and morning specimens were free from sugar. Urine collected at 9.15 contained 7·8 per 1000, and that passed at 10.45, 12·5 per 1000.

This case exemplifies the remarkable steadiness associated with the elimination of sugar in diabetes. Here is a patient who, during a period of observation extending over three years, was found to pass no sugar whilst on the properly restricted diabetic diet, and almost immediately after taking starchy food in the limited quantity named, passed urine containing a decided amount of sugar. The facts related stand in strict accord with common experience in such cases. There is a sharp line limiting the extent to which carbohydrate can be taken without affecting the urine, and it is within the bounds of possibility for the limiting line to show no variation not only for weeks and months, but even for several years. There is much diversity in different cases with respect to where the line stands, but no matter what may be its position, as long as the carbohydrate taken falls within the particular boundary existing, the urine remains unchanged, whilst if the boundary is overstepped by ever so little, the urine affords an indication of the fact.

In the instance of the particular case upon which these remarks are founded,

THE BOUNDARY LINE

comprises the carbohydrate present in the diabetic diet employed by the patient, for it must be taken as understood that it is impossible absolutely to exclude all carbohydrate matter, however rigidly framed a diet may be. The amount of toast that sufficed to produce the results that have been narrated may, from the statement made to me by the patient, be computed at about 15 grammes, or a little over half an ounce. I find that ordinarily made toast contains about 28 per cent. of water, and making deduction for the water, the 15 grammes will contain 10·8 of dry solid matter, which, reckoned to contain 82 per cent. of starch, gives 8·8 grammes as the amount of carbohydrate productive of the effects upon the urine described.

Interposed between the seat of elimination of sugar with the urine and the seat of absorption of sugar from the alimentary canal, we have the contents of the circulatory system. All are agreed upon the point that, in the glycosuria under consideration, the sugar escaping with the urine is derived from

SUGAR PRE-EXISTING IN THE BLOOD.

What is meant then by the appearance of sugar in the urine is that it was previously present in the blood as a result of the carbohydrate food taken, and, reciprocally, it may be said that the presence of sugar in the blood leads to its proportionate presence in the urine. That the two go together is shown by the effect of the direct experimental introduction of sugar into the circulatory system, and confirmed by rational deduction from the molecular-sized condition of sugar and water viewed in relation to the eliminative process. Unquestionably sugar does not stand apart from other small molecular bodies in escaping with the urine as a result of its presence in the blood. As a matter of fact, observation shows that the water does not pass off and leave the sugar behind.

Plainly looking at the phenomena in these cases of alimentary glycosuria, what do we find? That no altered condition of the urine is induced by the ingestion of carbohydrate within a certain limit, but that when this limit is reached and surpassed, sugar shows itself in the urine in proportion to the extent to which the overstepping has taken place. If this applies to the urine, it must, upon the strength of what has been said, equally apply to the blood, and this brings us to the conclusion that up to a certain point, carbohydrate can be taken without adding to the amount of sugar present in the blood, whilst if taken beyond the specific point, the amount of sugar in the blood becomes augmented in like manner to that observable in the case of the urine.

Obviously, there must be a different issue connected with the carbohydrate which fails, as in the healthy state, to show itself, and that which, in consequence of a larger quantity being taken, shows itself in an abnormal manner to us. By those who retain belief in the teachings of the glycogenic doctrine, it is held that the carbohydrate of our food passes through the circulatory system in the form of free sugar to become oxidised in the tissues, and the abnormal presence of sugar is ascribed to accumulation from faulty oxidation.

This plainly expressed represents the view that is nowadays adopted in explanation of the source of diabetes by partisans of the glycogenic theory. If such a view were correct, oxidation, which varies with functional activity, would always have to be standing on a par with the carbohydrate food-supply, a very variable item, to escape from accumulation. There is variability in consumption of carbohydrate by oxidation, and much variability in the supply of carbohydrate from without with the food, and yet the two are to stand in such balanced regulation as to provide the constant immunity from accumulation that is required to account for the steady maintenance of the urine in the state that is observed. Looking, indeed, at the very small amount of ingested carbohydrate that is instrumental in altering the state of things in these cases of alimentary glycosuria, the constancy with which the precise point at which the alteration that occurs is maintained over a lengthened period of time, and the fact that the different rates at which oxidation of carbohydrate is carried on under different circumstances exert no influence on the result, I consider it is rendered

IMPERMISSIBLE TO SEEK IN THIS DIRECTION

for the explanation that is required.

Is it then possible, in view of the facts that are before us, for the carbohydrate of the food to pass through the circulation to the tissues in the form of free sugar without the transit being revealed by the agency of the urine? Upon non-carbohydrate food, the blood and urine are practically in about the same condition as upon carbohydrate-containing food, and the same, it may be said, applies to the fasting state. Although, then, the urine is such a sensitive indicator of the state of the blood with reference to sugar, and, although, if the food carbohydrate passed in the form of sugar through the circulation there should be a transit of sugar in proportion to the food carbohydrate taken, yet this is to occur without any sign of it being revealed by the urine.

Nothing short of the occurrence of an instantaneous disappearance of the sugar on reaching the circulatory system would meet what is wanted to escape from the output of sugar with the urine, and experiments on the intravenous injection of sugar suffice to show that this does not ensue. Even in experiments with the injection of 0·25 gramme of dextrose per kilogramme body weight, which amounts to only 1-4000th of the weight of the animal, the results show not only a given immediate effect on the blood, but likewise that the effect that is produced only tardily, it may be said, subsides. Coincidently, as might be expected, with the effect on the blood, there occurs an accompanying effect on the urine.

The circumstances connected with the passage of sugar into the circulation

BY MEANS OF INTRAVENOUS INJECTION

are not strictly comparable with those connected with its passage as a sequence to absorption from the alimentary canal. In the latter case, the influence that is capable of being exerted by the interposed liver has to be taken into account. In connexion with the glycosuric state, sugar derived from alimentary absorption passes into the circulation and thence into the urine, just as though it had been intravenously injected. There is, obviously, neither a stoppage at the seat of absorption nor in the liver. But what happens in the case of the carbohydrate falling within the certain limit that can be taken by the glycosuric without rendering itself manifest? Does this also pass into the circulation and become instantly lost by destruction in the tissues? The facts are diametrically opposed to the tenability of such a view, and if, under such circumstances, the carbohydrate passed as sugar into the circulation, it ought rationally to be expected to give indication of doing so, similarly to what occurs after direct introduction by intravenous injection.

Looking from all points of view at the matter that has been considered, the conclusion seems to me to be inevitable that the urine could not escape being affected by carbohydrate food, in proportion to the amount ingested, if transport took place in the form of free sugar through the circulation to the seat of utilisation in the tissues. And yet the view is still seen in some quarters to receive credence. For instance, an *à propos* illustrative case is to be found in the article on the "Metabolism of the Carbohydrates" contained in as late a publication as Leonard

HILL'S WORK ON "RECENT ADVANCES IN PHYSIOLOGY

and Bio-Chemistry," 1906. The article was written by Professor J. J. R. Macleod, now in Cleveland, U.S.A., but formerly a demonstrator of physiology at the London Hospital. Let us look into what is said, and give an eye to the groundwork on which the credence is based.

The article starts with notifying that carbohydrate matter constitutes the greater portion of our food and then specifying that it may range in standard daily dietaries, constructed for different amounts of muscular work, from 240 to 700 grammes. The consideration of how this carbohydrate becomes disposed of within the system is next entered into and dealt with upon lines falling within the teachings of the glycogenic doctrine. Notwithstanding the professed nature of the work in which this article is contained—of the work itself it may be said that, looked at as a whole, it has ably and usefully met a want that existed—it is found that in the article what can be unreservedly spoken of as obsolete errors are in an unqualified manner adopted and made use of as a groundwork for the conclusions set forth.

For instance, in antagonism with the showing of all modern work, it is assumed that the sugar normally present in the blood does not pass out with the urine and that it is only when it stands in excess of 2·0 per 1000, which is put down as constituting the maximum representation of the normal range for the sugar constituent of the blood, that it shows itself in the urine. "With a normal percentage (of sugar) in the blood, the kidney allows none of the sugar to pass into the urine, but whenever this percentage is exceeded, immediate leakage of the excess through the kidney filter occurs" (p. 313). Such is the physiology that is placed before advanced physiologists in connexion with this matter!

The first part of the statement is demonstrably untrue, and the second part is pure fiction. What is there to determine that below 2 per 1000, there shall be no escape, and above, an escape of sugar? The whole thing is not only contrary to fact, but opposed to common-sense reasoning. In reality, with 2 per 1000 of sugar in the blood, an outflow may be looked for sufficient to produce marked glycosuria. The results from intravenous injection justify this conclusion. And these premises, which formed a part of the groundwork upon which the glycogenic doctrine was based, are, in spite of the advance of knowledge that has taken place, put forward in the article in question as if they rested upon a substantial foundation. Evidence in every direction, in reality, unequivocally shows that sugar in the urine runs concordant with that present in the blood.

The author of the article afterwards, in speaking of the

FATE OF THE GLYCOGEN STORED IN THE LIVER,

says (p. 334) "there are two so-called theories, the one by Bernard, the other by Pavy," and then proceeds to pass judgment upon them, by framing four aphoristic propositions, based on Bernard's conclusions, and opposing to them statements that he puts forward as representing conclusions drawn by me. His deduction, which is emphasised by insertion in italics, runs: "*The balance of evidence stands in favour of Bernard's theory.*"

No useful purpose will be served by entering into the details of the argument adduced. What are complacently spoken of, in the aphoristic propositions, as "facts," and "proofs," constitute, in reality, assumptions of the same order as those I have just been considering, and I do not admit that a faithful representation is given of the grounds of contention that emanate from me. The whole thing, in fact, stands upon too illusory a footing to permit of any conclusion bearing even an approach to substantiality being deducible.

A derisive footnote against my diction is inserted at p. 337 which I do not feel disposed to allow to pass unnoticed. The words of the footnote run: "He (Pavy) considers the intestinal epithelium the first barrier against the passage of sugar into the blood; what escapes this retention filter (*sic*) being caught up by the liver." I have searched and can nowhere find the solecism alleged to have emanated from me, and the style of expression is not such as I can recognise as belonging to me. I suggest that it has much more the aspect of coming from the writer himself, and possibly "caught up" since his transfer from the Physiological Department at the London Hospital to that at Chicago.

There is one point in the argument that ought perhaps to receive consideration because, from the frequency with which I have seen it referred to, it seems to constitute a stock datum for employment in support of the glycogenic theory. "Thirdly," the text runs, (p. 336) "the percentage of sugar in the blood of the hepatic is greater than that of the blood in the portal vein when no absorption of food from the intestine is in progress." In the criticism of what I have advanced upon this point, it is contended, that the quantitative analysis of the blood for sugar is a process which is technically very difficult and is subject to a considerable experimental error. Neither of these propositions I admit, but am content to let them pass. Then it is argued that if "the liver should add dextrose to the blood of the hepatic vein, the percentage increase of sugar thus created could be only very slight, on account of the enormous amount of blood which passes through the organ."

PROFESSOR HALLIBURTON,

whose writings we must all consider, whether agreeing with them or not, as entitled to respect, in his article on the subject of diabetes from the physiological standpoint, in the *Practitioner* for July, 1907, in a similar way deals with my having been unable to find more sugar in the hepatic blood than in the portal blood, saying (p. 3), "Other observers have found an increase in the sugar of the blood leaving the liver, but the estimation of sugar in a fluid rich in proteins is admittedly a matter of difficulty. Even (as the late Sir Michael Foster put it) if the increase is as small as hardly to be detected, it must be remembered that the whole blood of the body passes about once a minute through the liver, so that a very small increase each time would mount up to a large total."

The matter in question bearing

ON THE RELATION OF THE HEPATIC TO THE PORTAL BLOOD,

has become, with the progress of time, to a considerable extent shifted from the position it originally held. In the renowned experiment for showing the sugar-producing action of the liver, the animal was killed, and blood was afterwards collected from the portal and the hepatic veins. The two specimens were heated in capsules with sodic sulphate, and clear liquids obtained for testing with the copper solution. As a result, the contents of the test tube belonging to the portal blood were seen to retain their original blue colour, whilst those of the other showed the production of a copious orange yellow reduction. Upon this basis, and the fact that the liver gave strong evidence of containing sugar whilst the other organs did not, the glycogenic function was founded. The experimental collection of blood by catheterism during life constituted a measure employed by me to show that the hepatic vein blood during life was not in the condition that it had previously been assumed to be from the experimental collection after death. Such was the object of the experiment, and with the portal and hepatic venous blood examined side by side, no difference of behaviour was discernible between the two.

In reality, the proposition under consideration amounts to this. Without the supply of any fresh evidence in connexion with the matter, and upon the strength of the assumption that the hepatic venous blood contains more sugar than the portal blood, it is suggested that the amount of difference may be so small as to escape being susceptible of recognition by analysis, and yet, on account of the large volume of blood passing through the liver, the result might be attended with a large amount of sugar reaching the circulation. The superficial plausibility of this suggestion has produced a widespread effect upon the physiological mind and encouraged the idea that the proposition might in truth be looked upon as valid. The question has not been asked as to what would follow if the suggested passage of sugar into the circulation in reality took place.

In former times, when it was held that an active disappearance of sugar occurred during the passage of the blood

THROUGH THE SYSTEMIC CAPILLARIES,

the amount of difference in the sugar contents of arterial and venous blood was put down as something considerable. Citing one of Bernard's experimental records, the amount given for the arterial blood was 1·450 per 1000, and for the venous, 0·730, expressive of a loss of half of the sugar contained in the arterial blood in its transit through the capillaries. This is now fully known and recognised to be in error. Even by the French school, the contention of former days upon this point is no longer upheld. As long as credence was given to a disappearance of sugar in the systemic capillaries, feasibility existed for its passage into the circulation through the hepatic vein, but what is to occur if there is ingoing, as contended for, through the hepatic vein, and not the disappearance that was formerly conceived to be taking place within the systemic capillaries. The only issue that could follow would be accumulation in the circulation and outflow with the urine, giving rise to glycosuria, which is exactly what I affirm would constitute the state of things existing if the teaching of the glycogenic doctrine were actually carried out.

It must be borne in mind that the amount of sugar that would have to pass into the circulation from the hepatic vein

IF THE CARBOHYDRATE OF THE FOOD HAD TO BE TRANSPORTED

in the form of sugar through the circulation to the tissues for utilisation, would oftentimes be very great, and yet it is not found that any manifest show of it is to be recognised in the blood and in the urine. For instance, in connexion with the standard daily dietaries previously referred to, it was mentioned that the carbohydrate might mount up to 700 grammes. Now, whether the condition is viewed at a period of fasting, on animal food, or on a diet containing either a small amount or a large amount of carbohydrate, the state of things in relation to sugar in the blood and in the urine may be said to be practically the same, but how is this possibly reconcilable with transport through the circulation in the form of free sugar. When the carbohydrate of the food reaches the circulation in the form of sugar, as it obviously does in diabetes, the sugar is recognisable alike in the blood and in the urine, and in the state of health, I contend that the result would be the same if the carbohydrate of the food were similarly permitted to reach the circulation as sugar.

In the face of these considerations, it seems to me unquestionably evident that the carbohydrate of the food cannot pass into the circulation as sugar, as it is alleged to do under the glycogenic doctrine. The writer of the article in Hill's "Recent Advances in Physiology," to which reference has been made, sees the difficulty in relation to this point involved in the doctrine, and reckoning up the carbohydrate contained in the liver, blood, and tissues, states that it does not stand in accord with the absorption that may occur from the food, and admits that it must be concluded that a considerable amount becomes converted into fat or incorporated with proteid (p. 314).

As regards

THE LIVER, WHICH UNDOUBTEDLY PLAYS A PART

in checking the passage of sugar into the general circulation, (I have spoken of the organ as affording a second line of defence against the entry of sugar into the system, functionating upon the sugar that escapes being dealt with at the seat of absorption in the intestine, during the height of absorption activity, following a copious ingestion of carbohydrate food) the writer in question gives data to show that only a comparatively small portion of absorbed sugar can be accounted for by conversion into liver glycogen, and that therefore, under the view advocated, there must be a large amount of sugar passing into the circulation at the time absorption is going on—a proposition opposed to the fact that neither the blood nor the urine affords evidence of such entry, although both are eminently sensitive to the entry of minimum quantities of sugar effected by the medium of intravenous injection.

The contrast is very great between the effect of the intravenous injection of sugar and that which follows the ingestion of sugar. In the one case, as I have just stated, the blood and urine are influenced in an exceedingly sensitive manner. In the other, as is well known, large quantities of sugar may be ingested without producing any visible effect. If passage into the circulation succeeded absorption, how could it come about that evidence of it could escape being discernible? Here lies the great error under which physiologists have hitherto laboured—the error of assuming that absorbed sugar can reach the circulation without being subsequently open to recognition.

Too much stress must not be laid upon the part played by the liver. I look upon it as simply supplementing the action occurring at the seat of absorption, and that, with a moderate amount of carbohydrate food taken, it is possible that little or no work may be thrown upon the organ. The position assigned to it, however, under the glycogenic doctrine is a far more material one, looked at from the side of the urine being kept free from sugar, inasmuch as it is supposed to constitute the sole agency by which the sugar from the food at the time of active absorption is prevented reaching the circulation in sufficient quantity to affect the urine. If it were not for this, it is considered, a temporary glycosuria would be consequent on a meal. How does this stand in view of the demonstrable fact that in different ways, (Eck's fistula, &c.)

THE LIVER MAY BE CUT OUT OF THE CIRCUIT

of blood without leading to the production of glycosuria? If there were nothing besides the liver to bar the direct passage of absorbed sugar into the general circulation, it is impossible to conceive, after the operative procedure referred to, that the urine could any more escape becoming charged with sugar after ingestion of carbohydrate food than it does after the intravenous injection of sugar. I do not propose to proceed any further with this matter at present, but shall have occasion to refer to it again later.

As the issue of what has preceded, it seems to me impossible that the absorbed sugar from carbohydrate food could possibly reach the general circulation in the form of free sugar without revealing itself by passing into the urine, just as it does in diabetes. During fasting, there is a given amount of sugar in the blood which is revealed by a correlated presence of sugar in the urine. Add to the sugar in the blood, and is the urine to escape giving evidence of the addition? If it did the circumstances would amount to the smaller quantity revealing itself and the larger quantity failing to comport itself upon similar lines. For sugar to reach the circulation without influencing the urine, there must be an immediate disappearance on entrance into the blood, and this, it is known, does not occur.

I have spoken of the facts which lead up to the conclusion that if the carbohydrate of our food reached the circulation for transmission to the tissues in the form of free sugar, it could not fail to give rise, proportionately to the amount doing so, to the presence of sugar in the urine, and thus the condition existing in diabetes. Let us now see upon what ground we stand, in relation to the matter, on applying the transport of free sugar hypothesis as a basis to work upon in the treatment of diabetes.

Looked at in relation to physiology, the glycogenic doctrine is the source of no embarrassment. The dictum is pronounced and nothing further follows, seeing that it is in no way subjected to

THE TEST OF PRACTICAL APPLICATION.

In the case of medicine, it is far otherwise. Diabetes, which arises from a physiological defect connected with carbohydrate metabolism, falls to the province of the physician to deal with, and here the trial of the enunciated physiological hypothesis comes in. Physiologists can look on with complacency, inasmuch as they, in their position, remain untroubled by the effect of error. Whatever the conventional physiological view that may be held, Nature proceeds unobstructedly with her operations, and the issue remains unaffected. To the physician, on the other hand, whose work lies in endeavouring to restrain the ill-effects of the faulty physiological action, the rightness or wrongness of the hypothesis upon which he is basing his procedure, counts for everything.

Now, what does the glycogenic doctrine imply? It implies the entry of sugar into the circulation, and this implies the passage of sugar into the urine, and next follows, as a resulting corollary, the origin of glycosuria from carbohydrate food. How is such a doctrine compatible with the state in which the urine is normally found? It itself, if put into application, would lead to the production of the glycosuric state. It may be said there is always a certain amount of glycosuria existing, harmonising with the limited glycæmia (independent of the functioning connected with our carbohydrate food-supply) that is normally present, and if this latter were increased by the effect derivable from carbohydrate food-supply, a corresponding addition to the normal glycosuria ought to be observed. The output of sugar that occurs after carbohydrate food taken in the presence of alimentary diabetes, gives an indication of the rate and amount of sugar absorption actually occurring.

The glycogenic doctrine

FAILS IN SUPPLYING A RATIONAL BASIS

of action viewed in relation to the treatment of diabetes. Indeed, as has been before stated, it has contributed to leading persons off in the wrong direction and to giving rise to suggestions which, if put into practice, could not do otherwise, as experience shows, than produce a downright pernicious effect. Diabetes being the result of a faulty carbohydrate metabolism, the possession of a right comprehension of the mechanism of the normal metabolism, ought to throw a guiding light on the direction in which to apply our efforts for bringing a counteracting influence to bear on the disease.

It is in this way that knowledge is the source of power. It gives us command over phenomena by enabling us, through the instrumentality of designedly modified conditions, to bring about a desired result. For instance, as previously referred to, since the knowledge of the microbic nature of the zymotic diseases was obtained, we have been placed in a position to combat the group of diseases in question with a power altogether different from that which we possessed before. Applying the glycogenic doctrine as a working basis in the treatment of diabetes, a want of congruity confronts us. It is professed to be natural and necessary that sugar should be constantly reaching the circulation, and yet the act of doing so leads to elimination with the urine. In spite of the fact that the system is suffering disastrously from the effects of the presence of a redundance of sugar, there is nothing to suggest, under the tenets of the glycogenic doctrine, that the food-supply of carbohydrate should be cut off, although experience shows that this line of procedure constitutes absolutely the only means by which an improved state of things can be brought about.

By the glycogenic doctrine the

MIND OF THE MEDICAL PRACTITIONER HAS BEEN DIVERTED

from what experience shows to be the right course as regards the treatment of diabetes. There is another matter bearing on treatment which has given rise to an immense amount of confusion and misguidance. I refer to the delusion created by deceptive diabetic food. Persons are too apt to conclude that because an article is advertised and sold as a diabetic bread-stuff it is to be accepted as suitable for use as such. The amount of starchy matter or sugar present, constitutes in reality, the criterion. This can easily be determined by analysis, and analysis is often showing that the reputed diabetic food is but little, or even, it may be, no better than food of an ordinary nature. The opening that here exists for liability to error must be intelligible to all. Not only, on the one hand, is treatment thwarted, but on the other hand, the foundation is laid for erroneous conclusions, touching the disease and its treatment, to be framed.

This brings me to speak again of the work of Professof von Noorden. I notice in Dr. Boardman Reed's translation or von Noorden's work on Diabetes Mellitus, that the author announces himself to be an advocate of the restricted diet treatment of diabetes. At p. 173, he says, "The first rule that I must lay down is this: the reduction of the glycosuria to the smallest possible limit must be the goal that is never to be lost sight of." Again, at p. 180, after having, in the case of mild forms of glycosuria, advocated commencing the treatment with the restricted diet, notwithstanding even the existence of a certain amount of tolerating power of carbohydrate, and stated that carbohydrate is afterwards to be gradually added to the food, he proceeds: "Care must, of course, be taken that the amount always remains below the level of the toleration limit."

Although thus expressing himself upon principle of action in a manner to which no exception can be taken, what do we find amongst bis practical recommendations? That the "oat cure" is added to the longish list of special food cures that have been introduced. In the course of my experience, I can recall the introduction of the "treacle cure," the "honey cure," the "skimmed milk cure," von Duering's "rice cure," and Mossé's "potato cure," as food cures for diabetes. To the list is now added

VON NOORDEN'S "OAT CURE,"

and the claim is made for it that it is superior to the other cures. At p. 195, the statement occurs: "In comparing the potato cure and the oat cure, as I often did for the sake of comparison in the same patient, allowing the one treatment to follow the other, I became convinced of the decided superiority of the oat cure. Severe cases of diabetes react much more favourably on oats than on potatoes. I must, however, acknowledge that there are exceptions, and in appropriate cases [the kind of case to be appropriate is not mentioned] I myself have gladly made use of Mossé's treatment."

Comment is made on the effects of the cures being peculiar and paradoxical, and the limitation of the carbohydrate to *one particular* kind is referred to as constituting an underlying principle. "It would seem," says von Noorden, p. 195, "that the diabetic organism is able—temporarily at least—to regain the power of assimilation for one particular carbohydrate, while still unable to utilise the infinitely smaller amount of the various carbohydrates contained in ordinary food. In my laboratory," he continues, "we have tried to discover whether under the circumstances mentioned particular diastatic or antidiastatic ferments, which effect only one particular carbohydrate, occur in the blood; but the investigations, so far as they have gone, have yielded no positive results. We are obliged to leave to the future the elucidation of this practically and theoretically important question."

I am entering to the extent I am doing into this subject because the name of von Noorden is authoritatively associated with the subject of metabolism and is therefore calculated to exert a weighty influence on the medical mind in connexion with the matter that is under consideration. I must confess, however, that I cannot understand how such a proposition as is set forth above could have emanated from the quarter it has done. The whole thing, as it stands, is a medley of misconceptions and incongruities. What can diastatic or antidiastatic ferments in the blood have to do with the particular kind of starch that may happen to be taken? Starch does not reach the blood. No matter what kind is taken, all are agreed that the starch molecule, whatever its source, is hydrolysed into dextrose preparatory to entrance into the system. How, then, can the source of the starch bear on the question of the utilisation of carbohydrate occurring within the system? Utilisation seems to have been mixed up with the prefatory breaking-down process needed to permit of the passage of the carbohydrate into the system. Speaking upon the strength of my own experience, I can unhesitatingly say that I have seen nothing to lead me to consider that there is ground for surmising that one kind of starch behaves differently in the system of the diabetic from another. Indeed, it would be altogether contrary to rational expectation that it should do so.

As regards starch and sugar, the circumstances are different. Starch having to undergo transformation before absorption can occur, it is natural to conclude that it is placed in a position to be prevented entering the system as rapidly and freely as sugar, which is in a fit state for absorption at once. As a matter of fact, it is observable that glycosuria can be produced in the healthy subject by means of copious sugar ingestion, whilst it is possible, it seems, for starch to be tolerated to any extent without the production of glycosuria.

A large amount of fallacy is found to be mixed up with various matters connected with diabetes. Let us see how the "oat cure" stands in this respect. The origin of the oat cure is thus narrated by von Noorden (p. 190). "A few years ago I introduced the so-called oat cure into the treatment of diabetes. It was quite accidentally that I came to recognise its significance. A few patients in my clinic were suffering from severe disturbance of the stomach and intestine. I therefore permitted them nothing but oatmeal gruel. To my surprise the glycosuria did not increase, but became much less than it had been upon the very strict diet."

Now, what did the very strict diet include? We are told that it included the gluten food of Rademann of Frankfurt, mentioned in Table 1 (p. 199), which, it is stated, may find a place in even the most restricted dietary, and which the majority of diabetic individuals may have as much of as they may desire.

It has been my custom for very many years past to have the diabetic foods, foreign and otherwise, that I have been able in the course of practice to come across, analysed for the determination of their carbohydrate content, so that I might keep *au courant* with respect to knowledge of the nature of the supply obtained by patients. As a result I have a large collection of reports from which I often derive much serviceable information. In this way it happens that I have a record of analyses of samples of Rademann's food. The analyses were made a few years before von Noorden's work was published, and, therefore, are probably representative of the food actually referred to by him. One consisted of "diabetic white bread" examined in July, 1900. Taken in the water-free state, it contained 73·4 per cent. of starch. A sample of Zwieback (rusks), examined in March, 1898, contained 72·1 per cent. of starch, and another, examined in November, 1902, 64·8 per cent. of starch.

Where is the strict diet character to be found in connexion with these foods? The figures given for starch in ordinary wheaten bread in the water-free state, to which, for permitting of proper comparison to be drawn, all foods should be brought previous to analysis, run from about 85 to 90, or a little over, per cent. Oatmeal is known to contain less starch than wheaten flour, and the amount may not be greater, if it is not even less, than in the bread-stuff food belonging to the so-called restricted dietary of Professor von Noorden. Actual analysis in the accustomed manner has yielded the following figures:—Quaker oats 69·7 per cent., oatmeal groats 73·2, Scotch oatmeal 74·2. Hence, in the nature of things, there would be no justification for the surprise stated to have been experienced that the oatmeal food did not produce a greater glycosuria than what had been noticed to exist under the so-called very strict diet.

The illusory character of much of what is sold under the denomination of diabetic food has been the source of an immense amount of harm, not only from a practical point of view in connexion with the treatment of diabetes, but likewise through the erroneous impression brought to bear on our mental conceptions relative to the disease. It is easy to understand how readily false conclusions may be framed upon points connected with the disease by assuming a food to be constituted otherwise than it really is. I will leave this subject now but shall have occasion later to refer to it again.

The next point to which I will give consideration is the

STATE OF THINGS FOUND TO EXIST AFTER CUTTING OUT THE LIVER

from the blood circuit. Looked at in relation to the view taken under the glycogenic doctrine, the effect of the operation ought to be attended with the production of glycosuria after the administration of carbohydrate food. Special experimental procedures have been adopted for attaining the desired object, and let us see the nature of the result that has been obtained.

Minkowski, taking advantage of the anastomosis existing in birds between the portal and renal veins, as long ago as 1886,[1] experimented upon geese in relation to the point. It is found, through the anatomical condition existing, that the

[1] Archiv für Experimentelle Pathologie und Pharmakologie, Band xxi., S. 41, 1886.

portal vein can be ligatured and the liver extirpated, without interfering with the circulation through the other abdominal organs. In one recorded experiment, the liver was extirpated after the administration of 25 grammes of dextrose and 25 grammes of starch. During the succeeding 10 hours, 220 cubic centimetres of urine were collected, which, on subjection to alcoholic extraction, yielded an indication of the presence of 0·5 gramme of dextrose. A further 200 cubic centimetres were secreted during the night, and this was found to be free from sugar. In a second recorded experiment, 75 grammes of dextrose were employed. During 12 hours after the operation, 330 cubic centimetres of urine were obtained in which 4·2 grammes of dextrose are stated to have been found, which represent a minute portion only of the dextrose administered. The intestinal contents, it is mentioned, only contained a trace of sugar.

Eck's fistula is the name given to an operative junction of the portal vein with the inferior cava, permitting of the former vessel being tied above the junction and thus cutting off the flow through the liver without interfering with the circulation through the abdominal viscera. The operation is naturally a very delicate and risky one, but it has proved susceptible of being performed upon dogs with survival of the animals in a satisfactory condition for a considerable time afterwards.

Hahn, Massen, Nencki, and Pawlow have published a communication in Schmiedeberg's *Archives*,[2] containing the results of observations on the effects of the operation upon the system. The operative part of the undertaking was performed by Massen and Pawlow, and the chemical part by Hahn and Nencki. A striking effect noticed was the production of an intolerance of animal food. The dogs subsisted well upon bread and milk, but meat produced a toxæmic state accompanied with various manifestations of nerve disturbance. The authors state that they never found albumin, albumose or sugar in the urine, but there is no indication of any idea of looking for sugar in connexion with carbohydrate food administration as a sequence of the position in which the liver was placed.

A communication entitled "On Carbohydrate Metabolism in Dogs with Eck's Fistula, whereby the Portal Blood passes direct into the Vena Cava without traversing the

[2] Band xxxii., p. 161, 1893.

Liver" has been recently published by F. De Filippi of Rome in the *Zeitschrift für Biologie.*[3] A series of observations was conducted upon the toleration of various carbohydrates after recovery from the operation, and finally the actual occlusion of the portal vein was verified by post-mortem examination. The ordinary food administered consisted of bread and milk and wheat-flour porridge, which never, it is stated, produced glycosuria. After the different sugars, however, glycosuria occurred when certain quantities were reached standing below those required to produec glycosuria in the case of dogs in the normal state.

Corresponding results, I perceive, are stated to have been obtained by other experimentalists. For instance, I observe it stated[4] in connexion with the fate of sugar given to dogs with Eck's fistula, that Popelski, in 1898, found, after feeding with large quantities of saccharose, that against 1 per cent. of the ingested sugar eliminated by normal dogs, 13·5 per cent. was eliminated by the dog with the fistula; and quite recently mention is made by P. B. Hawk[5] of absence of glycosuria having been observed in a dog with Eck's fistula on a diet of milk, bread, and potatoes. The concurrent testimony seems to be that whilst sugar can lead to the pro. duction of glycosuria, starchy matter, on the other hand, fails to do so.

Everything points to the existence of a missing link in the chain of events thus far reckoned to occur in connexion with the passage of carbohydrate from the seat of absorption in the walls of the alimentary canal to that of utilisation in the tissues. We know that small quantities of sugar reaching the circulation by intravenous injection, lead to the production of glycosuria, and why should they not do so when absorbed from the alimentary canal? The liver has been credited with safeguarding the circulation from the entry of sugar in a manner to occasion glycosuria, but how do things stand in the face of the evidence that has been just adduced, founded upon the state observed to exist after the abolition of the influence of the organ?

[3] Band xlix., 1907.

[4] Maly's Jahresbericht, Band xxviii., p. 369.

[5] American Journal of Physiology, vol. xxi., p. 259, 1908.

LECTURE II.

Delivered on Nov. 19th.

Mr. President, Colleagues, and Gentlemen,—In my "Physiology of the Carbohydrates," published in 1894, I brought forward a new view with respect to the disposal of the food carbohydrate within the animal system. The clue was given to it by the work which had shown that carbohydrate entered into the constitution of protein matter. By general assent, it is now admitted to do so, and thus a new position is created, providing for the application of carbohydrate in a manner that had not previously been thought of. We know that the carbohydrate of the food is to be traced to the seat of absorption in the walls of the alimentary canal, where it presents itself in the form of sugar. What now becomes of it? If it passed straight on as sugar into the blood, it ought to give rise to glycosuria in the healthy state in like manner to what occurs in diabetes. From the line of experimenting, to which reference was made at the conclusion of the previous lecture, involving the removal of the liver from the field of action, we are driven to conclude, in order to account for the existing circumstances, that there must be an influence at work at the actual seat of absorption to arrest the onward passage of sugar, as such, towards the circulation.

As set forth in my published work referred to, conditions are found at the seat of absorption that suffice satisfactorily to account for the disappearance of sugar that is here observed to occur. We have, in the first place, the fact to deal with that, as can be shown by the effect of cleavage agencies, carbohydrate can be cleaved off from its locked-up state in protein, and in the next, that carbohydrate can, in the presence of nitrogenous matter, be built up into protein by the instrumentality of the synthetic power inherently belonging to bioplasm. Now, nowhere do we find such activity of protein formation existing as at the seat of intestinal absorption. Quiescence prevails at a period of fasting, but after food ingestion, extremely active bioplasmic growth starts into operation, the newly-formed bioplasm flowing, in the shape of lymphocytes, through the chyliferous vessels into the circulatory system, and giving rise to the digestion lymphocytosis which is observed to follow the ingestion of food.

Everything points to the occurrence of a

DISAPPEARANCE OF SUGAR AT THE SEAT OF ABSORPTION,

and with such an occurrence, everything falls harmoniously into line, both in relation to the conditions observed in connexion with the normal state and those observed in connexion with diabetes. But to what extent is it possible for sugar to become lost to view in this way? It is true, with our rough chemical methods put in operation outside the body, only a comparatively limited amount of carbohydrate is to be obtained from the disruption of protein, but it is evident that this is not to be taken as a measure of what may actually exist incorporated within.

Ground is given for the statement made through what is observed in the glycosuric state, induced alike by pancreas extirpation and the action of phloridzin, when the point is reached at which the eliminated sugar is solely derived from protein disintegration. The output of nitrogen being estimated, as well as the sugar, means are afforded for determining the protein destruction occurring. At first the output of sugar is large and variable in proportion to the nitrogen, on account of being partly derived from the carbohydrate (glycogen) existing in a free state in the body. In the course of time, with the observance of fasting, this becomes expelled, and then a fixed relationship is found to present itself between the outgoing nitrogen and sugar. From the nitrogen obtained, the amount of protein disintegrated can be calculated, and thus the data are given for determining the relation subsisting between

PROTEIN DISINTEGRATION AND SUGAR LIBERATION.

Reckoning upon the basis of the information in this way supplied, it may be roundly stated that protein yields up about half its weight of sugar, which may rationally be taken to have been previously incorporated with it from the food.

The disappearance of absorbed sugar by synthesis into protein before passage from the mucous membrane of the intestinal canal, harmoniously fits in with the absence of glycosuria as a result of Eck's fistula. With sugar locked up in protein reaching the general circulation through the lacteal system, the position is unaffected by the experimental prevention of the passage of the portal blood through the liver. Only a variable portion of the absorbed sugar would be left to find its way into the portal blood. I expressed myself upon this matter in my recent work on "Carbohydrate Metabolism and Diabetes," p. 66, 1906, in the following terms, and the remarks were made before the information supplied by Eck's fistula had been taken into consideration. "As yet I have only spoken of the assimilation of carbohydrate by being built up into proteid through the agency of bioplasm. Probably, when there is no particularly large supply of carbohydrate to be dealt with, this is the main result that occurs. When, however, the supply is extensive, it is evident that some escapes being disposed of at the seat of absorption, and thence reaches the portal blood. At a period of fasting, and likewise after the ingestion of animal food, the portal blood, as regards the amount of sugar present, corresponds with that belonging to the other parts of the circulatory system. After a free supply of starchy food, however, sugar may be found to be present in the portal blood to a considerably larger extent than anywhere else."

What is contended for then is that the main

DISPOSAL OF THE ABSORBED SUGAR

is effected by the assimilative action occurring within the mucous membrane of the intestinal canal, and that what escapes being disposed of here, passes through the portal vein to the liver, which exerts a supplementary action in checking its flow into the general circulation by producing transformation into glycogen. The conditions existing in connexion with Eck's fistula are of a nature to affect the latter action, and not the former, and thence it follows that as long as the ingested carbohydrate falls within the capacity of being disposed of at the seat of absorption in the walls of the alimentary canal, there will be no passage of sugar occurring into the general circulation, and, as a consequence, no glycosuria; but if the carbohydrate stands beyond the capacity referred to, sugar will be reaching the portal vein, and, passing through Eck's fistula, will flow into the general circulation and constitute the source of glycosuria. Now, according to the statement made by De Filippi upon the strength of his experiments with Eck's fistula, glycosuria was not observed after the administration of starchy food, but was observed after the administration of sugar when the quantity given reached a certain point which stood below that which was found to be required to produce glycosuria in the normal state, which means the existence of a diminished tolerance.

It is seen from the experiments recorded in my "Physiology of the Carbohydrates," p. 105, on the condition of the portal blood after the administration of carbohydrate food that, in the dog, there is in no instance any great effect produced on the sugar content. In the rabbit it is otherwise. In some of the instances in this animal, the figures after food come out conspicuously high. The highest in the list stands at 4·590 per 1000 before hydrolysis and 5·330 after. In many of the others, only a somewhat slight increase is observable. The tendency of the operation would be to give higher figures than for the actual circulating state, on account of the blood being somewhat delayed in the capillaries and being thereby put into a position to take up more sugar than it might otherwise do.

The bearings connected with the

DISPOSAL OF CARBOHYDRATE BY SYNTHESIS INTO PROTEIN

at the seat of absorption have been fully discussed in my "Carbohydrate Metabolism and Diabetes" already referred to (*vide* pp. 54 to 64). The lymphocyte is the agent concerned in the process, and the method by which the synthesis is effected is by bioplasmic growth. It is known that, in the mucous membrane of the intestine, there is a very active growth and renewal of lymphocytes carried on in concurrence with the absorption of the products of digestion. The rôle of the lymphocyte found in this situation is to grow upon the absorbed material supplied to it from the food. As occurs in conformity with a general law applying to living matter, the bioplasmic molecules take to themselves, from the molecules around, those of suitable configuration for being linked on by the combining influence of affinity. Thus the sugar molecules become built into the newly formed protein complex, and in this state are carried, within the lymphocyte, into the circulatory system.

What next occurs is that the lymphocytes undergo autolysis. Proof is afforded that this phenomenon actually takes place by the fact of the systematic disappearance that is noticeable after their entry into the blood. Accompanying each intake of food, there is a flow of lymphocytes into the circulatory system, which is followed by a subsidence till a fresh intake of food occurs. Thus is afforded a source for the fibrinogen, globulin, and albumin of the blood. It cannot be conceived that these bodies arise otherwise than through the medium of a preceding bioplasmic formation, and viewed in this way, the phenomena, as I have shown in the work referred to, not only receive the support of observation, but fit in consistently with the line of procedure that meets what is wanted in connexion with the matter. Locked up in the protein constituents of the blood in the manner depicted, the sugar molecule derived from the food is placed in a position to be transported from the seat of absorption to that of utilisation without running off with the urine.

I have been speaking about the course taken by the carbohydrate portion of the food, and it is interesting to note

THE CLOSE ANALOGY THAT EXISTS

between what occurs in connexion with this portion of the food on the one hand, and the nitrogenous portion on the other. With both, the first step is to place them, by enzyme action within the alimentary canal, into a suitable state for absorption and subsequent bioplasmic incorporation. I strongly hold the opinion which I urged in my "Physiology of the Carbohydrates" published in 1894, that what next occurs, as well for the products of digestion coming from the nitrogenous principles of food as for those coming from carbohydrate matter, is their assimilation, or re-synthesis, at the seat of absorption, into the proteins that are destined to be transmitted through the absorbent system to become proteins of the blood.

In former times, it was considered that it sufficed for the breaking-down process by enzyme action to be carried as far as the stages of albumose and peptone,—the extent to which it is carried by pepsin, and to which it is in the main carried by trypsin. Latterly, however, the view has sprung up that hydrolysis is carried to the production of the amino-acids; erepsin, which is discoverable in the mucous membrane of the intestine, being the agent that possesses the power of accomplishing this supplementary work. Cohnheim,[2] after showing the existence of erepsin in the mucous membrane of the intestine, speaks of it as holding an analogous position in connexion with protein digestion to that held by glucase in connexion with starch digestion. Whilst the latter, it is said, hydrolyses maltose, derived from the action of diastase, into glucose, erepsin hydrolyses the albumose and peptone, resulting from the peptic and tryptic digestion of protein, into the amino-acids, and in keeping with this view, it is stated to be found that health and nitrogenous equilibrium are capable of being maintained in animals fed upon these products in place of the parent protein.

What is wanted is that the molecules produced, whatever they may be, should be of a configuration to render them susceptible of being

TAKEN ON BY THE BIOPLASMIC MOLECULAR COMPLEX

in which the metabolic action at the foundation of the phenomena of life occurs. In the language of the side-chain theory, bioplasm consists of complex molecules, made up of a functioning centre provided with innumerable arms or side-chains with ends of various configurations adapting them for junction with suitably constructed food-stuff and other molecules. It is within the atomic groupings thus put together that the interactions occur that give rise to oxidation, and thence the development of the various manifestations of energy observed to take place. The theory involves the entry and storage of oxygen in the molecular complex, as well as the oxidisable materials, and as the two become used up, they are replaced by a fresh taking on. With arms having full-up side-chains tacked on, no capacity exists for the taking-on of outside food-stuff molecules, a state of things that may be likened to that which exists in connexion with the chemistry of the inorganic or non-living kingdom of Nature. A compound with its bonds of union in a satisfied state is not in the position for the occurrence of further linking-on, but with free or unsaturated bonds, linkage can occur with anything that is suitably conditioned for being taken on.

[2] Zeitschrift für physiologische Chemie, Band xxxiii., p. 451, 1901.

Food-stuff molecules, then, require to be incorporated within the bioplasmic molecules of the different components of the body as a preparatory step to subjection to utilisation. What actually takes place after entry into the molecule is, at present, altogether beyond our power of forming a conception. It is evident, however, from the products met with that there must indeed be a very complicated play of changes occurring. Whilst without cognisance of what in detail is going on within, we can nevertheless frame an idea of the general actions taking place by giving attention to the bodies that go in and those that come out. Besides oxidations, hydrolyses, and condensations, the capacity for re-groupings exists, rendering the entry of one body, as for instance a carbohydrate, and the exit of another, as for instance fat, in like manner to what occurs upon a more simple scale in the case of enzyme action, intelligible. Apparently, in

THE FUNCTIONING OF THE MOLECULAR COMPLEX,

side-chains taken on may be afterwards worked off and renewed without the disruption of the centre of the molecule, whilst circumstances may exist to conduct on to the occurrence of a full breaking-down.

The close parallelism that exists between starch and protein in relation to the course of events noticeable in connexion with their application as food principles, is exceedingly striking. They both become hydrolysed and broken down in a corresponding way by enzyme action to fit them for absorption, and for being subsequently taken on by, and incorporated into, the bioplasmic molecule wherein the metabolic actions occur that give issue to the phenomena of life. I think all are now agreed upon the point that entry of the food-stuff molecule, whatever its nature, into the bioplasmic complex is a necessary step towards utilisation, and this being the case, the preliminary procedures in reality merely make provision for the accomplishment of the end to be attained.

The knotty point connected with the subject now presents itself for consideration.

IN WHAT STATE DOES THE FOOD-SUPPLY TRAVEL

from the seat of absorption to that of utilisation in the tissues? I have put the question in a plainly expressed form, and it requires to be frankly met. Under the old view, certainly as regards carbohydrate, the absorbed material was looked upon as being transported through the circulation in an unchanged or free molecular state. I have shown how such a state of things is inconsistent with escape from running off with the urine during the passage of the blood through the kidney, as occurs in connexion with diabetes. Upon the principle of a similar line of action, it has been said of protein, since attention has been given to erepsin, that digestive disruption is carried to the amino-acids, and that it is by the transport of these in a free state through the circulation that the tissues obtain their nitrogenous nutrient supply. If such occurred, the urine ought to reveal it in the same manner as with sugar. We know, when a pathological source for leucine, tyrosine, &c., exists, that they readily enough find their way into the urine, and what is to keep them back if they passed through the circulation for the purpose of transmitting nitrogenous material from the food to the tissues. Even much larger molecular bodies than the amino-acids pass into the urine if they reach the blood, as is exemplified by the occurrence of peptonuria and albumosuria.

Under the view referred to, it has been considered then, alike for protein and carbohydrate, that the food-supply, after being brought by enzyme action into a small molecular state, is in this state conveyed through the circulation to the tissues to be taken in a direct manner on by them, and then utilised. This is tantamount to placing the blood, as far as its office in connexion with food transport is concerned, into the position of an agglomeration of small molecules emanating from food digestion. Why, under these circumstances, should the elaborated protein constituents met with in the blood exist? We have been accustomed to look upon these ingredients as constituting the pabulum from which the tissues draw their nutrient supply, but how does this stand in face of the contention that the food-stuff is conveyed direct to the tissues in the form of broken-down products of digestion?

The subject matter that is before us constitutes a deeply important link in the chain of events connected with the passage of food to utilisation in the body. It also has a collateral bearing in connexion with the urine, inasmuch as the state of the urine is dependent upon the character of the constituents of the blood with respect to molecular size of its ingredients ; and through this, the particular form in which the food-stuffs are transmitted from the seat of absorption to that of utilisation in the tissues is brought into relation with the

QUESTION OF LIABILITY TO ESCAPE WITH THE URINE,

in their passage through the kidney, in an unutilised state, or, on the other hand, their non-liability to do so, in which case retention for service in the system, instead of loss, is provided for.

The question of liability or non-liability to escape in the transit of the blood through the kidney is of sufficient importance to lead me to consider it compulsory to give consideration to a view which has been recently broached regarding the state in which the products of food digestion are conveyed through the circulatory system to the tissues. The view, it is true, relates to the protein portion of food, but it being considered that the line of procedure for the carbohydrate portion is of parallel nature to that for the protein, the discussion has a signal bearing on the subject of these lectures.

It was formerly taught that the digestion products issuing from the fatty and albuminous principles of food, reached the circulation through nature's specially constructed channel placed in connexion with the absorbing mechanism of the alimentary canal. Some 30 years ago, a changed idea was put forward upon the strength of experimental results obtained by Schmidt-Mülheim. In the experiments performed, the urinary nitrogen from nitrogenous food was estimated after obstructing the flow of lymph and chyle into the circulation, and compared with the amount found when the connexions between the absorbent and vascular systems were free. It appeared that no essential difference was discernible, and thence it was inferred that protein matter found its way from the alimentary canal into the circulation by passage through the walls of the vessels belonging to the portal system instead of through the thoracic duct.

Notwithstanding the incompatibilities involved in such a view it is surprising the extent to which it became adopted. In face of the settled knowledge possessed regarding the resistance offered to the transmission of proteins through membranes, we find that the portal vessels are freely talked of as constituting the

CHANNEL FOR THE PASSAGE OF PROTEIN EMANATING FROM THE FOOD

into the circulation. Still more strikingly in defiance of reason, we even find, amongst recently recorded work, an observer looking in the mesenteric veins for the lymphocytes emerging from the villi and supposed to pass, as the natural course taken, through the adjoining capillaries into the portal blood! Picture a lymphocyte forcing its way from a lymphoid lacuna through the membranous walls of a capillary, against the blood pressure existing within!

In the case of protein, with equal pressure on both sides of a capillary wall, the conditions are of a nature to prevent the passage of its molecules either way. If this is so with the equal pressure to deal with, is it permissible to conceive that protein can take the course suggested against the blood pressure existing within the vessels? With a reversal of the circumstances, however, the protein molecules can, and do, pass through in compliance with what is observed under ordinary physical conditions to occur. As a matter of fact, under the influence of the blood pressure within the capillaries, protein transudes into the lymph spaces. It does so in proportion to the existing pressure, and leucocytes even do the same, accounting for the migration that is known to occur. Physical laws permit of these procedures, but are altogether opposed to the idea of passage of protein in the reverse direction—namely, from the lymph spaces into the blood-vessels.

Since the discovery of erepsin, the enzyme which has the power of carrying the hydrolysis of the proteins on to the amino-acids, another view has sprung up regarding the procedure by which the proteins are rendered available for appropriation by the tissues. It embodies no less radical an alteration than the

PASSAGE OF PROTEIN IN THE STATE OF BROKEN-UP FRAGMENTS

consisting of amino-acids through the circulation to the tissues. Professor W. D. Halliburton has espoused this view and introduced it into the last edition of his "Handbook of Physiology." It is claimed by him that the proteins become hydrolysed at the seat of absorption into the amino-acids, and that these pass straightway into the blood and thence to the tissues where they become linked on to the tissue molecules and applied to the purposes of life.

Protein is thus assumed to be brought into a smaller molecular state than that of albumose and peptone for transmission through the circulation to the tissues. The conditions are parallel to the transmission of carbohydrate through the circulation in the form of sugar, and what applies to sugar running off with the urine, in proportion as it is present in the blood, will equally apply to the amino-acids. The amino-acids do, as a matter of fact, show themselves in the urine in association with the existence of certain pathological states, so that proof is not wanting that, as might be expected on account of their small molecular size, when they are demonstrably present in the system they become equally so in the urine. The existence of these acids in normal blood and urine constitutes a disputed point, and to overcome the difficulty here arising the convenient assumption is advanced that they are taken by the tissue cells as fast as they can reach the circulation. The same kind of argument has been applied in the case of sugar and we know that it does not here hold good.

In this, as it appears to me, extraordinary contention that the broken-down protein of food is conveyed through the circulation in small molecular fragments to the tissues to be there reconstructed into the specific protein belonging to the animal, the proteins of the blood are left out of consideration altogether, although good grounds exist for looking upon them as a pabulum from which the tissues draw their nutrient supply.

The new position that has been taken by Professor Halliburton contrasts strongly with that which he formerly held. In his "Handbook of Chemical Physiology and Pathology" published in 1891 he says (p. 337): "The increased percentage of proteids in the chyle as compared with the lymph illustrates the fact that the lacteals are not merely concerned in the absorption of fatty, but probably also of albuminous food. In the stomach and intestine the proteins of the food are converted into peptones, substances that diffuse with readiness through living membranes; but no peptones (or proteoses, the intermediate products in the formation of peptones) are found in the chyle; during their passage through the intestinal wall, or immediately on entering the lymph or blood stream, they are reconverted into albumin and globulin." This stands in accord with the view that was at the time generally held. Indeed the only unsettled point then engaging the mind was the question that had been raised by Schmidt-Mülheim's ligature of the thoracic duct experiment which bore upon the path through which the passage of the reconstructed protein took place, in connexion with which Professor Halliburton thus wrote: "Schmidt-Mülheim tied the thoracic duct in dogs and found that proteids were still absorbed; this however does not prove that the lacteals are not normally concerned in the absorption of proteid; it merely shows that animals thus treated can continue to absorb proteid by the other path—the blood-vessels."

Passing now to the last edition of Professor Halliburton's "Handbook of Physiology" (1907) we find it stated under the head of *Absorption of Proteins* (p. 530):—"The normal course of events is that the food proteins are broken up into their constituent amino-acids, and it is in this form that they are absorbed ...... Not many years ago it was held that proteins were mainly absorbed as peptone, and that the absence of proteoses and peptones in the stream was due to the fact that the intestinal epithelium had the power of re-synthesising the blood proteins from the peptones ...... Recent research has failed to substantiate such views, and the intestinal epithelium does not possess the exclusive power of building up heavy moleculed proteins either from 'peptones' or from amino-acids ...... There is something very attractive in this view, because it affords a rational explanation of why it is that the organism can construct the proteins peculiar to itself and maintain its chemical individuality, although the food taken varies so widely in composition."

What ground is there for this change of opinion? Is there any real justification for it? Recent research, it is said, has failed to substantiate the old view. Has it done anything, it may be asked, to substantiate the new? There is absolutely nothing beyond pure conjecture to deal with, and I protest against the acceptance of any view that implies the passage of nutrient matter through the circulation in a form to be susceptible of filtering off with the urine. Nature does not operate in such a defective way, and food put into a small molecular state for transit through the system could not be prevented, to a greater or less extent, from passing off as waste material with the urine.

Professor Halliburton seems to have been influenced by the attractiveness of the success that has attended Emil Fischer's

EFFORTS TO SYNTHESISE AMINO-ACIDS

into poly-peptides, which may be spoken of as the lower grades of protein. Because the chemist, however, can only, as yet, synthesise members of the amino-acid group of cleavage products of proteolysis into higher combinations, it is not to be argued that Nature is in the same position. In our laboratory procedures we lack the power of forging the implements that Nature in her building-up and breaking-down operations works with. When we get hold of and employ these implements—as, for instance, when we operate with enzymes—we can achieve in our laboratory experiments the same that is effected within the living organism.

It may be taken that chemistry works upon the same lines inside and outside living matter. Affinity and adaptability in molecular configuration are at the root of chemical union. If molecules are not of suitable configuration for linkage together, no chemical union can occur. It is intelligible that with molecules of simple construction adaptability for union rests upon a less complicated basis than with molecules of a complex nature. Thus, with the more simple molecules the required conditions for union may be susceptible of being found and supplied, whilst in the case of the more complicated ones our efforts may prove altogether fruitless. A complicated lock is as easily opened as a simple one if a right-fitting key is at hand for the purpose. Here lies the pith of the matter. There is far more difficulty in meeting with the right key for the complicated than there is for the simple lock.

If peptone as a product of proteolysis can be taken on, through the agency of the enzyme concerned in the synthetic operation, by the molecular complex of the living cell, there is no need for proteolysis to proceed further. Nature, with her enzyme, may be able to provide the requisite adaptability for union, whilst the laboratory worker, unsupplied with the enzyme, may be unable to do so. Working, however, with a more simple form of molecule, it is only natural to conclude that a greater possibility of success may present itself. It is only in this way, as far as I can see, that advantage is likely to be derivable from a more complete proteolysis. What is wanted to be attained is that the protein food molecule should be broken down into fragments that are susceptible of being re-synthesised into the reconstructed protein entering into the constitution of the organism that receives the food.

The all-important point connected with this matter is the

SEAT AT WHICH THE RECONSTRUCTION OF THE BROKEN-DOWN FOOD MOLECULE OCCURS.

Professor Halliburton says that the reconstruction takes place in the tissue cells, the fragments from the food proteolysis being conveyed thither by the blood in the form of amino-acid molecules. I have upon many occasions referred to the effect of the transmission of small molecular bodies through the circulation in relation to the urine, and I hold that their entry into the blood is attended with their appearance in the urine, so that alike for sugar and for the amino-acids, appeal may be made to the urine to afford an indication of what stands good in connexion with the blood. No one disputes that a re-synthesis of the products of proteolysis occurs. The point is, Does it occur at the seat of absorption or does it occur in the tissues? In the first case, the re-united cleavage products reach the blood in the form of protein which escapes from passing into the urine. In the second, the passage of the disjoined products to the tissues ought to be made manifest through the medium of the urine.

Professor Halliburton reproves Abderhalden, a distinguished worker in association with Emil Fischer on the proteins, for not coinciding with him in the view that has been set forth, and for advocating instead, in a recently published paper, the view antecedently entertained that the products of protein cleavage are re-synthesised in the intestinal wall. In his "Annual Report on Physiological Chemistry for 1907," issued by the Chemical Society, the following words are, at p. 235, to be found: "Abderhalden's reactionary conclusion on the matter shows a lack of the acumen which is usually noticeable in his writings." Is it not possible that opinions may differ as to the side on which the lack of acumen lies?

I will now proceed to show that if we look broadly into the matter, tangible evidence can be adduced to show that production of protein must take place in connexion with food absorption at the actual seat of its occurrence in the walls of the alimentary canal. Persons seem, upon the point before us, to have been led away by narrow experimental considerations and to have overlooked the broad facts that confront us. No one can dispute that

A FLOW OF CHYLE TAKES PLACE

through the thoracic duct into the circulatory system concurrently with the digestion and absorption of food. Now, what does the flow that thus takes place imply? Let us see the nature of the answer to be given to the question.

Anatomy teaches us that the absorbent system consists of an elaborate set of vessels dispersed throughout all the tissues within the body. Starting from the lacunæ or spaces intervening between the capillaries of the vascular system and the tissue elements, the vessels join in a complicated manner and proceed to each side of the lower part of the neck where they discharge their contents into vessels belonging to the venous system. One office of the absorbent system may be stated to be to convey back into the blood-vessels materials which have escaped from the blood capillaries and have not been made use of by the tissues. The escape from the capillaries is found to fluctuate with the amount of blood pressure in them. In a state of rest, the pressure may be such as to lead to only an insignificant transudation occurring. As the pressure rises, both quantity and quality of the exudate, or lymph, become altered. The quantity is increased, and protein bodies, which in the absence of hydrostatic pressure are not transmissible through membranes, find their way, in proportion to the existing pressure, through the walls of the vessels into the lymph spaces. The lymph which occupies the interstitial spaces between the blood-vessels and the tissue elements thus constitutes an exudate from the blood plasma varying in amount and character in an automatic manner according to the requirements of nutrition, for the conditions—tissue exercise, gland flow, &c.—which create an increased demand for nutrient supply, at the same time give birth to an increased capillary fulness involving increased capillary blood pressure.

The view that is here shaped into words represents that which is generally entertained, and it adequately serves to meet the facts that confront us in connexion with the matter. To the view that lymph production is the result of a secretory action of the endothelial cells of the capillary vessels, I give no credence. I am no believer in chemical and physical laws being set at naught in living beings and superseded by a mysterious supernatural "vital" agency, which, in the case before us, would lead up to exceedingly delicate and simply protective epithelial cells having a secreting function thrown upon them, and being employed in work which it is irrational to conceive could be accomplished by them. No doubt, in connexion with life, there is a power in operation of a determining or regulating nature, which leads to the performance of operations which cannot spring from mere chemistry and physics, but observation teaches us that this power manifests itself upon matter through the instrumentality of chemical and physical actions.

The absorbent system may be considered to pick up the unappropriated material which has escaped from the blood vessels for the purpose of tissue nutrition, and to convey it back in the form of lymph to the circulatory system. At a period of fasting, such is the nature of the fluid present in all parts of the absorbent system. At a period of digestion, however, the absorbents belonging to the alimentary canal become charged with products derived from the food, which thus supplement the contents that are ordinarily present, and far outweigh them in quantity and significance. We have, then, a product of absorption from the food, which visibly presents itself to our notice, and naturally passes into the blood stream through the thoracic duct.

Let us pursue this matter further and see how the evidence stands bearing on the

PASSAGE OF RECONSTRUCTED PROTEIN FROM FOOD INTO THE CIRCULATORY SYSTEM.

There is no question about the contents of the thoracic duct flowing into the blood stream. What do these contents consist of? At one time, lymph, and at another time, chyle: the former, representing the unutilised exudate from the blood for the nutrition of the tissues, and the latter, this exudate plus material derived from the food. Seeing that the exudate is likely to be, and, as a matter of fact is, very variable in quantity consequent upon the extent to which it is influenced by varying conditions, and that the food item is of a variable nature, it is not surprising to find that much difference exists in the estimates given of the amount of lymph and chyle flowing into the blood.

Amongst text-book authorities, Michael Foster speaks of its having been calculated that in a well-fed animal, a quantity of lymph and chyle equal to that of the whole blood may pass through the thoracic duct in 24 hours, and that of this, about half comes through the lacteals from the abdominal viscera, and therefore to a large extent from food. Upon this basis he reckons that for a man of average weight the quantity discharged into the blood per hour would be a quarter of a kilogramme, or a little under a quarter of a litre, a ratio giving something less than six litres for the 24 hours.

It is a matter that is beset with difficulties to obtain precise information experimentally regarding the rate of flow taking place under natural conditions. Hence many widely conflicting statements have been made by different authorities. Cases are from time to time come across in the human subject where from some unnatural condition connected with the thoracic duct an obstruction is offered to the flow of chyle in its proper direction and it becomes discharged from the lymphatics belonging to a particular portion of the skin.

One such case has recently formed the subject of a communication from the physiological laboratory of University College, London, by J. Molyneux Hamill in the *Journal of Physiology*, Vol. XXXV., 1906. The patient, who was an inmate in University College Hospital, was a man in a fairly healthy state, 20 years of age, and 140 pounds in weight. When a boy of 10 years, the cutaneous lymphatic distension showed itself and led on to the formation of a permanent fistulous opening in the upper part of the right thigh close against the groin. Through this opening lymph and chyle, when not controlled by a pad and bandage, escaped. When escape was prevented, accumulation took place in the affected parts and led on to a state of tension which required to be from day to day relieved by allowing a certain amount of exit to take place. An observation was conducted on

by leaving the opening free and allowing the chyle to trickle into a vessel placed to receive it. In this way, over four litres, it is stated, were collected in the course of 12 hours. Further escape was then stopped at the patient's request owing to the great exhaustion it produced. It is seen that the rate of flow was here greater than in the estimate given by Michael Foster. At the same time, however, the collected fluid, it is to be remarked, was considerably more watery than lymph and chyle collected in a direct manner.

Whatever may be the exact volume of liquid flowing from the absorbent into the vascular system, it is evident that it is one of considerable magnitude, and upon this point there is no need here to say more. In pursuing the train of reasoning in hand, I will pass to the consideration of the component nature of the current that flows into the blood. It is closely allied in constitution to the blood itself, and may, in fact, be said to represent rudimentary blood, minus the red corpuscular element. Fat in suspension is present as a collateral ingredient when absorption of fat has taken place from the alimentary canal. This principle, not being mixed up with the point before us, need not be further alluded to. The point of special concern is the presence of lymphocytes, as in blood, and of protein matter precisely under the forms met with in the blood—viz., as albumin, globulin and fibrinogen.

Professor Halliburton in his "Handbook of Chemical Physiology and Pathology," 1891, p. 331, speaking of lymph plasma says: "It may be briefly described as diluted blood plasma." With respect to distinction between lymph plasma and chyle plasma, it is generally admitted that the latter contains a larger percentage of protein than the former, and this falls in accord with the view expressed by Professor Halliburton in the quotation a short time back given from p. 337 of the work I have just referred to.

The flow from the absorbent system, then, carries

PROTEIN MATTER, THAT BECOMES BLOOD PROTEIN,

in company with lymphocytes into the blood stream. I consider it is not justifiable to conceive that the exudate from the blood into the lymph spaces is at all comparable to the product which passes from the absorbent system into the veins. An opportunity is afforded of seeing the comparatively watery character of the lymph space fluid when the quantity is preternaturally augmented as in dropsical conditions, and here, on account of the increased blood pressure in operation, the circumstances are such as even to promote more transudation of protein matter from the blood than is occurring naturally.

The conclusion to be drawn is that protein becomes developed within the absorbent system, and we have an elaborating agency present that suffices to accomplish the work. The lymphocytes represent bioplasmic growth, and it is the property of growing bioplasm to link on molecules of suitable configuration from around it and incorporate them into its substance. It may be reasonably conjectured that the plasmic material not appropriated by the tissues becomes taken up by the lymphocytes, and, in a re-elaborated state, thence restored to the circulation.

Such is what may be said regarding recovery and restoration to the blood, in protein form, of transuded and unapplied nutrient material. Let us next look at what occurs in connexion with the transport of food. It is beyond dispute that food protein is, in the first place, broken down and placed in a position to be capable of diffusing through the innermost layer of the intestinal canal into the subjacent lymph spaces. This is all that is here wanted, and, as far as the process in question is concerned, it is immaterial whether the breaking down stops, as has hitherto been believed, at peptone, or whether it passes on to the amino-acids. For the next step, a necessary condition is that the molecules produced should be susceptible of being taken on by the growing bioplasm with which they come into relation. If this condition is complied with, all that is wanted is here again, at this further stage, supplied.

Let it be supposed that food protein has been broken down and put into a diffusible condition, and that the molecules produced possess the requisite configuration to adapt them for being taken on by the molecules of bioplasm, within the reach of which they may happen to fall. What, it may be asked, next occurs? The view formerly held and systematically taught was that

A RE-SYNTHESIS INTO PROTEIN

was effected by the epithelial cells of the intestine, and that the regenerated protein, in some inexplicable way, made its escape from the cells, and then, upon the strength of the notion started by Schmidt-Mülheim's experiments and in opposition to recognised physical laws, reached the circulation by direct transmission through the walls of the capillaries of the portal system.

Now, besides the bioplasm belonging to the epithelial cells, there is another form of bioplasm present in close vicinity of the cells, namely, that of the lymphocytes existing in the lymph spaces, and there cannot be a doubt, in view of the known facts connected with these bodies, that they play a most important part in connexion with the synthetic reconstruction of the absorbed digestion products.

It is to be said of these lymphocytes that they are actively growing and proliferating bodies, particularly so when food is being absorbed. Kölliker, as far back as the middle of the last century, drew attention to the parenchyma of the villi being densely filled with them whilst digestion is going on, and remarked that, whilst never absent, they are, at other times, far fewer. It is only in connexion with the small intestinal part of the alimentary canal that this special development of lymphocytes is noticeable. Both in the case of the stomach and of the large intestine, a widely marked difference is observable, there being in these latter portions of the canal no more lymphocytes visible than may be seen in connexion with tissues generally.

A special lymphocyte growth, then, occurs in the villi in association with the absorption of the products of digestion from the intestinal canal. In my work on "Carbohydrate Metabolism and Diabetes," 1906, I entered fully into this subject in relation to the assimilation of carbohydrate by being embodied into protein, and gave photo-micrographic representations in illustration of the conditions observable. What was said in regard to carbohydrate equally applies to the nitrogenous part of the broken-down protein. They both disappear at the seat of absorption, and, accompanying their disappearance, there is an indisputable extensive

GENESIS OF PROTEIN THROUGH THE MEDIUM OF THE LYMPHOCYTE

formation that takes place.

With respect to mode of growth, lymphocytes may be looked upon as standing in the same position as unicellular organisms in a culture pabulum. The growth involves construction of protein out of surrounding more elementary principles. This constitutes an operation of universal occurrence in connexion with all living matter, seeing that protein is the constitutional basis of living matter, and that growth of living matter is attended with its formation. The construction of protein therefore runs concurrently with the growth of living matter, and, in the case of the intestinal lymphocytes, observation shows that the food-supply is at the foundation of their activity of growth.

Just as bacteria grow in a culture medium, so, it may be considered, do the intestinal lymphocytes grow upon the products of digestion that have passed by diffusion into the lymph spaces of villi. Anyone can satisfy himself of the influence exerted by food absorption on the state of the villi in relation to lymphocyte growth. If a rabbit, for instance, be killed at a period of full fasting, nothing is to be seen of lacteal vessels upon the intestine, and the receptaculum chyli even may not be susceptible of being discerned. The lacteal system seems to be in a state of quiescence, and to all appearances there cannot be any material flow of fluid taking place through the vessels. Killed at a period of full digestion, the contrast in appearance is very great. The lacteals are to be seen ramifying in a most conspicuous manner upon the surface of the intestine, the vessels that course through the mesentery stand out boldly as visible objects, and the receptaculum chyli is easily recognisable through the medium of its fluid contents. There cannot be the slightest question about an active flow of chyle taking place through the lacteal into the vascular system at a period of digestion, and if this is the case, does it not necessarily imply a corresponding transmission of protein, emanating from the food, into the blood?

The plasma of lymph and chyle is known to contain identically the same protein principles as the plasma of the blood. It is only in amount that a difference exists, and it is generally considered that the protein content of chyle plasma may be put down as being ordinarily equal to about half of that of the blood, or somewhere about 3·5 to 4 per cent., and that of lymph plasma to something less. I think it cannot be otherwise than conceded that the outflowing lymph and chyle derive their characters from within the absorbent system, and the lymphocytes may be regarded as constituting the source of the proteins met with. It is evident that these proteins cannot arise from self-production, but must be preceded by bioplasm, and be constructed by its synthesising agency. No other conclusion is permissible, and in the lymphocytes and their environment, the conditions exist for supplying what is wanted.

LYMPHOCYTE AUTOLYSIS

completes the process, and it may be reasonably concluded that this autolysis is not confined to lymphocytes that have entered the blood, but may also ensue antecedently to the blood being reached.

What I want to urge is that the reconstructed protein from the digestion products is formed at the seat of absorption and flows into the blood through the thoracic duct, instead of the digestion products being conveyed as such through the circulatory system to the tissues and there re-synthesised. It appears to me, if such a procedure as the latter actually occurred, it could not escape being revealed, as already insisted upon, alike in the case of carbohydrate and protein, by the state of the urine, upon the principle founded on observation that small molecular bodies, such as digestion products consist of, if permitted to reach the blood, find their way into the urine.

Under the view adopted, the blood is maintained in a renovated state by a supply of elaborated material thrown into it from the absorbent system, and derived in part from the food, and in part from the unutilised portion of the blood plasma which has escaped from the capillaries into the lymph spaces for the service of the tissues and subsequently become worked up by lymphocyte growth into the specific protein principles that flow into the blood.

With these circumstances confronting us, I do not see how the direct transmission of the digestion products from the food into the blood can be contended for, and the part played by the lacteal system in relation thereto, ignored. If anything at all approaching the quantity of chyle that is supposed to flow through the thoracic duct reaches the blood, the amount of protein passing with it must be something very considerable, and at the same time adequate to meet the required conditions belonging to tissue demand and food supply.

There are two forms in which protein passes into the blood—in the form of plasma protein, and in the form of lymphocytes. What is observed in connexion with

DIGESTION LYMPHOCYTOSIS

gives an idea of the extent of transmission of protein in the form of lymphocytes. Gulland, who has identified himself with the subject of blood counts, says that the lymphocytes show a continuous rise in number up to about the fourth or fifth hour after the ingestion of food, and that the total number per cubic millimetre of blood had often been found to be increased from 3000 up to 11,000 in the course of an hour. He also speaks of a fall in number being afterwards almost as rapid. I read the fall as constituting the result of autolysis, by the instrumentality of which the newly formed bioplasm becomes resolved into the protein constituents of the blood.

Cases have occurred in which, through injury to the thoracic duct, its contents have escaped, instead of flowing into the blood, and the effects observed have coincided with what might be looked for under the view that the nutrient supply from the food reaches the system in the manner contended for. A striking case of the kind is reported by Mr. R. T. H. Bucknall of University College Hospital, in the second volume of the *British Medical Journal* for 1905, p. 809. The patient was operated on for the removal of some tuberculous glands at the root of the neck. The thoracic duct was accidentally severed in the performance of the operation, without its being at first known that such had occurred. Instead of making favourable progress afterwards, great weakness, it is stated, was complained of, and, at the end of 24 hours, we are told the patient sank back in bed apparently very exhausted. It was then noticed that the dressing was soaked with a large quantity of clear yellowish fluid, and, on exploration, similar fluid was seen to be oozing rapidly from the wound. The wound was plugged, but the plugging proved of no avail, and from two to three pints of fluid leaked away every day, at times slowly, and at times more rapidly, clear and thin on the whole, but definitely chylous after meals. The patient, it is next said, lost strength in a remarkable manner and grew visibly thinner, so much so that it was obviously imperative to check any further leakage without delay. This was successfully accomplished by ligaturing the ends of the divided duct, after which, the account runs, the patient at once recovered his strength and spirits, and put on weight.

I think sufficient has been said to render it evident that, notwithstanding any conception to the contrary, the

THORACIC DUCT CONSTITUTES THE CHANNEL

through which the blood is maintained in a replenished condition by the agency of food. We are faced with the recognisable fact that, concomitantly with the absorption of food, there is a concordant flow of protein, partly in the form of lymphocytes, and partly in the form of plasma constituents, into the blood.

An underrated estimate, it must be mentioned, prevails in the minds of many with respect to the number of lymphocytes present in chyle. It is not uncommon for them to be looked upon as though they were devoid of significance, and, as I have mentioned elsewhere, this is probably attributable to a faulty method of manipulative procedure. It has to be borne in mind that they become entangled in the fibrinous coagulum, and to look for them in the serous liquid is tantamount to looking for blood corpuscles in blood serum. To obtain a correct representation, it is necessary to prevent the chyle from coagulating by means of an agent like the citrate of potash. Thus treated, and examined microscopically, the lymphocytes are seen to be as closely congregated on the slide as red corpuscles on a blood film slide. Photomicrographs showing the appearance presented are given in my work on "Carbohydrate Metabolism and Diabetes."

Growth and proliferation may be regarded as the attributes of lymphocytes, and growth means the building up of protein out of more elementary material. The life-history of phagocytes is comparable to that of lymphocytes as far as incorporating power is concerned. In the case of the former, however, the material incorporated is of a grosser nature than in the case of the latter, micro-organisms and other discernible particles of matter being appropriated by them. Having played their part of converting inert matter into living protoplasm, they, lymphocytes and leucocytes alike, melt down and disappear, and in this process the protein that has been built up is set free. Lymphocytolysis and leucocytolysis are processes of admitted occurrence. Just as there are agencies leading to building up, so there are agencies, lysins, leading to breaking down.

Leucocytolysis stands upon the same footing as hæmolysis and bacteriolysis. We are in possession of established knowledge with regard to the mechanism of the two latter processes, and leucocytolysis falls into line with them. Metchnikoff has found that by the agency of the injection of lymphocytes from a lymphatic gland of a rabbit into a guinea-pig, the serum of the guinea-pig's blood acquires the power of quickly dissolving rabbit's leucocytes, no matter what the type of leucocyte present. Evidence is thus afforded that leucocytes are actually susceptible of melting down, and in the melting down, the protein that has been generated within them passes, it may be reasonably concluded, into a state of solution under the form of the

ALBUMIN, GLOBULIN, AND FIBRINOGEN

appertaining to the plasma. Seeing, it may further be said, that the proteins of the lymph and chyle are identical with those of the blood, it is not irrational to conclude that the autolysis spoken of may in part occur before the lymphocytes quit the absorbent system. In this manner the genesis of the proteins in question is traceable throughout to a kindred source.

What has been said with reference to lymphocytolysis is supported by what may be seen to take place in the lymphocytes contained in chyle collected from the receptaculum chyli and afterwards kept for a day or two. I have some stained slides, prepared in the same way as for dry blood films, representing the condition observable shortly after collection and at subsequent periods. Taken on the first day, nothing beyond the ordinary character belonging to the lymphocyte is seen. After keeping the chyle in a small bottle till the following day, and then preparing the slide, the preparation shows that a number of large, round, very faintly stained, nebular bodies had become apparent, and with a specimen that had been kept for another day, these ghost-like bodies are seen to have become larger and still more nebular, and to have scarcely taken any stain at all. They give the idea of consisting of lymphocytes in a state of dissolution, and interspersed amongst them unchanged lymphocytes are to be seen. Mr. S. G. Shattock, to whom I have submitted the slides, concurs with this view and if it is accepted, direct evidence is supplied of the occurrence of autolytic action outside the body. Taking it that autolysis occurs, the built-up protein cannot vanish into nothing. The only legitimate conclusion, as far as I can see, is that it becomes resolved into the proteins of the plasma.

We have now to consider what subsequently happens. The broken-down products of food digestion having been re-synthesised (assimilated) at the seat of absorption by lymphocyte growth, and the lymphocytes having been resolved by autolysis into the proteins of the blood, the transmuted food is brought within reach of the tissue cells wherein utilisation occurs. The proteins of the blood, with their large complex molecules, thus become the

PABULUM FROM WHICH THE TISSUES DRAW THEIR SUPPLY,

according to the particular need existing.

If attention is given, it will be noticed that the state of things depicted is identical with that existing in the incubating egg. Do we here find the growing tissues of the chick drawing their supply from a collection of small molecular, broken-down products, as, it has been suggested, the food is converted into for the tissue supply of the developed animal? No, the material provided by Nature for tissue growth and service in connexion with incubation is comparable in character to the protein constituents of the blood.

Having followed the food to the protein constituents of the blood, the point now before us is to inquire into what next occurs. Utilisation in growth, in maintenance, and in energy production are the ends to be reached. For this to be carried out, incorporation with the bioplasmic molecule is necessary. In what precise way, it may be asked, does this incorporation take place? Do the protein molecules as such become linked on to the living cell molecules, or does any preliminary breaking-down action occur?

In the case of the vegetable kingdom, distinct evidence is before us of the occurrence of breaking down by enzyme action preparatory to utilisation. Take, for example, what is observable in the germinating tuber and seed. The store of starch lying within the range of influence of the germinating material becomes broken down into sugar before it is made use of. Again, in connexion with the operations taking place in the life-history of yeast, we know that a sugar, saccharose, which is not susceptible of being turned to account whilst existing as such, is rendered serviceable by the instrumentality of an enzyme, invertase, produced by the yeast, which splits the saccharose up into dextrose and levulose.

The side-chain theory bearing on immunity, &c., also brings in the taking-on of nutrient matter by the bioplasmic molecule, and something allied, as will be later seen, to what has just been mentioned with regard to molecular breaking down, is comprehended in the theory. The theory stands in conformity with the accepted doctrine applying to the dominating factors regulating ordinary chemical action. Affinity and suitable molecular configuration are conjointly at the foundation of chemical union. Let it be supposed that atoms have been joined by a strong bond of union into a group classified as a ring or nucleus. To any member of the group having a free or unsaturated bond, suitable atoms or molecules can be

LINKED ON IN THE FORM OF A SIDE-CHAIN,

which can not only be subsequently removed, but likewise replaced by another, without disturbing the integrity of the original group.

Now, a bioplasmic molecule is viewed as constituting a large and complex molecule, consisting of a nucleus or functioning centre, around which are innumerable arms or side-chains equipped with endings capable of taking on molecules or groups of molecules that are similarly provided with suitably adapted side-chain endings. There must be adaptability between the ending that takes on and that which is taken on, and it is conjectured that an infinite variety of endings exists, so as to make provision for the attachment of the diversity of groupings that become affixed. When linked on, a mutual interchange of influence occurs between the centre and the side-chain groups. At the same time, however, the latter can seemingly be used up or worked off, whilst the former is left intact. It is in this molecular complex that the various chemical changes occur which give rise to the diverse manifestations of life that present themselves to our notice. That a linked-on group can affect and upset the proceedings within the molecular complex is shown by the effect produced when a toxin molecule is taken on.

In the natural course of events, the receptors or arms are designed for taking on nutrient molecules of various kinds, and amongst these, protein molecules are included. Upon this point Ehrlich, in his Royal Society Croonian lecture, says: "If a cell of the organism has, with the assistance of an appropriate 'side-chain,' fixed to itself a giant molecule, there is provided one of the conditions essential for the cell nourishment. Such giant molecules cannot at first be utilised by the cells, and are only made available when, by means of a ferment-like process, they are split into smaller fragments. This will be very effectually attained if, figuratively speaking, the 'tentacle' or grappling arm of the protoplasm possesses a second haptophore group adapted to take to itself ferment-like material out of the blood fluid."

What is here meant is that the receptor or side-chain is not only provided with an ending for taking on the protein nutrient molecule, but in addition, another ending constructed for taking on a particular molecular group to which the name of complement is assigned in the nomenclature adopted. This body is regarded as possessing ferment-like properties, and as existing in a free state in the blood serum, so as to be ready for anchorage wherever a suitable molecular group ending is to be found. It is supposed to stand in the same position towards the nutrient molecule as the lysin complement does to the red blood corpuscle, action occurring through the amboceptor which links both together; and, like the lysin complement, it loses its activity, as a ferment does, by exposure to a temperature of about 55° C.

To briefly recapitulate,

THE VIEW THAT HAS BEEN FORMULATED

may be thus summarised. Food that has been broken down and placed in a fit state by digestion for absorption is at once dealt with at the seat of absorption, and rebuilt into an elaborated form. Dextrose and peptone are alike recognisable at the seat of absorption, but both thereafter disappear. At the same time, and at the same spot, there is an active bioplasmic growth taking place, and bioplasm is known to feed upon dextrose and upon peptone. The lymphocytes, which constitute the growing material, can be followed from the villi into the absorbent vessels, and thence through the thoracic duct into the vascular system. Concurrently and harmoniously with what has been represented, from the absorbent system aspect of the question, to occur, observation upon the blood has shown that during the digestion period there is so large an accession of lymphocytes as to have given origin to the application of the term digestion lymphocytosis to it.

The next event in the life-history of the lymphocyte is lymphocytolysis. There can be no doubt that production and disappearance constitute a routine procedure, and there are good grounds for inferring that the disappearance is attended with a melting down, and transformation into the protein constituents of chyle and blood plasma, thus bringing these principles, which we are accustomed to view as tissue pabulum, into direct relation with the food, and placing them, in fact, in the position of elaborated food.

Looked at in this way, the tissues draw their nutrient supply from material elaborated from the digestion products at the seat of absorption, instead of the digestion products being conveyed as such through the circulatory system to the tissues, an event that, on account of their small molecular nature should but does not, make itself evident to us by running off with the urine. Under the view advocated, the mode of tissue nourishment is brought into parallelism with what occurs in the incubation of the egg, for here it is noticeable that the nutrient supply exists under the form of elaborated material of a similar nature to that belonging to the blood.

It is not permissible to assume that all the protein that is formed enters as a component of the tissues before being broken down. It is known that the

UNUTILISABLE NITROGEN PASSES OUT OF THE BODY IN THE FORM OF UREA,

and it is also known that the urea eliminated stands proportionate to the protein matter ingested, instead of to the energy produced in the tissues. This being the case, protein breaking down must occur, with separation of the non-utilisable from the utilisable portion, independently of what occurs in association with energy production. To enter the tissue simply for the purpose of being broken down and giving off its unutilisable nitrogenous portion is an unlikely mode of procedure. Whilst within the lymphocyte, however, the process may very consistently take place through the instrumentality of intracellular enzyme action, and this view of the matter harmonises with the fact that the period at which the increased elimination of urea shows itself after the taking of food, about corresponds with that of maximum activity of lymphocyte autolysis.

The great point emanating from what has preceded is that the products of digestion become assimilated at the seat of absorption. By this assimilation they become rebuilt, before reaching the circulation, into molecules of sufficient size to be precluded from flowing off with the urine in their passage through the kidney, in contra-distinction to what is known to occur with the digestion products themselves when circumstances exist to lead to their demonstrable presence in the blood. All experimental work affords testimony of sugar standing in the same position as salines and urea in relation to the property of passing off with the urine.

Impermeability of the kidney to sugar is, as I have before stated, a pure

FICTION RAISED UPON THE FALSE CONCEPTION

of healthy urine being free from sugar. Facts show that the urine, indeed, stands in very sensitive relationship to the blood with respect to sugar. The behaviour of Fehling's solution may be considered to be answerable for having led to the error that has existed. It is now well understood that, whilst Fehling's solution is a test of extreme delicacy for sugar when in a pure state, the constituents belonging to the urine mask the reaction when the sugar is present in urine in small quantities only. After a long and hard struggle, the existence of sugar in healthy urine has come to be admitted, but a disposition to minimise its significance to the utmost possible extent is still noticeable.

The misconception that has so long prevailed has operated as a misguiding factor in connexion with the fundamental idea belonging to the glycogenic theory that the carbohydrate of our food is destined to pass through the circulatory system to the tissues in the form of sugar. In Michael Foster's textbook on "Physiology," at p. 613, we find it stated: "Now, a small amount of sugar is normally present in the blood, and *so long as this normal amount is not exceeded no sugar appears in the urine* [the italics are mine]. If, however, by some reason or other, the sugar in the blood is increased beyond that normal amount, the excess passes unchanged into the urine. And, the excess in the blood which thus leads to the excretion of unchanged sugar, is so small that we might expect it to be oxidised in the blood did the blood possess any considerable oxidising power." The identity of the idea here expressed with that expressed in the quotation from the author of the article in Hill's "Recent Advances in Physiology and Biochemistry" given in Lecture I., shows how deeply the groundless idea has become rooted in the minds of physiologists.

The misleading nature, upon a vital point, of such a conception cannot be otherwise than obvious to everyone. It implies, contrary to fact, that sugar may reach the blood of the general circulation without its presence being revealed by the urine. The real circumstances are that the urine constitutes an indicator of the state of the blood with respect to sugar, no matter whether the amount existing be large or small, and thence it may be concluded that if sugar were reaching the circulation, as is contended for under the glycogenic theory, it could not escape being rendered evident by the urine, just as indeed happens in connexion with diabetes.

LECTURE III.

Delivered on Nov. 24th.

Mr. President, Colleagues, and Gentlemen,—I will now give attention to the sugar that may fail to be assimilated at the seat of absorption. There are grounds for considering that, in the absence of any large ingestion of carbohydrate food, it becomes mainly disposed of at the seat of absorption. What, however, escapes being here dealt with, passes to the liver, and becomes checked from further progress by being taken into the cells and converted into glycogen. Thus the liver constitutes a second line of defence against the flow of absorbed sugar into the systemic circulation, obviating the production of more or less glycosuria that would otherwise ensue if the sugar flowed on instead of being stopped.

There is nothing in the

STOPPAGE OF SUGAR AND ITS CONVERSION INTO GLYCOGEN BY THE LIVER

cells but what is comparable to the effect that is capable of being produced by the agency of the living cells of yeast. By intracellular enzyme agency, condensation or synthesis of the sugar molecules with the elimination of water is evoked in like manner as is known elsewhere to occur, and the product constitutes a store ready to be drawn upon as need may arise.

It does not fall within the scope of the matter in hand to enter into the question of the transformation of carbohydrate into fat, but it may be stated that doubtless the liver performs a steatogenic office. It now stands as an established point that carbohydrate may constitute a source of fat, and the *foie gras* derived from the goose may be taken as affording an illustration of the liver being capable of functioning in this direction. The point to claim consideration is to see how the storage of carbohydrate under the form of glycogen in the liver can be transported to the seat of utilisation in the tissues without passing as free sugar, and thereby being placed in a position to flow off with the urine. We learn from Bernard's puncture of the fourth ventricle, that if glycogen does actually escape from the liver in the form of sugar, the fact is revealed through the production of glycosuria, varying in intensity according to the amount present in the organ.

The glycogen of the liver constitutes simply a storage of carbohydrate derived from the food, and responds in amount to that of the sugar that may happen to be reaching the organ through the portal vein. There is nothing unintelligible connected with it. Its accumulation runs strictly in line with that occurring in unicellular organisms, of which yeast may be adduced as an illustration. It is open to common observation to find in living nature that redundant carbohydrate, wherever existing, is put for storage into a form like that of glycogen, starch, cellulose, &c., in which form it steadily remains till a demand for it arises, when enzyme action is brought into play, and it is broken down into suitably adapted molecules for appropriation to the purpose needed.

Glycogen is known to be a body of wide distribution in the various textures throughout the animal organism. Viewed in the manner represented, its origin is readily to be accounted for. Let it be supposed that carbohydrate is taken on by a biogenic molecular complex. If employed in the production of energy, it will be consumed and disappear. If not, and the supply of carbohydrate is kept up, it will be cleaved off and stored up under the form of glycogen.

The operation is analogous to what occurs in the case of fat.

FAT SIMILARLY ENTERING THE MOLECULAR COMPLEX,

if utilised will disappear, whilst if not utilised, may be thrown off and stored, accounting for the fat granules and globules discoverable in cells on microscopic examination. The term fatty degeneration is ordinarily applied to this condition, and it is viewed as pathological, but it is in truth representative of a widely occurring physiological operation. It is true, it may occur under circumstances where cell action has been interfered with by a damaged cell state. Here, certainly, it may be regarded as falling within the domain of pathology. Muscular growth in response to increased muscular work is truly a physiological phenomenon, but when the work which gives rise to the growth is of an abnormal nature, as, for instance, in the case of the heart under the influence of valvular disease or arterial sclerosis, the condition falls under the name of hypertrophy, and is regarded as pathological, although the line of action is the same. Thus, a line of action which may be claimed as pathological may be based upon a physiological operative procedure.

The gist of what I am endeavouring to urge is that it is within the protoplasmic molecular complex that the play of changes takes place which gives rise to the phenomena of life; that carbohydrate, fat, nitrogen-containing matter, and, in addition, oxygen enter this complex; that the inter-actions occurring are attended with energy production through the instrumentality of oxidation as a final result, and that when it happens that the oxidisable supply is taken on in excess of consumption by oxidation, it is cleaved off as storage material under the form of glycogen in the one case, and of fat in the other, and thus circumstanced, it is available for subsequent utilisation when demand for it may exist. What is observed to occur in connexion with the leucocytes of the blood, and with muscular fibres, stands in illustration of the two kinds of cleavage spoken of.

Glycogen, then, is to be regarded as simply a reserve of carbohydrate material, ready, as in the case of fat reserve, to be drawn upon and utilised when it becomes wanted. Its special accumulation in the liver is to be accounted for by the position in which the organ stands in relation to food-supply. The main purposes to which it becomes applied are bioplasmic growth and energy production. For the latter, the chief seat of utilisation is in the muscles, and here the storage amount present is found to be in a great measure dependent on the rate of usage. With limb muscles deprived of activity by nerve section or tendon division, observation has shown that a larger accumulation is met with than in the muscles of the other limb left intact. Conversely, observation has likewise shown that under exercise, as, for instance, when a muscle is tetanised, a decrease of glycogen takes place.

Külz showed by his experiments on previously well-fed dogs, that under very forced exercise, glycogen might be made almost completely to disappear from the muscles and the liver in about six to seven hours. As far as the muscles are concerned, the glycogen is lying close at hand and has simply to be taken by the bioplasmic material that uses it up. I consider it must be assumed that, as in the case of starch in the vegetable kingdom, the glycogen molecule requires to be broken down into sugar molecules before passing into the molecular complex in which consumption takes place, and it may be reasonably inferred that, in accord with what is commonly noticeable, there is concerted enzyme action set into play to bring about what is required.

With regard to the glycogen in the liver, which, as seen, equally disappears, this is seated at a distance from where utilisation occurs, and the point now to be considered is how it becomes transported from one spot to the other and meanwhile escapes being placed in a position to show itself in the urine. We know when it happens, as after Bernard's puncture of the fourth ventricle, that the glycogen passes into the blood in the form of free sugar, the fact is revealed through the medium of the urine, but we have no disclosure recorded of any glycosuric effect having been produced by forced exercise, notwithstanding the short period within which the liver has been found to have become emptied of its glycogen.

The problem, then, now before us is, how is the transport service carried on between the seat of glycogen accumulation in the liver and the seat of utilisation in the tissues, without leading to any show of its occurrence through the detectable appearance of sugar?

I have dealt with this matter in my "Carbohydrate Metabolism and Diabetes" (p. 68), and have suggested that the

TRANSPORT IS EFFECTED BY THE GLYCOGEN MOLECULES BECOMING IN THE FIRST INSTANCE BROKEN DOWN

by enzyme action, just as occurs with starch molecules in the vegetable kingdom, into molecules of sugar, and then that these sugar molecules become linked on as side-chains to protein molecules and thus conveyed in a locked-up, large molecular state to the tissues, where they become taken off according as they are wanted.

This is nothing more than what happens in the ordinary course of chemical procedure. I have previously spoken about side-chains being taken on to a central ring or nucleus, and the capability of their being afterwards withdrawn without disruption of the nuclear body. The matter resolves itself into a question of the strength of affinity operating in one direction or the other. So it may be with sugar molecules linked on to a molecular blood complex. If they should be brought under the influence of a tissue complex in want of them, and thereby possessing a stronger affinity for them, it is only in the natural order of things that they should pass from the one to the other.

The train of phenomena would be that as the side-chains of the complex tissue molecules become worked off, they require to be replaced by fresh side-chains from the blood, and, in turn, the removal of these side-chains creates a demand which leads to the storage being drawn upon. Now, if the storage, as in the case of glycogen, is not of a nature to be adapted for shifting its position, it must of necessity be placed in a suitable condition for doing so. Here comes in the requirement for enzyme action, and it is suggested that as the storage is wanted, provision is made, through enzyme agency, for its supply in a form to meet what is needed.

Viewing matters in this way, the

SIDE-CHAIN WANT IN THE BLOOD LEADS TO THE STORAGE GLYCOGEN BEING

put into a suitable state to fill the void, and thus circumstanced, the carbohydrate becomes transported from the seat of accumulation in the liver to the seat of utilisation in the tissues without passing in a state to run off with the urine, as, in the free small molecular state of sugar, it would otherwise do in proportion to its extent of presence in the blood.

The idea here broached stands in conformity with the accepted view of what occurs in connexion with the transport of oxygen. Hæmoglobin is the agent concerned in the process. Taking on oxygen in the lungs, it travels as oxyhæmoglobin to the tissues, and gives up the oxygen that is needed to replace that which has been consumed in the bioplasmic molecules. Thus unloaded and made ready for recharging, the hæmoglobin is conveyed back to the lungs, where a fresh intake of oxygen occurs. Thus the round is effected by the capacity possessed by hæmoglobin of taking oxygen into chemical union of a sufficiently feeble nature to permit of its being subsequently dissociated to meet the demand of the tissues. I urge that we have here a parallel of what occurs in the case of the transport of carbohydrate from the seat of accumulation in the liver to that of utilisation in the tissues.

In this transport of carbohydrate I have assumed that it passes in the form of a side-chain linked on to a large moleculed constituent of the blood. As yet we have no distinct evidence before us to show what this constituent really is. Probably it is of a protein nature, and if so, we have material at hand to open out a consistent train of reasoning of much interest and importance standing at the root of what is being dealt with. Let me enter into particulars and expound what I refer to.

What is wanted for transport service is that the

CARBOHYDRATE SHOULD BE LOOSELY LINKED ON TO THE CARRYING MOLECULE,

so as to be susceptible of being disjoined without involving the disruption of the molecule itself. Evidence, as we shall see, is producible attesting the existence of such a state. At the same time, let me say that evidence is also producible having the effect of showing the existence of carbohydrate in another state in the molecule—in a state so closely locked-up as not to be susceptible of liberation apart from the disintegration of the molecule. Both points, it will be found, have important practical bearings connected with them.

That the existence of carbohydrate in a loosely combined and in a firmly locked-up state in a molecule is no mere hypothesis is capable of being made manifest by what is seen when amygdalin is exposed to different kinds of enzyme action. A molecule of amygdalin has two molecules of carbohydrate within it. When subjected to the action of glucase, the ferment which transforms maltose into glucose, a molecule of glucose is split off without the production of any further effect, which means that the other molecule is left untouched. In contact with emulsin, however, both molecules are liberated, with benzoic aldehyde and hydrocyanic acid as associated products. The conclusion to be drawn from these results is that the two carbohydrate molecules within the amygdalin molecule are differently placed—that one is in a position to be easily detached without leading to other disturbance, whilst in the case of the other, its liberation involves molecular disruption as an attendant phenomenon.

A study of the effects of

PHLORIDZIN AFFORDS IMMENSE HELP IN UNRAVELLING

the intricacies of the question that is being considered, and it points in a very decisive manner to the existence of carbohydrate within the molecular complex, as a side-chain attachment on the one hand, and in a locked-up state in the nuclear centre on the other. It, moreover, goes further, and gives grounds for associating the side-chain attachment with transport service, leaving the locked-up portion as constituting a component incorporated during the construction of the molecule, whether in lymphocyte growth from food, or in bioplasmic growth elsewhere.

Phloridzin, as is well known, is an active producer of glycosuria, and its action in this direction is exerted through the coöperation of the blood and the renal cells. The sugar does not, as in other forms of glycosuria, take origin elsewhere and travel to the kidney preparatory to elimination, but comes into view during the act of secretion of the urine, and in the absence of the kidneys phloridzin fails to produce any visible effect within the system. It is obvious, therefore, that some constituent of the blood other than sugar must be concerned in the production of the glycosuria. The output of sugar is sufficiently large and continuous to show that there must be something to feed the blood to keep up the discharge occurring, and, coincidently with the outflow, it is noticed that a disappearance of storage glycogen occurs. Indeed, phloridzin supplies us with one of the most effective means of rapidly clearing away glycogen from the liver and the muscles.

That the blood is fed in the way suggested is supported by the

EVIDENCE DERIVABLE FROM LIVER ABLATION EXPERIMENTS.

It is possible for the life of an animal to be maintained for some hours after the removal of the liver and its associated viscera in the abdomen. In a paper published in the *Journal of Physiology*[2] "On the Mechanism of Phloridzin Glycosuria" by Pavy, Brodie, and Siau, results are given which show that

[2] Vol. xxix., 1903.

the sugar elimination declines after phloridzin injection at an infinitely greater rate in the liver ablation experiments than in control experiments where the viscera in question were left intact. It further appeared, when the sugar elimination had almost completely stopped, that a fresh start was given to it by transfusing into the vessels defibrinated blood derived from another animal.

Taking the fact that glycogen, as a result of phloridzin administration, disappears from its seats of accumulation, and that sugar contemporaneously shows itself in the urine, let us follow the matter on and see what the fact mentioned leads up to. The glycogen itself does not travel to the kidney and there constitute the source of the sugar that springs into view. As a first step in the operation occurring, it is not permissible to do otherwise than conceive that the glycogen molecules must be broken down into molecules of sugar. Now comes the important point bearing upon what next transpires. The condition is unassociated with hyperglycæmia, but hyperglycæmia should be present if the sugar molecules passed as such into the blood. It seems to me that we are driven to the conclusion that the sugar molecules must enter into combination with a constituent of the blood and then become set free again by the influence brought to bear when the kidney is reached. If a transport of sugar in one way or another occurs, as the evidence before us denotes it does, and it is not effected by passage in a free state, the only inference to be drawn is that the sugar is thrown out of sight by entering into a combined state.

Physiologists accept this

EXPLANATION OF THE PHENOMENON OF TRANSPORT

connected with phloridzin glycosuria. If admitted here, why should it not be equally admitted as applicable to what happens in connexion with the ordinary occurrences of life? Forced exercise leads to a rapid emptying of the liver of its glycogen, without producing any show of the passage of sugar through the circulation in a free state. If the sugar goes into combination in the one case, why should it not do so in the other? The circumstances stand in reality upon an analogous footing. The abstraction of carbohydrate from the blood to compensate for its consumption in the muscles during forced exercise, will create a demand for its replenishment, and thence lead to the store of glycogen in the liver being drawn upon. In the case of phloridzin glycosuria, the outflow of sugar that occurs in the kidney will, similarly to forced exercise, draw off carbohydrate and give rise to a demand for reinstatement from the glycogen store. The line of procedure is the same in the two cases, but the initial condition that leads to the demand for the replenishment of carbohydrate in the blood is different.

Support is given to the view that has been set forth by the modified

CONDITIONS BELONGING TO PANCREATIC GLYCOSURIA.

Here hyperglycæmia precedes the glycosuria. The disappearance of glycogen occurs just as in phloridzin glycosuria, but the source of disappearance is conversion into sugar at the seat of storage. The kidney simply eliminates the sugar that is conveyed to it in the blood, and if the elimination is prevented by extirpation of the kidneys, the sugar goes on increasing, with the result of exceedingly high percentages having been noticed. The abnormality proceeds from a local transformation of glycogen into sugar, which recognisably passes into the blood in a free state, and subsequently flows off with the urine.

The instance that has been cited in reality shows what occurs when sugar from vanishing glycogen reaches the blood in a free state. In phloridzin glycosuria, there is equally a disappearance of glycogen, but nothing is seen, as far as the blood is concerned, of the sugar derivable from it. Proof is given that the sugar has not undergone destruction by the fact of its coming into view when the kidney is reached. It is simply for the time being concealed by entering, as may be legitimately assumed it does, into combination with a constituent of the blood. If, in the presence of these circumstances, things can run on in this way, is it not permissible to assume that sugar may be transported in a locked-up state from the intestinal seat of food absorption, and from that of glycogen storage, to where it is required for service? By admitting this, all difficulties at once disappear.

I have previously referred to Professor Macleod's article in Leonard Hill's "Recent Advances in Physiology and Bio-Chemistry" and criticised the grounds upon which he has sought to maintain the validity of the glycogenic doctrine. Although, in dealing with this point, he contends that there is a functional transit of sugar through the circulation in a free state, he falls in with the view of transit in a combined state, declaring in the first place (p. 319) "there is reason to believe that a loose chemical compound—of a colloidal nature—exists between serum globulin and dextrose"; next remarking (p. 363), that the mother substance of the sugar eliminated in phloridzin glycosuria is undoubtedly the serum proteid; and then saying (p. 364) that the proteid which has been thus deprived of its sugar "becomes re-combined with more of it during its circulation through the rest of the body." This, it will be seen, precisely represents what is claimed as constituting the physiological mode of transit.

There are further facts connected with phloridzin glycosuria that give support to the view that has been expressed. If repeated administrations of phloridzin are employed in a well-fed animal, continued elimination of sugar occurs without any material alteration of the associated nitrogen elimination. The carbohydrate of the food, in the first part of its onward march after absorption, follows the normal course, but afterwards, through the agency of what occurs in the kidney, becomes diverted into a wrong direction and flows off with the urine as sugar. This is what happens whilst there is

FOOD-SUPPLY OR A GLYCOGEN RESERVE TO BE DRAWN UPON,

and the circumstances are compatible with the carbohydrate being linked on as a side-chain to a blood-contained molecular complex.

With the absence of food, and when the glycogen has been swept away from its seats of storage, the position of things with regard to the relative elimination of sugar and nitrogen becomes altered. The sugar falls until it arrives at a fixed relationship to the nitrogen, and when this point is reached, it is assumable that both sugar and nitrogen are being derived from the breaking down of the molecular nuclear centre that was constructed at the time of the building up of the protein molecule. Evidently, in the one case, the carbohydrate is liberated without the destruction of the molecule, and in the other, the liberation is an accompaniment of molecular disintegration.

I have just spoken of the elimination of sugar in phloridzin glycosuria being connected with food supply. The carbohydrate in the food runs off as sugar in the urine, and it does this without showing itself as sugar in the blood. The only deduction that can be drawn from this occurrence is that it passes in a state of combination, and, in view of the intensity of the glycosuria that is sometimes observed, it is evident that the capacity for transit in this state must be very great. In pancreatic diabetes, the eliminated sugar is similarly connected with food supply, but the carbohydrate of the food reaches the circulation, and passes through it to the kidney in the form of free sugar. Thus, in both these conditions, the food carbohydrate passes through the system and makes its appearance in the urine as sugar. In connexion with the one, it passes through in a concealed (combined) state, as I contend happens in its conveyance in the healthy person to the tissues for utilisation. In connexion with the other, it passes through in a free or uncombined (unassimilated) state, just as it does in ordinary diabetes. Herein, then, it may be considered that we have

THE TWO MODES OF TRANSIT, THAT IN HEALTH AND THAT IN DIABETES, REPRESENTED.

I must not allow the remarks made by Professor Halliburton, in his advocacy of the glycogenic doctrine, contained in the article that has been already referred to on "Diabetes Mellitus from the Physiological Standpoint" inserted in the July number of the *Practitioner*, 1907, to pass without comment. At the present stage a fitting place is offered for referring to them, and I will proceed to avail myself of it. The question of the sugar formation by the liver is being spoken of, and the following line of reasoning is set forth. "At the present day, the prevalent opinion among physiologists is of the nature of a compromise between the two extreme views. The liver is, no doubt, able to convert part of its glycogen into fat, but most of its glycogen is regarded as leaving the liver as sugar (dextrose). In coming to the latter conclusion, physiologists are influenced by what they learn from surviving organs generally. An excised organ is undoubtedly on the road to death, but while it still retains vitality, the phenomena it exhibits are similar in kind to, though they may be different in degree from, those which it exhibits during life. It is impossible to suppose that, at a given moment, arbitrarily called death, an organ can turn round and do what it never did before. Even in the case of blood coagulation, which appears to be a direct instance to the contrary, there is no doubt, from recent research, that the blood is always tending to clot even during life, and is prevented from doing so by the production of anti-substances (anti-thrombin produced in the liver), which neutralise the activity of the thrombin or fibrin ferment."

It is a matter of

SURPRISE TO ME TO FIND THAT PROFESSOR HALLIBURTON HAS WRITTEN IN THIS WAY

in the face of what is contained in my work on "Carbo-hydrate Metabolism and Diabetes," a presentation copy of which was forwarded to him. At p. 68, the text runs: "The suggestion presents itself that sugar is taken on as a side-chain by a proteid constituent of the blood and transported to the tissues, where it is taken off for subjection to utilisation. The suggested operation is identical with what occurs in connexion with the transport of oxygen. Oxygen is taken on by hæmoglobin, and, in a state of combination, transported to the tissues, where it is taken off and applied to utilisation. Glycogen is a storage material consisting of very large molecules and therefore not adapted for shifting its position. I should think that the first action that occurs is the breaking down of its molecule into molecules of glucose, which become instantly taken on by the alluded-to molecules of the blood. There may be concerted action between the breaking-down and taking-on processes, and that there is such in operation is rendered probable by the fact that there is no show of sugar in connexion with the occurrence. Enzyme action, it may be considered, of necessity constitutes a part of the process, and the enzyme concerned, and set in motion as needed, may, in the presence of altered conditions, be intelligibly conceived to be capable of producing the deviation from the natural living state with respect to sugar that so quickly takes place as a post-mortem occurrence in the liver."

On the following page, in speaking of the effect of phloridzin, the statement is to be found: "The first effect of the phloridzin is to sweep away the glycogen that is present in the different parts of the body. If this passed through the circulatory system as free sugar there ought to be hyperglycæmia in proportion to the glycosuria, which there certainly is not. This being the case, the only conclusion to be drawn is that the katabolised glycogen (sugar) enters into side-chain or loose combination with a constituent (proteid) of the blood, and is thus conveyed to the kidney where it is set free and eliminated."

It will be seen that the view that can be now put forth, emanating from the knowledge that has been acquired during the last few years, and embodied in the work alluded to, has failed to receive Professor Halliburton's consideration. The effect of the proposition is to take away the ground from beneath his argument and destroy its reality. Previous to the recognition of carbohydrate as a constituent of protein, there could be no conception of what is permissibly entertainable now, and it must be admitted that a difficulty stood in the way of reconciling the facts observable in connexion with the changed state of things occurring in the liver at the moment of death. On the one side, evidence showed that if sugar passed into the circulation as had been suggested, the fact of its doing so could not escape being revealed by the urine, and the state of the urine negatived the possibility of the occurrence taking place. On the other side, there was the active production of sugar that was observed to occur in the liver as a post-mortem effect, and which, if occurring during life, would have established a different state of things from that actually found to exist. In these circumstances, it could only be said that the enzyme action allowed to come into play after death must be inhibited by the conditions existing during life.

With the knowledge that we now possess, it may be considered that no incompatibility exists. Concerning enzyme action, a considerable advance has been made, and it is consistent with what is now known to consider, in relation to the transformation of glycogen into sugar, that the agent concerned in effecting the process does not primarily exist in the liver in the state of enzyme, but in that of zymogen. Enzymes are dual bodies, and the mother substance of them, zymogen, possesses no activity. The coöperation of another body, the activator, is required to give it enzymic power. In other instances, the activator is brought into play as it is required, and here the conditions leading to a

DEMAND FOR CARBOHYDRATE FROM ITS STORAGE MAY SET THE ACTIVATOR FREE AND START THE ENZYME INTO MOTION

in the manner needed. It may well be that the altered conditions occurring at death may lead to a removal of the restraining influence that held things in proper check during life. The same may be said with regard to blood coagulation. The zymogen, or pro-ferment, of thrombin is present, but is devoid of activity, so long as the coöperative agent is held from exerting its activating effect.

Looking at the distinguished position that Professcr Halliburton holds as a teacher of physiology and the weight that his writings carry in the mind of members of the medical profession, I cannot help regarding it as very regrettable that the evidence which nullifies his argument should have escaped being noticed. It is medicine that suffers in connexion with the matter, for without a right physiological basis, there can be no rational comprehension to guide the medical practitioner in dealing with the wrong metabolism which stands at the root of diabetes.

Is it to reversed enzyme action that the conversion of glycogen into sugar is due? Everyone admits that the building up of glycogen from sugar constitutes an important function of the liver. We look to enzyme action as the agency effecting the process, and it is now recognised that, by altered surrounding conditions, the line of action that has been in operation may be changed into one of a reverse nature. I see nothing inconsistent with the building-up enzyme in the cells of the liver being influenced by its environment in such a manner as to lead to the occurrence of a reversal of action, and thus to give rise to a breaking down of the previously built-up glycogen into sugar.

It is interesting to note the analogous behaviour that is traceable between

CARBOHYDRATE AND FAT IN THEIR CONNEXION WITH BIOPLASM,

and to this point I will now proceed to direct attention. We have seen that carbohydrate becomes incorporated in the bioplasmic complex, and that, if not consumed when there brought into relation with oxygen, another component of the complex, it may, under circumstances of redundancy, be cleaved off as storage material.

The effect of modern research is to give to fat a place in the bioplasmic molecule, and thus to put it into the same position as carbohydrate. I need not, I consider, here enter into the details of this matter. It will suffice to state that there is evidence to show that fat may exist in a locked-up state in a protein compound in like manner to what occurs with carbohydrate. In these circumstances, the fat is in an out-of-sight state, but is susceptible of being brought into view by the disruptive agency of peptic digestion. It is only recently that this subject has fallen under consideration, but already it has made its way into prominent notice.

With the point reached, the position of things stands as follows: the bioplasmic molecular complex, which may be regarded as the representative of a living unit and thereby as the seat of the metabolic changes which give rise to the phenomena of life, contains both carbohydrate and fat incorporated within it. Through intramolecular action, set in motion by agencies of an enzymic nature, the various occurrences noticed to ensue may be conceived to be brought about. In the molecule, oxygen also enters as a constituent, and thus circumstanced, it is brought into close relationship with the carbohydrate and fat components with which the interactions occur that give rise to the development of energy. The play that takes place is not considered to consist of straight off or unbroken oxidation, but of oxidation, step by step, of the components of the chain of which the vanishing molecule is made up. The result, when the intramolecular procedure is normally carried out, is the production of carbon dioxide, water, and ammonia,—products devoid of latent energy. Should it happen, as may in the presence of abnormal conditions be the case, that arrest at an intermediate stage takes place, the effect is the throwing off of a product retaining unexhausted energy.

I have shown that, with a redundancy of carbohydrate, glycogen is dissociated for storage purposes. Condensation, or building up within the bioplasmic molecule, must be here in operation, seeing that it is in the form of sugar, and not glycogen, that the carbohydrate enters the molecule. Precisely the same sort of thing happens in the case of fat. Under the existence of a redundancy, fat becomes, by cleavage from the bioplasmic molecule, microscopically visible where none, whilst in a locked-up state, was previously to be seen. Here again constructive work must be performed, inasmuch as neutral fat is devoid of the needed dialysability to permit of its passage through cell membranes to reach the bioplasm within. The transport must occur in association with a dialysable state, and an enzyme—lipase—exists widely distributed through the body, which performs the office of breaking down fat into fatty acid and glycerine, when transmission through a cell membrane is wanted. This operation, followed by saponification, provides for the transmission, and then, should the conditions be such as to lead to neutral fat coming into view, a re-synthetic action is brought into play. What has been stated stands in accord with the teachings of the present day, and it is seen that the line of procedure in the case of fat fits in with that appertaining to carbohydrate.

These phenomena cannot for a moment be conceived to issue from the effect of mere chemical action working independently of the influence of living power. Everything tends to show that actual

INCORPORATION IN LIVING MATTER PRECEDES METABOLIC ACTIVITY.

Living matter is made up of more or less highly complex molecules, and, thence, saying that a body enters into the constitution of living matter is tantamount to saying that it enters into the composition of the complex molecules of which it is made up. This renders it justifiable to speak of living action as resulting from incorporation of food-stuff in the bioplasmic molecules and its subjection to the influences that are there existing. Intramolecular activity in this way stands at the foundation of living action.

Now, taking carbohydrate and fat, it has to be said of them that they both, in a suitably hydrolysed state, become linked on to the bioplasmic molecules. What subsequently occurs depends upon the circumstances at the time existing. If they are oxidised, they disappear in the form of carbon dioxide and water, giving rise to the liberation of a concordant amount of energy of one kind or another. If they are not consumed in this way, and the supply of nutrient material goes on, they become dissociated and laid by as storage stuff—the carbohydrate in the form of glycogen, and the fat in the form of glyceride or neutral fat.

I strongly demur to the terminology that is in common use among pathologists in connexion with this matter. It is a "terminological inexactitude" to speak of these operations as falling generically in the category of degenerations. They are virtually in themselves of a physiological nature, and, moreover, constitute representations of, it may be said, the largest and the widest spread class of action occurring in the living world. Look at the production of starch, cellulose,

&c., and of fats in the vegetable kingdom, and of glycogen and fats in the animal kingdom, as the issue of indisputable physiological procedures. It is through bioplasmic agency that the phenomenon is brought about. Either carbohydrate or fat, entering the bioplasmic complex and not being oxidised or consumed, will not remain fixed there, but be dissociated or thrown off in one form or another, according to the potential conditions existing. Carbohydrate may enter and be thrown off as carbohydrate, and fat as fat; or, it may be, that carbohydrate may be taken on and fat cleaved off, or fat enter and carbohydrate be cleaved off.

Illustrations demonstrative of these actions are readily obtainable from the vegetable kingdom. With respect to the production of fat from carbohydrate, I may cite a passage from Sachs, quoted in my "Physiology of the Carbohydrates" (p. 247): "Before maturity such [oily] seeds contain no fat, but only starch and sugar. Such unripe seeds (e.g. of *Pæonia*) may be detached from the mother plant, and allowed to lie in moist air with the result that the starch disappears and is replaced by fatty oil." With respect to the production of carbohydrate from fat, the growth of the oily seed suffices to afford a demonstration. From the oily seed placed in contact with water, a young plant springs, just as happens with its starchy congener, the fat obviously constituting the source of the cellulose that comes into existence. Concordantly, there cannot be any doubt about fat emanating from carbohydrate as a metabolic procedure in the animal kingdom, but concerning the production of carbohydrate from fat, I do not consider that any point of evidence is yet before us that can be definitely said to settle the question.

I submit that, in the dissociation process of which I have been speaking,

CARBOHYDRATE AND FAT STAND UPON IDENTICALLY THE SAME GROUND.

The matter is very simple and intelligible. Both form an integral part of bioplasm. If in excess, arising from supply, or from production within as in the case of fat from carbohydrate, of the consumption taking place, they become dissociated as storage material.

The dissociation seems to play a balancing rôle. What is not used is for the time thrown off. This is well seen in the case of yeast cell growth in association with a plentiful supply of sugar. The sugar is taken, and that which is in excess of application is thrown off as glycogen. The adipose tissue cells, although replete with fat, go on taking it if it is presented to them. Because it is not actually wanted does not stop the process of taking on. When the supply fails and it is wanted elsewhere, then a reverse action occurs, and it is taken back and transported to where it is needed for consumption, just in the same way as occurs with carbohydrate. What I submit is that, as a general principle of action, the taking on does not necessarily cease when what is taken on is not consumed.

Here lies the

FOUNDATION OF THE SO-CALLED DEGENERATIONS.

They simply represent thrown off material which has been incorporated into bioplasm, or produced within it, in excess of consumption. The liver is full of activity in this way. Standing in the position it does in relation to food, it is brought into contact with supply material to a greater extent than happens elsewhere, and do we not accordingly find that in this organ, more than anywhere else, accumulation of fat and carbohydrate is observed to take place?

Thus far I have been dealing with the supply as standing at the foundation of the condition that may happen to be met with. Taking the other side of the question, a check to consumption may be the determining cause of accumulation. Whilst consumption is balanced to supply, no opportunity exists for the occurrence of dissociation. Should consumption, however, fall short, surplus material will come into existence and show itself as a dissociated product. The two main sources of dissociation of this kind are deficient supply of oxygen and inactivity. From whatever cause arising, these conditions are known to give rise to accumulations of both fat and glycogen. Damage of cell bioplasm through toxic agency, as for instance from diphtheria, &c., will, by the instrumentality of its check to activity, give rise to the condition that is being considered.

Under the view set forth, the whole matter is placed upon a rational basis and made clear and intelligible. Degradation of protein into fat, after the manner that was formerly entertained, does not enter into the question. The operation, in fact, consists of a throwing off, precisely as is done upon a most extensive scale, as a normal metabolic procedure, in both kingdoms of living nature. The act of throwing off, as has been seen, is subordinated to the influence of the collateral conditions existing. When these conditions are normal, the process is a physiological one, and there is nothing of a degenerative nature about it. It is only when the throwing off is occasioned by a pathological state that the term "degeneration" can be justifiably applied to it. The distinction that applies to the terms "growth" and "hypertrophy" is strictly applicable in connexion with the point under consideration. To use the term "degeneration" in the manner that is too often done, is absolutely unscientific and misleading.

We learn, both experimentally and clinically, that

THE PANCREAS IS MIXED UP WITH CARBOHYDRATE METABOLISM,

and let me now pass to the consideration of this subject, and see the kind of reading that may permissibly be put upon the facts that have been disclosed in connexion with it.

Our predecessors of many years back recognised that disease of the pancreas was from time to time met with in the post-mortem examination of persons who had died from diabetes. The recognition in modern times that diabetes follows experimental extirpation of the pancreas, stands in conformity with this, and, as it is found experimentally that for the production of the effect the extirpation must be complete, so from modern clinical experience it is learnt that partial disease of the organ may exist without being attended with diabetes, whilst with extensive disease of it, diabetes may be expected to be found as a concomitant.

Something, then, derived from the pancreas is apparently concerned in contributing to the normal metabolism of carbohydrate, inasmuch as in the absence of this something, carbohydrate shows itself as sugar in the system in a manner that does not occur when the proper passage to utilisation is carried out. Now, in the proper passage of food molecules to utilisation, a preliminary linking on to the various bioplasmic molecules of the body is, at the present time, pretty generally admitted to take place. It is not conceived, as at one time was done, that the food molecule is consumed in the form of an isolated entity. Toxins, when in a position to be incapable of being taken on by the constituent molecules of bioplasm, fail to exert any toxic effect. It is only when they become actually linked on to the bioplasmic molecules that the interactions that are needed to evoke the results which are capable of being produced by the particular toxin concerned, can occur. So with food molecules, they must be embodied into the bioplasmic molecules as a preliminary step to utilisation. Thus placed in these molecules, they are brought into relation with the other constituents, notably oxygen, which presumably is present in a loosely combined state as in oxyhæmoglobin, and put into a position to permit of the interactions attended with oxidation and the liberation of energy that are observed to take place.

Analogy may be appealed to for assistance in the comprehension of the procedure involved in

THE LINKING ON OF THE FOOD MOLECULE TO THE BIOPLASMIC COMPLEX.

We learn from what occurs in connexion with toxins and with lysins (hæmolysins and bacteriolysins), that there is an intermediary body, the amboceptor, through which the junction with the bioplasmic molecule is effected. In the absence of the play of this intermediary body, no junction and no effect follow the presence of the toxin and the lysin in the blood. A large amount of closely reasoned experimental work, with much of it of a test-tube nature, stands at the foundation of the conception that has been put forward, and gives to it a well-grounded qualification for acceptance.

Proceeding with the matter, it may further be said that, whilst the body that is linked on (in immunity phraseology called the complement) is thermo-labile or susceptible of destruction under exposure to a moderately elevated temperature, the agent that links on (amboceptor) may be exposed to a boiling temperature without losing its linking-on power, and is, therefore, inco ntradistinction spoken of as thermo-stable. This is an important point in connexion with the train of reasoning that I am about to set forth.

It is contended that the first step towards the utilisation of carbohydrate is linking on to the bioplasmic complex. Without susceptibility of being linked on, it simply filters through the body and runs out with the urine without being in any way touched. This is the case, for instance, with the disaccharides,—saccharose, lactose, and maltose, when under any circumstances reaching the circulatory system as such. With the monosaccharides,—dextrose, levulose, and galactose, on the other hand, we find that these, when present in the circulation, do not wholly escape in a similar manner. A portion fails to pass out with the urine, and this portion, it may be assumed, becomes put into the combined state, and subsequently made use of in the ordinary manner. If no capacity existed for linking on these monosaccharides, it is not conceivable that they would be any more susceptible of utilisation than the group which is not utilisable.

The effect following the introduction of the different sugars into the circulation by intravenous injection has been already alluded to. It has been seen that a certain amount of power exists of putting the monosaccharides into a position to be made susceptible of retention in the system. A great contrast, however, is to be perceived in the extent of power that exists at the seat of absorption in the alimentary canal to deal with the sugar derived from the food, as compared with that existing in the blood. Notwithstanding the large amount of carbohydrate that may be ingested with the food, we find, with its reception into the organism in a normal way, that it effectually becomes assimilated, or put into an altered state, and thus prevented reaching the general circulation as sugar. Introduced, on the other hand, in a direct manner into the circulation, the evidence afforded, alike by the urine and by analytical examination of the blood, shows that it is only comparatively slowly and in limited quantity susceptible of being thrown out of view, by the power that is here encountered.

Protein and carbohydrate are similarly circumstanced in connexion with this point. The digestion products of both are rapidly put out of sight after absorption from the alimentary canal, and are not to be traced on into the general circulation. Introduced into the circulation, both are, to a certain extent, susceptible of being dealt with and removed from view, that which is not so dealt with, flowing off, in each case with the urine. Professor E. H. Starling, in a paper published in Vol. XIV. of the *Journal of Physiology*, says with reference to the results obtained from the injection of peptone and sugar into the blood: "It will be seen from them that the behaviour of peptone after injection is almost exactly analogous to that of sugar."

What is it that occurs in connexion with the disappearance of carbohydrate to account for the phenomenon? A portion may be taken by the tissue bioplasmic molecules, if there is a want of it to replace side-chains that have been worked off. Evidence, however, is forthcoming to show that there is to be found within the blood itself a means by which sugar may be carried out of view.

Besides carbohydrate in the form of sugar,

CARBOHYDRATE IN THE AMYLOSE FORM IS OBTAINABLE FROM BLOOD.

After the removal of the sugar by treatment with alcohol, the precipitated matter is capable of yielding a certain amount of carbohydrate in the amylose form, after having been subjected to the breaking-down influence of boiling with potash. This, under ordinary circumstances, is found to amount to about 1 per 1000 of blood. I have for a long time known that the amylose carbohydrate that is thus capable of being obtained from blood, shows itself in greater amount after the introduction of sugar into the circulation. I gave illustrations of this in my "Physiology of the Carbohydrates," published in 1894, and regarded the fact as constituting a noteworthy point.

Later, I recognised that if I introduced sugar into the circulation in conjunction with a boiled aqueous extract of pancreas, the amylose carbohydrate was to a decided extent further increased. The experiments on this point are set forth in my "Carbohydrate Metabolism and Diabetes" (p. 71 *et seq.*). It seems to me that, without doubt, the conclusion may be drawn from them that the pancreatic extract supplies something which contributes to the conversion, by the bioplasm existing in the blood, of sugar into amylose carbohydrate. The following supplies an epitome of the results obtained.

I need not here enter into the question of the mode of estimation of the amylose carbohydrate. This matter has been fully referred to in my previous writings, extending over many years past. Suffice it to say, that, upon the strength of some hundreds of estimations, I consider that confidence may be placed in the trustworthiness of the results yielded by the procedure adopted.

In the first place, 11 determinations are given derived from normal rabbit's blood. The figures for the mean of these stand at 1·41 grammes of amylose carbohydrate per 1000 grammes of blood, the maximum figures being 1·55, and the minimum 1·25. The figures, therefore, throughout the list stand very closely together.

In five determinations made from blood collected at varying periods up to 30 minutes after the intravenous injection of one gramme per kilogramme bodyweight of dextrose dissolved in saline solution, the mean figures were 1·61 per 1000, the maximum being 1·80, and the minimum 1·52. Two determinations were made after the lapse of an hour from the time of the injection. The figures came out at 1·43 and 1·34, showing that any effect that might have been previously produced had passed off.

In the case of levulose similarly dealt with, the figures in two experiments from blood collected 15 and 30 minutes after the injection were 2·60 per 1000 and 2·67 per 1000 as against 1·81 in one experiment from blood collected at the end of an hour. Looking at these figures, no doubt can exist of the amylose carbohydrate having been raised by the levulose injection.

Two experiments were made to see the effect of injecting saline solution alone. The figures from blood collected at the end of 15 minutes came out in each case at 1·35 per 1000.

Passing to the experiments with the pancreatic extract, two experiments were conducted in which the extract alone was injected. In one, the blood was collected at the end of 15 minutes, and the figures given were 1·77 per 1000. In the other, the blood was collected at the end of 30 minutes, and the figures given were 1·52 per 1000.

In 13 experiments, the pancreatic extract was employed with 1 gramme per kilogramme bodyweight of dextrose. The mean of the figures yielded came out at 2·03 per 1000, the maximum being 2·47 and the minimum 1·57.

In four experiments of a similar nature with levulose, the mean figures stood at 2·07 per 1000 with the maximum at 2·56 and the minimum at 1·74.

One experiment was conducted with the injection of the raw extract of pancreas in association with dextrose. The injection proved immediately fatal, and the figures met with were 1·04 per 1000. These low figures are not surprising, seeing that the physical effect of the injection of the sugar solution would be to lead to a dilution of the blood, firstly from the fluid injected, and next from the hypertonicity given to the blood leading to fluid being drawn into it from the tissues.

Five experiments are recorded with the subcutaneous, instead of intravenous, injection of pancreatic extract and dextrose. The mean figures stood at 1·77 per 1000, the maximum being 2·09, and the minimum 1·52.

In one experiment of a like nature with the employment of levulose, the figures stood at 2·30 per 1000.

With reference to the precise signification of these experiments, all that is at the present moment needed to be done is to urge that they suffice to show that the pancreatic extract really exerts an action in relation to the passage of sugar into amylose carbohydrate. I will now enter upon the question of *modus operandi.*

The amboceptor in immunity phraseology seems to stand as the representative of the co-ferment concerned in enzyme action. It is now known that enzymes are dual bodies, and that the two parts are capable of being separated from each other. When separated, neither possesses any enzymic power. One is destructible by heat and seems to be the active agent, corresponding with the complement in immunity language. The other does not lose its virtue by subjection to boiling, and thus stands in the position of that which gives power to thyroid and suprarenal extracts. Taking the expressed juice of yeast, which contains zymase—the enzyme which converts sugar into alcohol and carbonic acid—a given quantity of the fresh juice has been found experimentally to have its enzymic power doubled by the addition of an equal quantity of boiled juice. This means that an extra quantity of the co-ferment, which possesses no inherent active power, gives increased power to the essentially active principle of a "complement" nature that is present in the juice.

The effect of the co-ferment is seen to be comparable to that of the pancreatic extract, and both, on account of having been exposed to a boiling temperature, must be devoid of energy-exerting power. It is obvious that the co-ferment must, in some way or other, contribute the assistance to the potential part of the enzyme which enables it to bring about the increased effect that has been spoken of. The possession of a linking-on power of an

AMBOCEPTOR

nature would suffice to supply what is wanted, and in functioning in this way, an explanation is afforded of its mode of action which satisfactorily fits in with the explanation given in connexion with operations of another, but probably allied, nature.

In the case of hæmolysins and bacteriolysins, it seems to have been experimentally reduced to demonstration that a something becomes developed within the blood which plays the passive part of connecting a lytic body (complement), present as an ordinary constituent of the blood, with that which undergoes dissolution. Without the aid of this connecting body (amboceptor), the red corpuscle and the bacterium fail to be attacked, notwithstanding they are surrounded by "complement." The amboceptor is reasonably assumed to possess a linkage capacity which leads to its joining up the complement with the red corpuscle or the bacterium, and thus placing it in a position to exert its lytic influence upon them, which, in the absence of the junction, it is powerless to do.

Through the instrumentality of the amboceptor, then, the complement is linked on to the bioplasm, and until this occurs no action takes place. The food molecule also requires, as I have before said, to be linked on to bioplasm before it can be turned to account. I think it is now pretty generally admitted that it is within, or as an integral part of bioplasm, that it is made use of, and that whilst outside bioplasm, it can no more be metabolised than a toxin molecule that has had its linking-on capacity abolished can produce a toxic effect.

Molecular configuration has been spoken of in connexion with the chemical union of bodies and it has been asserted that there must be a mutually adapted configuration to permit of junction taking place. Now, why may it not happen that amboceptor aid is required for linking the sugar molecule on to bioplasm? The facts before us bearing-on the position held by the pancreas in relation to the matter under consideration suggest that it is. Acceding to the proposition that an amboceptor is needed for the linking-on of the sugar molecule to bioplasm, and that the pancreas is concerned in its supply, everything fits in and becomes placed on a clear and intelligible footing. If the aptitude does not exist for the monosaccharide molecule to be linked on to bioplasm, it becomes placed in the same position as a disaccharide molecule, which, whilst remaining as such, plays no part in connexion with living matter, and, if reaching the system, becomes thrown off with the urine in the same way as any other extraneous or unutilisable material.

The point reached is that the facts before us suggest that

THE PANCREAS SUPPLIES AMBOCEPTORS

which, by effecting the attachment of the sugar molecule to the bioplasmic molecule, place it in a position to be disposed of according to the existing environment. It may undergo oxidation and disappear with the liberation of energy. It may become transmuted into glycogen (amylose carbohydrate). For this, it must be conceived to pass in the first place into bioplasm, in the same manner as the hydrolyte is conceived to pass into union with the enzyme preparatory to being converted into another form. Or it may be transformed into fat by a process analogous to that of transmutation into glycogen—that is to say, as a result of a molecular rearrangement taking place within the bioplasmic complex. The liver cells, in a marked manner, afford illustrations of the capacity existing in bioplasm of producing glycogen and fat from sugar. The action is comparable to that of a ferment, in so far that a body enters in one form and is thrown off in another.

In the case of the intravenously injected sugar without the pancreatic extract, it has been seen that a small increase in the amount of amylose carbohydrate obtained upon that normally obtainable, occurred. This may be taken to be attributable, under the view adopted, to amboceptor derivation from the pancreas normally existing in the blood. The linking-on agency would be increased by the association of the pancreatic extract with the sugar solution, and here the amylose carbohydrate was found in a very distinct manner to be further augmented. The facts exist with which the reading given fits in as a rational deduction.

I look upon the leucocytes of the blood as one of the

AGENCIES CONCERNED IN THE PRIMARY METABOLISM OF CARBOHYDRATE MATTER.

They admittedly feed upon material that may chance to be present in the blood, and in this way extrinsic nutrient matter that may happen incidentally to reach the blood may be appropriated and built up into bioplasm, which, like that of the lymphocytes, may pass by autolysis into the blood proteins. We have here an agency that may be instrumental in putting available matter of any kind that may in any way get into the blood, into a condition of elaborated blood pabulum.

As yet I have only applied the line of argument adduced to action occurring in the blood. But the blood is not the medium designed for the food carbohydrate to be dealt with. The work of construction into bioplasm is performed before the blood is reached by the agency of the lymphocytes. Upon this subject I have already fully spoken. Leucocytes are little masses of growing bioplasm. Lymphocytes are, in this sense, the same, and the same train of occurrences in connexion with growth may be reasonably assumed to ensue. By analogy the line of working with respect to the point before us may be carried from the one to the other. If the amboceptor is in operation, as a means of linkage of the sugar molecule to the bioplasmic molecule in the leucocyte, it may be equally taken to be similarly in operation in the lymphocyte.

This brings the amboceptor factor into connexion with the broad question of the passage of carbohydrate into the assimilated state. That it does become an incorporated constituent of protein is regarded as an accepted fact. With this before us, let it be supposed that through faulty action the carbohydrate molecule should fail to become linked on to the bioplasmic molecule, what, it may be asked, would be the state of things produced ? The sugar molecule would be left untouched, and would thence pass on into the circulation in a free state, which is tantamount to saying that there would be glycosuria proportionate in extent to the carbohydrate ingested and failing to become assimilated.

If the amboceptor is concerned in performing the office suggested in connexion with the appropriation of carbohydrate by incorporation into bioplasm, it may not unreasonably be considered to be similarly concerned in the transmutation of sugar into glycogen in the liver. The passage of sugar into glycogen constitutes a building-up operation. There are grounds for believing that the sugar in the first instance becomes taken into bioplasm. Afterwards, from the redundancy existing, a shedding off in the form of glycogen would follow, in conformity with what is conceived in circumstances of the kind to ordinarily occur. Viewed in this way, the amboceptor, if needed for the bioplasmic assimilative operation, may be reckoned to be also needed for the transmutation of sugar into glycogen in the liver.

Experience in connexion with diabetes points strongly to a fault of the nature here depicted, standing at the foundation of the show of sugar that occurs. In the passage of ingested carbohydrate to its natural destination, a certain chain of events is passed through. A faulty link in the chain, through such a defect as has been spoken of, would suffice to lead to a breakage of action continuity. A faulty cog in the metabolic mechanism is amply sufficient to account for the arrested progress of onward movement that renders itself perceptible through the sugar that comes into, and ought not to come into, view.

The theory of

GLYCOLYSIS, AS ENUNCIATED BY LEPINE,

appropriately falls in here for consideration. As long as Lépine held to the canons of the glycogenic doctrine, which imply destruction, and thereby disappearance, of sugar in the transit of the blood through the systemic capillaries, there was a show of reason in seeking for an explanation of the disappearance. But how does the matter stand when he retires from his former position and denies the occurrence of the disappearance? This, in reality, is the issue of his recent experimental work, evidence being adduced by him showing the existence of more sugar (instead of less) in the blood returning by the veins than in that contained in the arteries. He, at the same time, speaks of a *virtuel* sugar (which I take to be the same as my combined or locked-up carbohydrate) as a source of the sugar that thus comes into view.

Lépine now endorses what I have all along contended for —namely, that there is not the evidence of sugar being destroyed in its transit through the systemic capillaries that was formerly taken to exist. If such be the case, glycolysis stands upon nugatory ground, and it has always been a mystery to me how a proposition resting upon so inconsistent and illogical a basis should have received the attention that has been given to it.

Even supposing there should be an element of truth contained in the results derived by Lépine from his pancreatic extract and blood incubation experiments, I think a different interpretation can be assigned to them from that which he has given. On the question of validity, the general opinion is that they are open to mistrust, but supposing any loss of sugar to have taken place, may it not have been

THROUGH INCORPORATION INTO BIOPLASM INSTEAD OF THROUGH DESTRUCTION?

He affirms that the leucocytes are mixed up with the action, and likewise that chyle, with its lymphocytes and absence of red corpuscles, possesses greater glycolytic power than blood.

The trend of all modern work is to point to the chemical actions connected with living matter being of an intra-molecular nature, and it is difficult to conceive that action occurring outside the living molecule, as Lépine contends for, can constitute the mode of operation. No one thinks of structural formative power being otherwise than associated with the operations of actual living matter. Ought not the chemical phenomena to be viewed in the same way?

Under the assumption of the occurrence of glycolysis in the blood, Otto Cohnheim and others, particularly on the American side of the Atlantic, speak of diabetes being due to sugar failing to be *burnt* in the system. Nothing could be more gratuitous, unfounded, and misleading. There is not a particle of evidence to show that defective oxidising power exists in connexion with diabetes. The real fault is a condition antecedent to the oxidising operation. The food carbohydrate, when permitted to reach the general circulation in the form of free sugar through failing to be assimilated, cannot do otherwise than run off with the urine, and thence escape being placed in a position to undergo oxidation. In the case of the dissociation of sugar from built-up bioplasm in the "composite" type of diabetes, there is no ground for thinking that defective oxygenating power has anything to do with the matter. Whilst the sugar molecule is being thrown off by the operation of a wrong lytic action, oxidisation is proceeding in an ordinary way to permit of life being maintained.

I will now pass on to the consideration of a subject which holds a position of great importance in connexion with diabetes. I have dealt at some length with the incorporation of carbohydrate in the building up of bioplasm, and, under a redundancy, with its dissociation in the form of glycogen as a storage material to be subsequently brought into use when need may arise. As glycogen is of higher construction than the sugar which enters the molecular complex, the transmutation operation must be looked upon as constituting the result of building up.

Dissociation of carbohydrate in another form—that of sugar, occurs in association with

THE PATHOLOGICAL STATE EXISTING IN THE SEVERER KIND OF DIABETES.

To this kind of diabetes I have applied the term "composite," because the eliminated sugar is derived from a twofold source. It comes in part from defective assimilation of the food carbohydrate, and in part from the carbohydrate which has been previously put into combination, and is, from a wrong katabolic action, dissociated.

There must be a flaw of some kind or other in the bioplasmic mechanism to lead to this dissociation of sugar. When the normal katabolic procedure passes on to its proper destination, metabolism proceeds to the attainment of an exhaustion of the latent energy contained in the food-stuff products that are being utilised, and the end-products consist of carbon dioxide, water, and ammonia. In the place of progress to this natural destination, it is found, in the condition being referred to, that the chain of continuity in the bioplasmic mechanism is broken in a manner to lead to the dissociation of sugar. An influence is brought into play which leads to the sugar being broken off from the bioplasmic complex, and, perforce, carrying with it unutilised energy.

This

MOLECULAR DISRUPTION ATTENDED WITH THE DISSOCIATION OF SUGAR

stands, in reality, in the position of a reversed natural action, occurring in place of the line of change that ought to be passed through. The built-up molecule, under the influence of the environment existing, fails to continue functioning in a proper manner, and, instead, undergoes the dissociation observed. As we have already seen, a similar disruption occurs whilst blood impregnated with phloridzin is circulating through the kidney. Away from the kidney, phloridzin exerts no action, but in association with a condition supplied by the kidney structure, it brings about, after the manner of enzymic agency, the severance noticed.

I must here state that, because a certain amount of sugar is being eliminated upon what may be regarded as a properly restricted diet for diabetes, it must not necessarily be taken that the sugar is derived from the wrong breaking-down process being referred to. Meat contains a limited quantity of free carbohydrate. It also contains locked-up carbohydrate in its protein ingredient. From these sources, sugar may pass into the urine in a purely alimentary case of diabetes. If it does, the defect in carbohydrate assimilative power must be of an extreme character and closely border on the next step in which, in addition to the absence of assimilative power, there is a commencing breaking-down of protein in which carbohydrate has been previously locked up.

Facts can be adduced in substantiation of the proposition just set forth. I have now and then observed in cases of diabetes without the coexistence of associated elimination of the acetone series that, after a large quantity of meat taken at a meal, there has been a show of sugar in the urine, whilst after a moderate quantity, there has been none. Two large helpings of meat, in other words, might give rise to an appearance of sugar when one might fail to do so. This agrees with results that I notice recorded showing the effects of the ingestion of meat on the elimination of sugar in experimental pancreatic diabetes. If reference be made to Hill's "Recent Advances in Physiology and Bio-chemistry," 1906, p. 348, it will be found that an experiment on a dog is mentioned in which, in the absence of food, the sugar fell to 0·77 gramme in the 24 hours, and that, after then giving meat, it rose in the first 24 hours to 3·61, and in the next to 6·09.

Allied to the sugar elimination that has its source in a wrong breaking-down of the bioplasmic molecule may, I consider, be classed the

ELIMINATION OF THE ACETONE SERIES OF BODIES.

This constitutes one of the most important matters connected with diabetes, inasmuch as it is through its instrumentality that the fatal termination of the disease is ordinarily brought about. Sugar, in proportion as it is present in the blood, produces toxic effects of various kinds, which may lead indirectly to death, but it does not, in a direct manner, kill. With regard to the acids belonging to the acetone series, however, the same cannot be said. Their effect in the blood is to interfere with the performance of one of the necessary functions of life.

The continuance of life is dependent upon the elimination of the carbon dioxide produced as a result of vital activity. The sodic carbonate, and, to a certain extent, the sodic phosphate, are the cardinal agents for conveying the carbon dioxide from the tissues to the lungs. If, through any abnormality, there should be an entry of acid into the blood, establishing what is known as a state of acidosis, the alkaline base will be appropriated by it, and thence be prevented contributing to the transport function, as normally designed it should do.

With such circumstances present, and with the acidosis condition growing in intensity, as it will proceed to do, unless it should happen, as where the diabetic state has not attained too advanced a stage, to prove susceptible of being checked, death must sooner or later prove an inevitable result. For vital activity, as for enzyme activity, it is necessary that the products of change should become removed. Their accumulation leads to a stoppage of action, and the issue in connexion with diabetes resolves itself into a question of when the non-removal has attained a sufficient height to reduce the occurrence of action to a point that is no longer consistent with the continuance of life. If, preparatory to this stage being actually reached, a fresh power be given to the blood to take up carbon dioxide, as by the intravenous injection of a sodic carbonate solution or the ingestion of it by the mouth, a speedy restoration of activity temporarily, but unfortunately only more or less temporarily, ensues.

The view here detailed was brought forward by me in an article, published in THE LANCET in 1902,[3] entitled

"ON THE ACETONE SERIES OF PRODUCTS IN CONNEXION WITH DIABETIC COMA."

In this article I state that "writers speak of the altered constitution of the blood by the reduction of its alkalinity as the cause of the coma connected with acidosis and refer the result to the effect of the altered condition of the blood on the tissues of the body. This, however, amounts only to an assertion which gives no insight into the actual pathogeny of the coma." I then open out the view I have mentioned, and in what has preceded, reference is distinctly made to its having been discovered that, in connexion with the acidosis, a great fall in the carbon dioxide content of the blood has been observed. Not long after the article was published, exception was taken by Dr. A. P. Beddard, Dr. M. S. Pembrey, and Dr. E. I. Spriggs to the view I had announced, and they have based their conclusions upon the meaning they give to the fall of carbon dioxide in the blood noticed in their experiments. I will avail myself of this opportunity to give an answer to what they have said.

They have furnished an elaborate series of experiments which, judging from appearances, may be credited with

[3] THE LANCET, July 12th, 1902, p. 64 et seq.

having been carried out in a commendably careful and pains-taking manner. These experiments, however, throw no additional light upon the subject. They simply give confirmation and precision to what had been ascertained before, rendering it quite evident that the acidosis in diabetes is attended with an advancing fall in the carbon dioxide content of the venous blood, and, secondarily to this, with a fall of it in the pulmonary alveolar air. A major point, in the eyes of the experimentalists, belonging to the matter, is the effect produced upon the blood by the hyperpnœa that shows itself in diabetic coma. I agree with them to the extent that hyperpnœa has something to answer for in connexion with the reduced carbon dioxide content of the blood associated with the coma. It is only naturally to be expected that the exalted respiration should contribute to the reduction that occurs, and the hyperpnœa may be looked upon as constituting an effort of Nature to rectify the defect existing in connexion with tissue respiration, by producing, through reduced carbon dioxide tension in the blood, as favourable a condition as possible for promoting the drawing off of carbon dioxide from the tissues.

The conditions belonging to the blood, however, represent only one side of the question. On the other side, there is the tissue production of carbon dioxide as an act concurrent with life, and the necessity of its removal when formed, in order to sustain the continuance of life. The supply of oxygen and the removal of carbon dioxide are necessary factors in connexion with vital activity. Arrest either operation, and vital activity will cease. To give greater security to life, the mechanism of respiration is brought into concerted action with the demand existing for its functional activity. Does anyone say that exalted respiratory action is not induced by a deficient supply of oxygen on the one hand, or a defective removal of carbon dioxide on the other? By a stimulus generated within the body by the existence of either of these conditions, a response is called forth from the respiratory nerve centre, which leads automatically to the result that follows. The recent work of Haldane and Priestley stands in accord with this view, and it is supported by the still later work of Hill and Flack.

According to my opponents, however, things are to stand on a different basis, and a new factor is gratuitously invoked, holding a place altogether outside the realm of respiratory action. Through the prolonged acidosis, they suggest that the protoplasm of the cells is made more sensitive to the stimulating influence of any acid body produced during metabolism, and thus, by the direct action of acid, the diabetic coma becomes evoked. To quote their own words, they say :—"It is suggested that the following process is taking place in the nerve-cells of the medulla : the decreased 'reactivity' of the protoplasm of the cells due to the prolonged acidosis renders their reaction more easily disturbed by, and therefore makes them more sensitive to, the stimulating influence of any acid body, including carbon dioxide and other acids produced during metabolism."[4]

Now, no need exists for going outside respiratory action and bringing in a vague, unsubstantiated, extraneous explanation of the kind here offered. The effect of acidosis is to lessen the carbon dioxide transport service performed by the sodic carbonate and sodic phosphate of the blood in proportion to the extent to which the base of these salts becomes appropriated by the acids present. Carbon dioxide is constantly being produced as a result of living action, and I think no one will contend that it does not require to be removed *pari passu* with its production. Observation shows that in enzymic and living action the effect of retention of the products generated is to inhibit, in proportion to their retention, the continuance of action, and thus, in the case under consideration, to slow down the production of carbon dioxide. This is the essential point connected with the matter, and to it the experimentalists referred to have given no attention, thereby, I consider, placing themselves upon false ground by taking too narrow a view of the subject. Their work has been limited to a study bearing on the blood, which only plays a secondary part by effecting the removal of the carbon dioxide produced, and, obviously, if the alkaline bases of it are placed in a position to be unable to contribute to the removal of the carbon dioxide, the production of it must be interfered with, and the amount entering the blood lowered, as is found to be the case in advancing acidosis. I do not consider that what is said about the blood in diabetic coma still possessing in the circumstances named some absorbing power over carbon dioxide can be taken to invalidate the considerations belonging to the other side. It is not permissible to conceive that all power of taking on carbon dioxide can be lost. Such a condition is not consistent with the existence of any

[4] Journal of Physiology, 1908, vols. xxxvii. and xli.

evidence of life. The question hinges on degree of power, and what is of concern in the matter is the capacity of the blood for drawing off the carbon dioxide from the tissues whilst it is normally traversing the capillaries. There is nothing to show the degree of carbon dioxide tension in the tissues that is detrimental to bioplasmic activity, but I should think it may be taken that the gas, as it is produced, requires at once to be removed.

The agents producing the acidosis are the

β-OXYBUTYRIC AND DIACETIC ACIDS.

The former is the acid started with, and from it the latter is evolved by oxidation, and this, by escape of carbon dioxide, passes into acetone. The bodies are thus linked together into a series, and in speaking of their source, the question resolves itself into that of β-oxybutyric acid.

From chemistry we learn that butyric acid stands as a lower member of the class of fatty acids to the higher members of which belong stearic, palmitic, and oleic acids, components of the fats largely occurring in the human body. In the process of oxidation, it is usually the β carbon atom of the fatty acids which primarily, both inside and outside the living organism, becomes oxidised. By oxidations in the β position, followed by hydrolytic cleavage, descent can be made from a higher to a lower member of the fatty acid series. A succession of these downward steps leads to the formation of butyric acid, which subsequently passes, by oxidation, into β-oxybutyric acid. In this way, the derivation of β-oxybutyric acid from the normally occurring higher fatty acids can intelligibly be accounted for.

Now, such being the chemical position in which oxybutyric acid stands, ought we not to look to fat for its clinical source? Fat has been already spoken of as a constituent of the bioplasmic complex, thereby standing in the same position as carbohydrate. By wrong katabolism, we have seen that sugar is thrown off, and it is only an analogous procedure for the throwing off of oxybutyric acid likewise to occur. Under the existence of a redundancy, fat and glycogen are thrown off as a normal occurrence for storage purposes, and these are both of them principles suitable for storage on account of the non-diffusible property they possess. In the case, on the other hand, of the abnormal dissociations spoken of, in each instance alike the product thrown off is of a diffusible nature and thereby incapable of retention in the system. Hence the elimination of both the sugar and the oxybutyric acid with the urine.

Sugar, under the circumstances, is the result of a faulty molecular breaking down, and must not the same be said of oxybutyric acid? The two seem to stand in a parallel position, carbohydrate in the one case, and fat in the other, being implicated, but not necessarily acted upon by the same specific cause. As to what stands at the foundation of the intramolecular error that is attended with

DISSOCIATION OF OXYBUTYRIC ACID

is beyond us at present to discuss. The fact of the dissociation is a point of the deepest clinical interest, and I will proceed to give consideration to it, setting forth the information that we can claim to be possessed of, that will help us in dealing with the matter as medical practitioners.

It would seem, from the fact that acetone is not absolutely a foreign body in connexion with the normal state, that there must be some subsidiary action normally occurring in the direction of its production. Under certain conditions, the acetone bodies come into more prominent view. Amongst these may be mentioned, starvation and other conditions of a nature to lead to inanition, the exclusion of carbohydrate from the food as by restriction to a flesh and fat diet, and some febrile diseases, especially when occurring in children. In these cases, the bodies in question do not show themselves to a sufficient extent to produce any damaging effect; there is, however, another class of case with associated acidosis to which attention has been recently directed—delayed chloroform poisoning and cyclical or recurrent vomiting in children —where fatal effects as in diabetic coma have been observed to occur.

It is ordinarily in connexion with diabetes that the elimination of the acetone group assumes significance. With no other disease is it in a like manner associated. It had been for a very long time known that the urine and breath of diabetics might possess a peculiar odour, since found to be attributable to acetone, but until the recognition of diacetic acid in the urine by Gerhardt of Berlin in 1865, no idea existed of the intrinsic nature of this associated condition from which such serious consequences may arise in connexion with diabetes. Although the cleavage process that leads to the appearance of the bodies is virtually independent of that which leads to the dissociation of sugar, yet experience shows that some kind of relationship exists between the two. They seem, in other words, to march on in a parallel manner together.

If a case is dealt with in a way to permit of the elimination of a large quantity of sugar, which implies that the system is being subjected to the toxic influence of the sugar traversing it preparatory to elimination, sooner or later the acetone series may be expected to come into view. It is true it may happen, only very rarely have I seen it do so, that through want of proper attention being given to food, a more or less marked amount of sugar may be voided for several years without the acidosis condition becoming developed. At the same time, however, the patient, in the circumstances specified, is not exempt from the supervention of the other ill-effects arising from the toxic action of the sugar in the system, and has to pay the penalty for the injudicious course taken, by becoming the subject of neuritis, gangrene of the toe, carbuncle, cataract or some other concomitant trouble.

There can, I consider, be no doubt that individuality has much to answer for in connexion with the supervention of the

ACIDOSIS CONDITION.

With a sensitive, high-strung nerve organisation, experience leads me to look for a proneness to the appearance of acidosis. In persons of a worrying, restless, dissatisfied nature, its greater liability to show itself gives an increased gravity to this class of case. Perhaps the greater liability to show itself depends upon the nature alluded to constituting an unfavourable factor in connexion with the progress of the disease itself. In children, it is ordinary for it to set in close to the onset of the disease, and for it soon to assume a more or less pronounced character. Moreover, in children it does not usually disappear during the time the sugar is susceptible of removal by dieting, as it may do in the adult.

I have already stated that, apart from diabetes, the acidosis condition is susceptible of being evoked by, amongst other causes, absence of food. Deprivation of carbohydrate alone suffices to act in a similar way. Now, food is found to constitute an influencing factor on the elimination of the acetone bodies in the diabetic, and it here stands in a position to be invested with bearings of the deepest importance. According to the reading adopted of the results producible by food on the acetone bodies in diabetes, the medical practitioner may be conducted along a right or a wrong path in the treatment of the disease. In the interests of medical art, and, through it, of the patient, the subject therefore demands consideration of the broadest, the most substantially grounded, and the most judiciously weighed nature, that can be brought to bear upon it.

Experience shows that the acidosis which occurs in connexion with diabetes is influenced in the manner I will proceed to speak of by the

EFFECT OF THE RESTRICTION FROM CARBOHYDRATE FOOD

which is put into force in bringing down the sugar in the treatment of the disease. I have been in the habit, for several years past, of having the urine examined for the acetone series in all cases as a part of the examination conducted. The routine plan has been to look for diacetic acid, and this, in a multitude of instances, has been supplemented by looking also for acetone, and, in many instances, likewise for oxybutyric acid. In this way, some thousands of reports upon the point have passed under my notice, and when a positive result has been obtained, a measure of quantity has been inserted by + signs ranging from one up to five or six. It is upon this evidence that what I am about to state is founded.

As a preliminary, it must be mentioned that what is comprised under the term "restricted" diet has a very varied meaning. In reality it should mean the exclusion of carbohydrate as far as can be practically done, and this implies that the substitute for bread-stuff employed should be virtually, and not merely nominally, free from starch. There are foods of this kind to be obtained from establishments in London, whose praiseworthy and successful efforts have been brought to bear to produce it. Unfortunately another side presents itself that nowhere escapes being encountered, and here the foods contain a varying amount of starch, which may even, in some cases, be found to reach that belonging to the bread-stuff food in common use. A moment's reflection will suffice to show that no proper knowledge can be obtained with reference to the matter under consideration in the absence of a knowledge of the actual state of the food consumed by the patient.

Generally, at an early stage of the disease (children excepted), the effect of putting the patient on a restricted diet is not attended with the production of an appearance of the acetone bodies. At a later stage, in the case where dieting has not been in a proper manner carried out, and where sugar has been all along voided, the effect of cutting off carbohydrate food may be expected to lead to a certain amount of show of the acetone bodies. Afterwards, when, as a result of the dieting, the sugar is reduced and subsequently removed, the acetone bodies may also, in the course of a little time, be counted upon to make their disappearance.

In a case of a somewhat advanced nature, where the acetone bodies have already become present, the change of diet leads to a certain amount of augmentation of them, but the augmentation that shows itself does not afterwards intrinsically tend to proceed further. In fact, the future issue is dependent upon the stage of disease that has been reached. If too advanced to admit of rectification, the disease and its associated acidosis make headway together till it happens that the acidosis becomes greater than the power of the system to withstand, and death ensues. If not sufficiently advanced inevitably to lead to this issue, and the case should be of a suitable type subsequently to yield, the sugar, as time goes on, may be found to become more and more reduced and ultimately to disappear, and, with this, the acetone bodies may be expected to follow a similar, but more tardy, course. In this way, from what may have seemed at the beginning a very unpromising state, progress may be made through the instrumentality of the influence exerted by the food in bringing down the sugar, for this is at the root of the change induced, to the attainment of a condition in which a totally new aspect is given to the life tenure prospects.

There have been those who have deprecated the strict diet in the treatment of diabetes on account of the relation that has been referred to between acetonuria and the exclusion of carbohydrate from the food. The effect of the acids of the acetone group in leading up to coma should, it has been suggested, demand first consideration and prohibit the cutting off of carbohydrate food. If such a maxim were acted upon, diabetics would stand, as indeed they did in former times before dieting was applied as it is now, in a very bad position. It is within my own recollection to have known that the outlook in diabetes was vastly different from what it is now. Experience shows that the

WAY TO GET RID OF THE ACETONE BODIES

is to bring the sugar down, and if this is not done, all that can be looked for is that they will go on increasing. The sugar in the system, by its direct toxic influence, may be regarded as a main factor in causing the acidosis in the first place to set in, and then to grow. In a case where sugar and the acetone bodies have existed, and, by cutting off carbohydrate, have become removed, as long as sugar-free urine is maintained, there is no return of the acetone bodies. Let sugar reappear by relaxation of diet, and a return of the acetone bodies may be expected to likewise occur. I could cite many cases where such has happened, and have further observed a renewed disappearance on a return to the proper food.

The effect of what I have stated is to suggest that, in ordinary cases, the cutting off of carbohydrate should at once be put into force for the purpose of dealing with the acetone bodies. At the same time, however, I do not mean to say that cases may not now and then present themselves in which it would be unwise to adopt such a course. In extreme cases, where the patient is on the brink of the supervention of coma, a little increase in the acidosis existing may suffice to turn the scale and bring about a fatal issue. The sudden withdrawal of carbohydrate has been seen to lead to such increase, and thereby a demand is created for the exercise of judgment in connexion with the course to be adopted.

The frailness of the condition as a whole, in the circumstances under consideration, has also to be taken into account. We know how easily, through the general state, the acetone bodies may be increased. A severe attack of migraine, for instance, may send them up, and influenza pneumonia, &c., may do so sufficiently to suddenly bring about the supervention of coma. There is too much instability of system to withstand the influence of sudden change, and thus an added condition presents itself to that emanating from the direct action of the cutting off of carbohydrate on the dissociation process, which tends to promote the augmentation of the acetone bodies passing into the blood.

I have entered at some length into the question of acidosis and its bearings on food treatment in diabetes in my work on "Carbohydrate Metabolism and Diabetes," and at pages 117–22 will be found what I have said upon the subject.

Mal-application of carbohydrate food within the system constitutes the essential error existing in diabetes, and what is wanted to be effected by

TREATMENT

is to bring conditions back into line for it to be again turned to proper account. In a state of health, carbohydrate is taken and can be followed to the seat of absorption belonging to the alimentary canal. Here, however, it becomes lost to view. Neither the blood nor the urine affords evidence of the absorption that manifestly occurs. Physiologists say, notwithstanding they are confronted with this fact, that passage of the absorbed sugar into the blood occurs, but that its removal by the tissues prevents its coming into view. This constitutes an assumption which is not only not supported, but is opposed by experimental evidence. In former times, when it was held that a tangible disappearance of sugar took place in the passage of the blood from the arteries to the veins, some show of foundation presented itself for the entrance of sugar into the circulation, but now that it is admitted that no such disappearance is to be recognised, the entrance could only lead to presence in the blood and outflow with the urine, which represents the state of things existing in diabetes. For sugar to reach the circulation without showing itself in the urine, it would be necessary for a capacity to exist for effecting its instantaneous removal, and that no such capacity is present is made evident by the experimental injection of minimum quantities intravenously.

To keep sugar out of the urine, it must be kept out of the circulation, and any hypothesis explanatory of the procedure connected with the physiological application of carbohydrate must be based upon this principle. To regard it as falling within the natural course of events that the food carbohydrate should pass through the circulation to the tissues in the form of sugar is tantamount to taking the pathological as representative of the physiological state, seeing that it is just such passage which is productive of diabetes.

To escape from diabetes, the food carbohydrate must not be allowed to reach the general circulation in the form of sugar. This is

THE BASIS TO PROCEED UPON,

and the view that has been enunciated in these lectures fits in with it. It is contended that the absorbed sugar becomes dealt with at the seat of absorption, and, in company with the products derived from protein digestion, is, by the bio-plasmic action attending lymphocyte growth, put into an elaborated state. The process falls under the denomination of assimilation, and when the sugar is thus disposed of and incorporated as a constituent of the large newly-constructed molecule, it is placed in a position to be secure from running off with the urine during the transit of the blood through the kidney.

Looked at in this way, the error in diabetes consists of a faulty assimilation of the sugar absorbed from the alimentary canal. Digestion prepares for absorption, and assimilation, which follows immediately upon it, puts the absorbed digestion products into an elaborated state, in which form they pass through the thoracic duct into the blood and there constitute the pabulum from which the tissues draw their nutrient supply. This agrees with what used to be the idea entertained by physiologists with regard to the course taken by the food principles—namely, that they became elaborated into chyle, which served as a feeder to the blood. It is only in more recent years, as I have previously notified, that the shunting on to a wrong track has occurred, and that, notwithstanding chyle so obviously consists of elaborated food, the food principles have been looked upon as reaching the circulation in an uncombined, small molecular state, for transmission in such state to the tissues.

The view I am advocating not only fits in consistently from beginning to end with what I take to be properly read physiological considerations, but supplies a working basis for the treatment of diabetes which places us upon perfectly intelligible ground. It provides for the occurrence of assimilative action preparatory to the circulation being reached, and thereby for conveyance in an assimilated state to the seat of utilisation. Thus circumstanced, the digested food products are not in a condition to run off with the urine in traversing the kidney, but stand in the blood as a retainable reserve, ready to be drawn upon by the tissues as need may arise.

To mal-assimilation of carbohydrate food is to be assigned the error existing in diabetes, and what is wanted to be effected by treatment is

RESTORATION OF THE DEFECTIVE ASSIMILATIVE POWER.

Restore this power, and the patient will be no longer diabetic. Assimilative power being restored, he will then be able to take carbohydrate, and this, meeting with the power to assimilate it, will no longer pass through the system as sugar to be thrown out as waste material with the urine.

Restoration of carbohydrate assimilative power, then, is the goal of the medical practitioner in the treatment of diabetes. For the attainment of his object, it may without hesitation be said that food is the prime factor to be brought into play. Sugar in the system is the baneful agent, and unless this is brought down, no real good can be expected to arrive. The toxicity of the sugar will nullify every other effort. If the sugar can be reduced and removed, the foundation is laid for the desired restoration of assimilative power, whilst in the absence of its reduction, the condition, with varying degrees of rapidity in different cases, may be reckoned upon to grow worse and worse.

This being found from practical experience to be the case, any hypothesis which encourages the idea that it is a natural condition for free sugar to be reaching the circulatory system from carbohydrate food acts detrimentally to the interests of the art of medicine by suggesting the absence of the need for putting into force the one measure that the circumstances show to be essential for beneficial treatment. Upon these premises, the medical practitioner has ground for exclaiming against the misguiding influence derived from his physiological training. But physiologists see nothing of the testing of the truth of their teaching that is afforded by the application of endeavours to correct the physiological error constituting the source of diabetes, and they thereby are shut off from the enlightenment contributed by practical medical experience.

It will be seen that under this view the error is located in the first link of the metabolic chain instead of the last, which is assigned as its seat under the glycogenic doctrine. There is absolutely nothing to lend support to the view that the fault in diabetes (the simple or alimentary form of it) consists of a non-consumption of carbohydrate, except in so far as consumption is prevented by exit in the form of sugar with the urine in consequence of being permitted to enter the circulation as free sugar.

With faulty assimilation, as represented, at the foundation of diabetes, it is perfectly intelligible how it is that sugar finds its way into the urine from the food. From the principle of action involved, it is also explicable how the blood and urine under normal conditions remain unaffected, in relation to sugar content, in the face of the very varying quantities of carbohydrate ingested. Under all circumstances, alike in health and diabetes, as long as the carbohydrate taken is within the assimilative power existing, it becomes assimilated, and thence fails to reach the blood and urine as sugar, whilst should it surpass in amount the power existing to assimilate it, that which is not assimilated will find its way as sugar into both blood and urine.

This harmonises with what is observed in cases of diabetes in which the curtailment of carbohydrate tolerating power is susceptible of being displayed—that is, in the alimentary type of the disease. Experience tells us that varied extents of tolerating capacity are found to exist and that they are associated with a very sharp boundary line. The ingestion of carbohydrate within a given quantity fails to produce any visible effect, whilst if the given quantity is exceeded by ever so little, sugar is discoverable in the urine in proportion to the extent to which the line has been overstepped. It is easy to understand that there may be a definitely limited assimilative power—indeed, there is a definite limit to the assimilative power existing in the healthy state—and that whilst the power that exists surpasses that required for the work to be performed, there will be no show of anything wrong, whereas if the work to be performed—the amount of carbohydrate to be assimilated—should exceed the power to perform it, the effect will be that the work which escapes being performed will render itself manifest by the unassimilated carbohydrate passing into the circulation as sugar, and thence flowing off with the urine.

Regarded in this way our position in relation to the management of diabetes becomes one of great clearness and simplicity. We know precisely the ground upon which we stand, and can shape our measures into form with great definiteness to bring about a desired result. How, on the other hand, does the matter stand under the supposition that it is natural for the food carbohydrate to traverse the circulation in the form of sugar? Not the slightest relationship is discoverable between the proposition and the working result obtained. Whatever may be effected by the measure adopted, no rational explanation applicable to it can be educed from the proposition.

Restoration of carbohydrate assimilative power is, as I have said, the great object to be attained in the treatment of diabetes and, as I have further said, for the attainment of this object, it is necessary to reduce and remove, by dietetic measures, the sugar which is acting perniciously in traversing the system. The primary effect of the removal of sugar from the urine is to bring back health and strength to the patient. Virtually, as long as the urine is maintained in a sugar-free state, there is nothing to exert a damaging influence upon the system, and the only perceptible difference existing between a patient in this state and a healthy person is the different effect arising from partaking of carbohydrate food. Only when such food is taken beyond the power existing to assimilate it does the patient betray the existence of anything wrong.

Restoration of health is something for the patient to be thankful for, but this is by no means all that the removal of sugar from the urine by proper dieting effects. By maintaining a sugar-free state of urine—in other words, by maintaining a normal state of things within the system,—Nature steps in and starts mending what is wrong by reinstating the lost assimilative power. In this way there occurs a reversal of what happens whilst sugar is pervading the system, for here there is an advancing loss taking place, as is testified by the progressive growth of a case previous to the disease being recognised and dietetic treatment adopted. At first the condition may be mild, so much so as not to excite attention, when it may be taken that a considerable amount of assimilative power exists, and then, with the growth of the symptoms, a fall of power must obviously be taking place.

When a case falls under observation, everything depends, with respect to capacity for and

SPEEDINESS OF RESTORATION OF ASSIMILATIVE POWER,

upon the extent to which the disease has become developed. If only of recent onset, a few days may suffice for the removal of the sugar, and, shortly after, for signs to present themselves of returning power; whilst if the disease has, through faulty management, been allowed to run on into the development of a thoroughly established condition associated with marked acidosis, the prospect is a poor one of being able to bring about the requisite control of sugar elimination to permit of anything otherwise than continued progress in a wrong direction being looked for. The presence of acidosis is not by any means, it may be said, to be regarded as a bar to subsequent satisfactory progress. It is the point to which it has advanced that determines the issue. I have known cases where more or less return of assimilative power has occurred notwithstanding a considerable amount of acidosis has existed to start upon.

When the setting in of restoration of carbohydrate assimilative power will occur, cannot in any case be predicted. It may be within a few weeks, or a few months, or it may be delayed for a few years. A striking instance of long delay is afforded by the following case of a patient who was 42 years of age when he first came to me on Oct. 14th, 1904. He was then in a very broken-down state and his urine contained 71·4 per 1000 of sugar associated with a certain amount of diacetic acid and acetone. Notwithstanding close attention to a properly restricted diet, the declining sugar did not disappear till the end of about six weeks. On Nov. 18th there was a little sugar present, but on Dec. 3rd there was none. The patient became restored to health and continued on the strict diet till July 28th, 1906, before any sign was afforded of returning assimilative power. Acting upon the indication then presented, three ounces of ordinary wheaten bread per diem were tried and found to be tolerated. At the end of September there were indications of further restoration of assimilative power, and the bread was increased to four and a half ounces per diem without any return of sugar. No further indication of growth of power has since appeared, and the patient, who was last seen on Nov. 14th, 1908, is so far maintaining a perfect state of health with food adjusted to the curtailed carbohydrate assimilative power that he possesses.

The

RETURN OF ASSIMILATIVE POWER IS REVEALED BY UNMISTAKEABLE SIGNS.

These consist of a fall in weight and a bodily feeling of sinking or food want. As long as there is no return of assimilative power, the restricted diet suffices to meet the requirements of the system, and a proper state of equilibrium exists within. Not so, however, when restoration of carbohydrate assimilative power has taken place. Here the restricted diet, as in the healthy person, fails to meet the demands of life and Nature reveals it through the signs that have been referred to. Whilst no carbohydrate assimilative power exists, a supply of carbohydrate cannot be needed by the system. When, however, the power becomes restored, carbohydrate becomes immediately to a proportionate extent wanted—a fact that is plainly shown by Nature's revelations. These revelations, associated with sugar-free urine, may be safely read as meaning the setting in of returning assimilative power, and that action should be taken accordingly. The action needed is the supply at first of a limited amount of starchy food. The urine immediately tells the tale if too much is given. Afterwards, the starchy food must be increased as the restoration of power advances, always keeping the amount given within the boundary line of the power existing.

The

EXTENT TO WHICH THE ASSIMILATIVE POWER BECOMES RESTORED

varies greatly in different cases, but in each a sharply defined line throughout the progress exists. In a certain number of instances it becomes restored completely, which implies that the attack of diabetes has been in a direct manner thrown off. It is usual for it to become restored up to a certain point, and there to remain more or less fixed. If a patient, in the presence of these circumstances, should take carbohydrate food beyond the power existing to assimilate it, and thus give rise to a renewal of the transit of sugar through the system, the assimilative power will again decrease, and should [a marked amount be allowed to pass through, the condition may be expected in the course of time to become as bad as it was at the beginning, if not even worse. It is in this way that relapses take place, and for the maintenance of a satisfactory state, the maintenance of sugar-free urine constitutes a *sine quâ non.* The sugar that pervades the system as an effect of the disease thus becomes a paramount factor in relation to issue.

The class of case upon which the remarks I have made have been based is that belonging to the "alimentary" type, which is the common form met with in patients above the middle period of life. Ordinarily in young subjects the case at the beginning runs upon the lines that have been depicted, but later, on account of the existence of an inherent progressiveness, the treatment which at one time succeeded in keeping things right fails any longer to do so, and a relentless onward march ensues. Progress into the "composite" or bad type is not always to be averted in later years, but it is very much accelerated by improper dietetic management, and when the advanced stage is reached, the case, on account of sugar being derived from tissue disintegration as well as from food, is naturally no longer susceptible of being influenced by diet in precisely the same manner as whilst belonging to the "alimentary" type. Unfortunately for the training of the student, the class of case that is usually met with in the hospital belongs to the "composite" and not to the "alimentary" type.

It is something to achieve to be able to effect a restoration of assimilative power that will permit of a certain quantity of starchy food being taken. The patient is placed in a much less difficult and much more comfortable position. I first hinted at the recovery of the power in the supplementary Croonian lecture delivered by me at the Royal College of Physicians of London in November, 1897,[5] and subsequently, in a communication published in THE LANCET in 1900[6] under the title of "Differentiation in Diabetes," I entered into a detailed consideration of the matter. The subject has also been fully dealt with in the section on diabetes contained in my work on "Carbohydrate Metabolism and Diabetes," 1906, and notwithstanding the light that the information throws upon the whole question concerned, and the satisfactory basis that it supplies in connexion with the application of treatment, I have not seen that the attention it deserves has been given to it.

It follows from what has preceded that the physician is dependent for success in treatment upon the character of the food that is available for his patient. Through the incentive that has been created for meeting the demand that has arisen for a pure and palatable

DIABETIC BREAD-STUFF,

endeavours have been successfully applied in the direction needed, and there are now establishments in London from

[5] Brit. Med. Jour., 1897, vol. ii.
[6] THE LANCET, June 16th, 1900, p. 1706 et seq.

which the diabetic can reliably obtain his required supply. At the same time, there are foods produced and sold under the name of diabetic foods that are not entitled to receive this designation, and they constitute the source of a great amount of harm. Many are no better than ordinary domestic foods, and others contain too much carbohydrate to permit of its being possible, in the usual run of case, to get rid of the sugar from the urine.

In illustration I may refer to some foods that fell under my notice about a year ago in the following way. In connexion with the case of a boy patient, a physician from Paris on a visit to London was, at the request of an uncle residing in France, permitted to see the patient, and on his return home dispatched a parcel of diabetic foods obtained from a well-known supply establishment in Paris. Here are the figures showing the percentage of carbohydrate expressed as starch that they contained in the water-free state, into which, for apt comparison, all foods should be brought previously to analysis :—

	Carbohydrate as starch.
Gluten flour	72·0 per cent.
,, bread	50·0 ,,
,, biscuit	54·7 ,,
Granulated gluten	63·9 ,,

Food supplied by Rademann of Frankfurt was referred to when I was speaking of Professor von Noorden's "oat" cure. Samples were obtained from this maker at the early part of the present year, and the figures here given show the percentage of starch present in the articles in the water-free state. An improvement is perceptible upon the figures previously yielded :—

	Carbohydrate as starch.
Diabetic white bread	47·2 per cent.
Diabetic Graham bread	40·8 ,,
Diabetic black bread	41·9 ,,
"D.K." bread	74·5 ,,
Diabetic rusks	46·5 ,,
Diabetic cakes	44·4 ,,
Diabetic meal	62·0 ,,

I have said nothing about drug treatment, and for the reason that I know of nothing that by itself exerts a direct and immediate arresting influence over the elimination of sugar. In reality, something is wanted to set metabolism right, in like manner as it is set right by the thyroid extract in myxœdema. This something has not yet been discovered, but science ought sooner or later to place us in a better position than we at present stand in relation to the matter. We, however, know that metabolism is influenced through the instrumentality of the nervous system, and this is suggestive that it may, in connexion with the point under consideration, be likewise open to being influenced in a collateral way by drug agency. I am a strong believer in help being given towards promoting the restoration of carbohydrate assimilative power by the administration of opium and some of its derivatives.