THE LUMLEIAN LECTURES

ON THE DIGESTIVE FERMENTS, AND THE PREPARATION AND USE OF ARTIFICIALLY DIGESTED FOOD.

Delivered before the Royal College of Physicians.

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LECTURE I.

DIGESTION has been usually regarded as the special attribute of animals. They receive into their alimentary canal the food which they require for their sustenance in a crude form. It is there subjected to the action of certain ferments which transmute its elements, by a peculiar chemical process, into new forms which are fitted for absorption. Looked at in this restrictive sense, plants have no digestive function. They possess no alimentary canal, nor any vestige of a digestive apparatus. But when the matter is examined more profoundly, it is seen that plants digest as well as animals, and that the process in both kingdoms of nature is fundamentally the same.

In order to understand this generalisation—which was first propounded by Claude Bernard, and constitutes one of the most important fruits of his splendid labours*—it is necessary to recognise digestion under two types or conditions, namely, a digestion which takes place exteriorly at the surface of the organism, and a digestion which takes place interstitially in the interior of the organs and tissues.

Exterior digestion is that common process with which we are familiar as taking place in the alimentary canal of animals, by which the crude food introduced from without is prepared for absorption.

Interstitial digestion, on the other hand, is that more recondite process by which the reserves of food lodged in the interior of plants and animals are modified and made available for the purposes of nutrition.

These two types of digestion are essentially alike, both as regards the agents and the processes by which they are carried out; and, although one type of digestion is more developed in the animal kingdom, and the other type more developed in the vegetable kingdom, both types are represented in the two kingdoms, and bear witness to the fundamental unity of the nutritive operations in plants and animals. I shall only be able to indicate in outline the facts and arguments on which Bernard sought to establish these propositions.

Exterior Digestion.—We all know that the alimentary canal is simply a prolongation of the external surface; that the skin is continued, at each extremity, without a break, into the alimentary mucous membrane. Accordingly, the processes which take place in the digestive tube are, strictly speaking, as much outside the body as if they took place on the surface of the skin. Upon this inner surface, if I may so call it, are poured out the digestive juices, charged with the ferments which are the special agents of the digestive processes. This is the common condition of exterior digestion as it occurs in animals; but it is not the only condition. Among some of the lowest members of the animal series, a permanent alimentary canal does not exist. In the amoeba, any portion of the exterior is adapted for the reception of food. The morsel sinks into a depression formed on the surface at the point of impact; it is digested in this improvised stomach; and the indigestible portions are expelled through an improvised anus.

Among plants, exterior digestion is a much less prominent feature than among animals; but examples of its occurrence and evidence of its importance are not difficult to point out. In the lowest orders of plants—fungi and saprophytes, which are devoid of chlorophyll—exterior digestion is probably a function of prime necessity. In all likelihood, their carbon-containing food is only absorbed after undergoing a process of true digestion. The transformation of cane-sugar by the yeast-plant is a striking example—though a distorted one—of exterior digestion. Cane-sugar is a crude form of food both to plants and to animals, and requires to be transformed into invert-sugar (a mixture of equal parts of dextrose or grape-sugar and lævulose or fruit-sugar) before it

can be made available for nutrition. The yeast-plant is no exception to this rule; and, when placed in a solution of cane-sugar, it is under the necessity of transforming that compound into invert-sugar before it can use it for its profit in fermentation. This transformation is effected by a soluble ferment attached to the yeast-cell, which can be dissolved from it by water. We shall see later on that a similar ferment exists, for a similar purpose, in the small intestine of animals, having the same property of changing cane-sugar into invert-sugar.

Even among the higher plants, exterior digestion is not quite unknown. The function may be said to be foreshadowed in the excretion of an acid fluid by the rootlets of some plants, which serves to dissolve and render absorbable the mineral matters in their vicinity. But genuine and most remarkable examples of this type of digestion occur among the so-called insectivorous plants, of which Mr. Darwin has given so interesting an account. In the sun-dews, the plant, by a peculiar mechanism provided on its foliage, seizes the insects which fortuitously alight on its leaves. A stomach is extemporised around the prey, into which is poured out a digestive fluid. The prey is digested, and the products absorbed, in essentially the same manner as in the gastric digestion of animals.

Interstitial Digestion.—Both animals and plants lay up reserves or stores of food in various parts of their tissues for contingent use, so that, if you suddenly withdraw from them their food-supplies, neither animal nor plant immediately dies—it lives for a certain time on its reserves. But, before these reserves can be made available for the operations of nutrition, they must first be converted from their inert and mostly insoluble state into a state of solution and adaptability to circulate in the nutritive fluid which constitutes the alimentary atmosphere of the protoplasmic elements. This conversion of inert store-food into available nutriment is brought about—certainly in some, presumably in all, cases—by the same agents and processes as the digestion which takes place in the alimentary canal of animals; and it is this identity in the agents and the processes which Bernard insisted on as the proof of the fundamental identity of the two kinds of digestion.

The storing up of food is carried on to a larger extent in the vegetable than in the animal kingdom, owing to the intermittent life of most plants. In their seeds, tubers, bulbs, and other receptacles, are laid up stores of albumen, starch, cane-sugar, and oil—designed primarily for the growth and nutrition of the plant or its offspring—but which are largely seized on by animals and utilised for their food. Owing to their more continuous life, animals store up food less than plants. Nevertheless, they accumulate stores of fat in various parts of their body—of animal starch (glycogen) in their livers and elsewhere, and of albumen in their blood. Birds also store up large quantities of albumen and fat in their eggs.

The transformation of store-food has been followed out most completely in regard to starch, its congener glycogen, and cane-sugar. Bernard worked out this subject with marvellous minuteness and success. It has long been known that the transformation of starch into sugar in germinating seeds was effected by diastase; and that a similar ferment, existing in saliva and pancreatic juice, performed the same office on the starchy food of animals. It has also been proved that the stores of starch laid up in the tuber of the potato and in various parts of other plants are changed at the periods of budding and growth in the same way, and by the same agent. Bernard showed that animal starch or glycogen is stored up largely, not only in the liver, but in a variety of other situations, and especially that it is widely distributed and invariably present in large quantities in embryonic conditions. In juxtaposition with the glycogen is found a diastatic ferment which transforms it into grape-sugar, as it is required for the active operations of growth and nutrition.

The stores of cane-sugar which exist in the beet-root and in the sugar-cane are transformed or digested in like manner into invert-sugar when the plants enter on the second phase of their life—the phase of inflorescence and fructification. Here, again, it has been proved that the converting agent is a soluble ferment, the same ferment which, as already mentioned, is attached to the yeast-cell, and the same ferment which exists in the small intestine of animals for a similar purpose.

The transformation of store-proteids and fats has not been followed out with the same success as that of starch and cane-sugar. But the evidence, as far as it goes, and analogy point to the conclusion that the stores of albuminous and oily matters contained in the seeds, bulbs, and other receptacles of vegetables are subjected to a digestive process before they are made available for the nutritive operations of the plants, and that the changes thus effected are of the same nature and accomplished by the same agents as those which take place in the digestion of proteids and fats in the alimentary canals of animals.

I have, I think, said enough to show the scope of the evidence and the analogies from which Bernard deduced certain far-reaching general-

* Claude Bernard, *Leçons sur les Phénomènes de la Vie*, tome ii; edited after his death by Dastre. Paris: 1879.

isations, which I have ventured to summarise in my own language in the following propositions.

1. Digestion, or the process by which crude food is changed into available nutriment, is a function of capital importance in every form of active life. 2. This function is exercised partly on food brought into proximity with the surface of the organism (exterior, chiefly intestinal digestion) and partly on reserves of food laid up in the interior of the organism (interstitial digestion). 3. The agents concerned in this function and their mode of action are essentially the same, whether the organism be a plant or an animal, and whether the action take place in the interior of the tissues or on the general or intestinal surfaces.

GENERAL CHARACTERS AND PROPERTIES OF THE DIGESTIVE FERMENTS.

The essential work of digestion is carried out by a remarkable group of agents, called soluble or unorganised ferments. These are found dissolved in the several digestive juices or secretions, which are thrown out on the path of the food as it travels along the alimentary canal. The physical and mechanical processes to which food is subjected in the mouth and stomach are all purely introductory or preparatory, and are solely intended to facilitate the essential work of digestion, which consists in the action of the digestive ferments on the alimentary principles.

The number of distinct ferments employed in the digestion of the miscellaneous food used by man is not accurately known; but there are at least seven or eight of them. The accompanying table presents in one view a scheme of the several digestive secretions or juices, and the ferments which they contain, together with an indication of the action of each ferment on the several alimentary principles.

Table of the Digestive Juices and their Ferments.

Digestive Juices.	Ferments contained in them.	Action on Food-Materials.
Saliva	Salivary diastase, or ptyalin	Changes starch into sugar and dextrin.
Gastric juice ..	a. Pepsin	{ Changes proteids into peptones in an acid medium. Curdles the casein of milk.
	b. Curdling ferment..	
Pancreatic juice-	a. Trypsin	{ Changes proteids into peptones in alkaline and neutral media. Curdles the casein of milk. Changes starch into sugar and dextrin. Emulsifies and partially saponifies fats.
	b. Curdling ferment..	
	c. Pancreatic diastase	
	d. Emulsive ferment	
Bile	(?)	Assists in emulsifying fats.
Intestinal juice..	a. Invertin	Changes cane-sugar into invert-sugar. Curdles the casein of milk.
	b. (?) Curdling ferment	

An examination of the table shows that a long and complicated series of ferment-actions is required to accomplish the digestion of our food. Starch is attacked at two points—in the mouth and in the duodenum—by two ferments, salivary and pancreatic diastase, which are substantially identical. Albuminous matters are also attacked at two points, in the stomach and in the small intestine; but here the two ferments—pepsin and trypsin—are certainly not identical. The ferment, of which the only known characteristic is to curdle milk, is found in the stomach and in the pancreas, and I think also in the small intestine. The bile is not known to possess any true ferment-action; but it assists, by its alkaline reaction and by its physical properties, in emulsifying and promoting the absorption of fatty matters. The ferment which transforms cane-sugar, strange to say, is not encountered until the food reaches the small intestine.

The known digestive ferments all belong to the class of soluble or unorganised ferments. They are sharply distinguished from the insoluble or organised ferments, of which the type is yeast, in not having the power of self-nutrition and self-multiplication. All living organisms possess this power either in a dormant (potential) or in an active (kinetic) state. Soluble ferments cannot therefore be said to be alive; but they are exclusively associated with living organisms, and take an essential part in their vital operations.

The digestive ferments are all the direct products of living cells, and may be regarded as detached repositories of cell-force. They are quite unknown in the domain of ordinary chemistry. Their mode of action bears no resemblance to that of ordinary chemical affinity, and has a distinctively physiological character. They do not derive their marvelous endowments from their material substance. They give nothing material to, and take nothing material from, the substance acted on.

The albuminoid matter which constitutes their mass is evidently no more than the material substratum of a special kind of energy—just as the steel of a magnet is the material substratum of the magnetic energy—but is not itself that energy. This albuminoid matter of the ferment may be said to become charged, at the moment of elaboration by the gland-cells, with potential energy of a special kind, in the same way that a piece of steel becomes charged with magnetism by contact with a pre-existing magnet. The potential energy of the ferment is changed into the active form (*i.e.*, becomes kinetic) when it is brought into contact with the alimentary substance on which it is designed to act.

The chemical and physical characters of the digestive ferments appear to be tolerably uniform. In composition, they resemble proteid substances, and contain carbon, oxygen, hydrogen, and nitrogen in the same or somewhat similar centesimal proportions as albumen. But, as not one of them has yet been obtained in a state of absolute isolation and purity, this is, strictly speaking, a matter of inference rather than an ascertained fact. They are all soluble in water; they are all diffusible, though with difficulty, through animal membranes and parchment paper. They are also capable (all those I have tried) of passing through porous earthenware by filtration under pressure; but some of them pass through readily, and others with the utmost difficulty, and only in the smallest proportions. They are precipitated from their watery solutions by absolute alcohol; but, unlike other proteids (peptones excepted), they are not truly coagulated by alcohol. When the alcohol is removed, the ferments are still found to be soluble in water and to retain their activity unimpaired. They are coagulated and rendered permanently inert by the heat of boiling water; and, when in solution, they are coagulated and destroyed by a heat of about 160° Fahr. (71° C.)

Each digestive ferment has its special correlative alimentary principle, or group of principles, on which alone it is capable of acting. Diastase acts exclusively on amylaceous substances. Pepsin and trypsin act only on the azotised principles; the emulsive ferment of the pancreas is only capable of acting on fatty bodies; the inversive ferment of the small intestine has no activity except on cane-sugar.

The changes impressed on alimentary principles by the digestive ferments are not, chemically speaking, of a profound character; and they affect much more the physical state of these principles than their chemical composition. In the main, they are processes of deduplication and hydration; and the result is to render the substances operated on more soluble and more diffusible, to diminish their colloidal state, and to make them approach, or even to reach, the crystalloid state. This does not appear to be an invariable event, however. Cane-sugar is a marked exception; it is converted in the small intestine into invert-sugar (a mixture of equal parts of grape-sugar or dextrose and fruit-sugar or lævulose). But invert-sugar, though more highly hydrated than cane-sugar, is neither more diffusible nor more soluble.

It does not appear to be absolutely true that all food requires digestion before it can be absorbed. Fat is largely taken up by the lacteals in its unaltered state, except in so far that it is finely divided or emulsified. Grape-sugar (dextrose) is not known to suffer any digestive operation, but to be absorbed unchanged. Perhaps it would be more correct to say that grape-sugar is an article of food predigested for us by the agency of plants.

Although the mode of action of digestive ferments is special and peculiar, the results of that action are not peculiar, but can be obtained in other ways by ordinary chemical forces. By long continued boiling in water—and more rapidly by boiling with acidulated water—starch is converted into dextrine and sugar, and albumen is changed into a substance resembling peptone. The peculiarity of the action of ferments consists in this: that the ferments are able swiftly and without violence to produce changes which by ordinary chemical agencies can only be produced either by strong reagents or by long continued and very slow action of weaker reagents. It is interesting to remark that the changes produced in food by digestion are, in their ultimate results, very similar to, if not identical with, those produced by protracted cooking.

THE PREPARATION OF ARTIFICIAL DIGESTIVE JUICES.—The study of the digestive ferments has been immensely facilitated by a method first introduced by Eberle. Eberle discovered that an aqueous infusion or extract of the digestive glands possessed the same properties as the natural secretions or juices of those glands. The reason of this is, that the glands which secrete the digestive juices contain within them a reserve stock of their respective ferments. Accordingly, when the glands are infused in water, their reserve stock of ferments passes into solution. These infusions or extracts then constitute artificial digestive juices, which operate in a flask or beaker in the same way as the corresponding glandular secretions act in the alimentary canal. Solutions of organic matters are, however, extremely perishable; they pass

quickly into putrefaction. In order to obviate this inconvenience, and to obtain an extract which is always handy for use, various preservative means have been employed. Bernard used carbolic acid; others have used glycerine or common salt. These preservatives, although perfect for the purpose intended, have a pronounced taste which it is impossible to get rid of. I have made a good number of experiments on this point. As the ultimate object I had in view was to obtain a solution which could be administered as a medicine by the mouth, or which could be employed in the preparation of artificially digested food, I sought for a preservative which had either little taste or smell, or one which was volatile and could be got rid of by vaporisation. After a good many trials, I adopted the three following solutions as, on the whole, the best suited for the purpose.

I. *Boric Solution*.—This solution contains three or four per cent. of a mixture of two parts of boric acid and one part of borax. An extract of the stomach or of the pancreas made with this solution keeps perfectly, and has little taste and no smell. For experimental purposes, this extract is, I believe, all that can be desired; it is neutral in reaction and is chemically inert. It answers well also for administration by the mouth when the dose does not exceed one or two teaspoonsful. But when larger quantities are required for the preparation of artificially digested food, and when food thus prepared has to be used day after day in quantity sufficient to sustain nutrition, larger quantities of boric acid and borax are taken into the stomach than that organ can always comfortably tolerate.

II. *Dilute Spirit*.—The second solution is water mixed with twelve or fifteen per cent. of rectified spirit. This solution makes a most excellent extracting medium, and the quantity of spirit in it is so small as rarely to be an objection to its use. In the preparation of artificially digested food, a final boiling is usually requisite, and in this final boiling the alcohol is dissipated. On the whole, this is, perhaps, the most generally useful of the three solutions.

III. *Chloroform-Water*.—Chloroform dissolves in water in the proportion of about one in two hundred; these are the proportions employed in the preparation of the *aqua chloroformi* of the *British Pharmacopœia*. This forms a perfect solvent for the digestive ferments, and its keeping qualities are unrivalled. But, though the quantity of chloroform dissolved is so minute (about two and a half drops in a fluid-ounce), it communicates a somewhat powerful smell and taste to the solution. This taste and smell are agreeable to most persons, but not to all. It is, however, quite easy to get rid of the chloroform. If the dose to be used be first poured into a wineglass or saucer, and left exposed to the air for three or four hours, the chloroform passes off almost entirely in vapour, and leaves behind a simple aqueous solution of the ferments; or, if the solution be employed for the preparation of artificially digested food, the chloroform, being very volatile, disappears in the final boiling. It is, perhaps, well to mention that chloroform-water has the property of reducing Fehling's solution, and that this property has to be taken into account in making experiments on digestion which involve testing for sugar.

Alimentary substances fall naturally into three well-marked groups; namely, *Carbohydrates*, *Proteids*, and *Fats*. I propose to consider the digestion of the three groups in the order here indicated. I have, however, no intention of dealing systematically with these subjects, but rather to take up certain points and questions in regard to which I have myself made observations, or which have a bearing on the preparation of artificially digested food and its administration to patients. I shall treat the digestive transformation of starch in some detail, because this has been worked out almost to completeness, and because it probably furnishes a type which will hereafter be of service as a guide to the study of the more complex problem of the digestion of proteids.

DIASTATIC FERMENTS: DIGESTION OF STARCH.

The importance of starch as an article of human food has, perhaps, scarcely been duly recognised. If we regard the enormous proportion in which the seeds of cereals and leguminous plants, and the tuber of the potato, enter into our dietary, and the immense percentage of starch in these articles, it is probably not too much to say that fully two-thirds of the food of mankind consists of starch. In the raw state, starch is to man an almost indigestible substance; but, when previously subjected to the operation of cooking, it is digested with great facility.

Diastase has only a feeble action on the unbroken starch-granule, even at the temperature of the body. In the lower animals, and in germinating seeds, the starch-granule is probably attacked in the first instance by some other solvent, which penetrates its outer membrane, and thus enables the diastase to reach and act on the starchy matter contained within. By the aid of heat and moisture in the process of

cooking, the starch-granule is much more effectively broken up. Its contents swell out enormously by imbibition of water, and the whole is converted, more or less completely, into a paste or jelly or mucilaginous gruel. It is in this gelatinous form exclusively, or almost exclusively, that starch is presented for digestion to man. The digestion of starch is accomplished by the saliva and pancreatic juice, both of which are rich in diastase. Diastase also exists abundantly in the liver, and in smaller quantities in the intestinal juice, in the blood, the urine, and apparently in all the interstitial juices. Diastase from all these diverse sources appears to act substantially in the same manner as starch, changing it by a progressive hydrolysis into sugar and dextrine.

If the action of a fluid containing diastase—say saliva or extract of pancreas—on starch-paste be watched, the first effect observed is the liquefaction of the paste and the production of a diffused solution. This change is effected with great celerity; in two or three minutes, the stiff paste becomes a watery liquid. This is evidently a distinct act, and antecedent to the saccharifying process which follows. By operating with small proportions of diastase and large proportions of pure starch-paste, it is possible to hit on a moment when liquefaction is complete and saccharification is not yet begun. At this moment, the solution yields a pure starch reaction, and no reaction of dextrine nor of sugar. The process of saccharification follows immediately on the heels of liquefaction; and, in ordinary manipulations, the one process runs into the other.

The speed of the action depends primarily on the proportion of the diastase. By adjusting the proportions of diastase and starch in such degrees that saccharification will be completed in about a couple of hours, the successive steps of the process can be leisurely followed by applying from time to time the appropriate tests.

If you test as soon as liquefaction is complete, you get a pure blue with iodine and a slight reaction of sugar with Fehling's solution. In a few minutes, the sugar-reaction becomes more decided; and, although you still get a pure blue with iodine in the ordinary way of testing, you will get, by greatly diluting the blue solution and then adding more iodine, a deep violet tint—showing the presence of erythro-dextrine mixed with starch. The next step is the total disappearance of the blue reaction with iodine, and the substitution for it of an intense reddish-brown coloration of erythro-dextrine. By-and-bye, the reddish-brown colour is replaced by a yellowish-brown, indicating the preponderating presence of a different kind of erythro-dextrine. Meanwhile, the sugar-reaction goes on increasing. The next step is the entire disappearance of any kind of coloration with iodine. But the action is still very far from complete; the proportion of sugar goes on increasing for a considerable time after iodine has ceased to tint the solution. At length, however, matters come to a standstill, and the proportion of sugar ceases to increase.

The explanation of this series of reactions is impossible on the old view of the constitution of starch. Until recently, it was supposed that the starch-molecule was represented by the comparatively simple formula $C_{12}H_{20}O_{10}$; and that, under the influence of diastase, this molecule was resolved by hydration into two molecules—one of dextrine and one of grape-sugar.

The researches of Musculus and O'Sullivan* have shown that this is not a correct account of the transformation. In the first place, it was found that the sugar produced was not grape-sugar (dextrose), but another kind of sugar called *maltose*. It was also found that the dextrines first produced, and which were coloured red or brown by iodine, were progressively changed, with simultaneous production of sugar, into a series of dextrines of a lower type, which did not yield any coloration with iodine. To these latter kinds of dextrine the term *achroo-dextrines* has been applied.

As maltose is now ascertained to be the kind of sugar which is mainly produced in the digestion of starch by diastase, this body assumes a new and considerable importance in physiological chemistry; and it will not be out of place here to give some description of its properties. Maltose is a fermentescible crystalline sugar of the saccharose (cane-sugar) class, having very little sweetening power, and possessing one atom less water than grape-sugar. Its formula is $C_{12}H_{22}O_{11}$. It possesses more rotatory power on polarised light than grape-sugar, but has considerably less power of reducing cupric oxide. The rotatory power of maltose is +150, that of grape-sugar +58. The reducing power of maltose is 61, compared to that of grape-sugar as 100. Maltose can be hydrolysed into grape-sugar by prolonged boiling with dilute acids. Malt-diastase does not possess this power; but we shall presently see that the diastatic ferments of the small intestine are able slowly to effect the same change.

* O'Sullivan's papers are published in the *Journal of the Chemical Society* from 1872 to 1876. A full account of these researches is given in a paper in the same journal for September 1879, by T. H. Brown and J. Heron.

The researches of Musculus and O'Sullivan have rendered it necessary to assume that the molecule of soluble or liquefied starch is a composite molecule, containing several members of the group $C_{12}H_{20}O_{10}$, which is to be regarded as the constituent radical of the composite starch-molecule. The starch-molecule must in the future be represented by the formula $n(C_{12}H_{20}O_{10})$ —the value of n not being yet definitely agreed upon.

Two able chemists of Burton-on-Trent, H. T. Brown and J. Heron, have extended these researches, and fully confirmed the main conclusions of Musculus and O'Sullivan. In a recent publication (*Journal of the Chemical Society*, September 1879), they have for the first time presented a fairly complete scheme of the succession of changes undergone by starch under the action of diastase. These chemists assume that the molecule of soluble starch consists of ten members of the group $C_{12}H_{20}O_{10}$, and that its formula should be written $10(C_{12}H_{20}O_{10})$. This view greatly facilitates the comprehension of the progressive hydrolysis of starch by diastase.

We have seen that starch in the condition of paste or jelly is distinguished sharply by its physical properties from liquefied or soluble starch. There must, therefore, in all probability, be some difference of molecular aggregation between starch in these two states; and it will not be a very bold assumption to suppose that starch in the gelatinous state consists of still more complex molecules than soluble starch, and that several molecules of soluble starch are grouped together to form the molecule of starch in the gelatinous state.

On the ground of these assumptions, we may represent the successive steps of the digestion of gelatinous starch by the following series of equations.

The molecule of gelatinous starch $= n(C_{12}H_{20}O_{10})$ is first resolved into n molecules of soluble starch. The molecule of soluble starch is then resolved by progressive deduplication and hydration into dextrine and maltose by the following succession of steps.

One molecule of soluble starch $= 10(C_{12}H_{20}O_{10}) + 8(H_2O) =$

1. Erythro-dextrine α $9(C_{12}H_{20}O_{10}) + (C_{12}H_{22}O_{11})$ maltose.
2. Erythro-dextrine β $8(C_{12}H_{20}O_{10}) + 2(C_{12}H_{22}O_{11})$ „
3. Achroo-dextrine α $7(C_{12}H_{20}O_{10}) + 3(C_{12}H_{22}O_{11})$ „
4. Achroo-dextrine β $6(C_{12}H_{20}O_{10}) + 4(C_{12}H_{22}O_{11})$ „
5. Achroo-dextrine γ $5(C_{12}H_{20}O_{10}) + 5(C_{12}H_{22}O_{11})$ „
6. Achroo-dextrine δ $4(C_{12}H_{20}O_{10}) + 6(C_{12}H_{22}O_{11})$ „
7. Achroo-dextrine ϵ $3(C_{12}H_{20}O_{10}) + 7(C_{12}H_{22}O_{11})$ „
8. Achroo-dextrine θ $2(C_{12}H_{20}O_{10}) + 8(C_{12}H_{22}O_{11})$ „

The final result of the transformation is represented by the equation
 $10(C_{12}H_{20}O_{10}) + 8H_2O = 8(C_{12}H_{22}O_{11}) + 2(C_{12}H_{20}O_{10})$
 Soluble starch. Water. Maltose. Achroo-dextrine.

We must conceive that the energy of the ferment is exercised in gradually pulling asunder the component groups or radicals of the unstable molecule of soluble starch, detaching one after another from the parent molecule; each radical, as soon as detached, assuming an atom of water and becoming an atom of maltose. At each detachment, the parent molecule draws its remaining groups together to form a new kind of dextrine. As the process goes on, the dextrine-molecule becomes smaller and smaller—that is, contains fewer and fewer component radicals; the higher dextrines giving a red or brown coloration with iodine, but the lower dextrines giving no reaction with iodine. It is to be noted that, after the transformation has reached its final term, there still remains a portion of achroo-dextrine unconverted into maltose. Upon this remnant, diastase has only a very slow action. The percentage result, when the reaction is completed, gives, in round numbers, eighty parts of maltose and twenty parts of achroo-dextrine. The eight varieties of dextrine indicated in the above table of equations have not all been obtained in the separate state; but there is strong evidence of the existence of at least several of them as distinct bodies.

The account just given of the transformation of starch has been deduced from a study of the action of diastase derived from malt. The question arises—physiologically an important question—whether the action of salivary and pancreatic diastase is identical with that of malt-diastase. The researches of Musculus and von Mering* give an affirmative answer to this question. These observers found that saliva and pancreatic extract act on starch-paste in the same way as malt-diastase; the final products in all cases being achroo-dextrine and maltose, and not dextrose (grape-sugar). At my suggestion, Mr. H. T. Brown was good enough to submit the question to a fresh examination in regard to pancreatic extract. His results fully confirm the conclusions of Musculus and von Mering. He found, however, that there was a slight difference in the results when the action of pancreatic extract and malt-diastase on starch was continued a long time. The pancreatic ferment,

in addition to the power, which it shares with malt-diastase, of slowly converting the lowest achroo-dextrine into maltose, exhibited a power of slowly changing maltose into dextrose (grape-sugar) which is not possessed in any degree by malt-diastase. Mr. Brown also informs me that there is in the small intestine a ferment which possesses similar properties.

The respective Shares of Saliva and Pancreatic Juice in the Digestion of Starch.—The respective shares of saliva and of pancreatic juice in the digestion of our farinaceous food are probably variable, and perhaps not quite identical.

As all our farinaceous food is eaten after being cooked, the starch in it is more or less completely gelatinised; it is, therefore, probable that one of the chief uses of salivary diastase in man is to liquefy starch-jelly. A very brief contact suffices for this; and it is manifest that the accomplishment of this change is an important advantage in the subsequent operations in the stomach. Our gruels, blanchmanges, puddings, and similar farinaceous dishes, owe their thick pasty condition to starch in the gelatinous state; and nothing can be imagined more resistant to the rapid permeation of the meal by the gastric juice, and to the pulping of it into an uniform chyme, than the presence of coherent masses of starch-paste. If the saliva performed no other service than this, it would furnish an important aid to the digestion of a meal. There has been considerable dispute as to whether, and how far, the saccharification of starch goes on in the stomach. My observations lead to the conclusion that this depends on the degree of acidity of the contents of the stomach; and it is known that this varies within very wide limits. When a meal is swallowed, it takes some time for the gastric juice to permeate the mass, and the acidity of the gastric contents is for some time very feeble. As digestion proceeds, the contents of the stomach tend to become more and more acid. This is a point which each one can observe for himself. The stomach is by no means reticent of its doings. The possetting which we see in infants goes on in a less degree in the adult; and we are perforce made aware, sometimes inconveniently so, by our palates, of the ascending scale of acidity in the stomach. Saliva acts energetically in neutral and in slightly acid media; but its activity is checked and finally arrested when the acidity becomes pronounced. When digestion is proceeding comfortably and normally, a certain interval elapses before the acidity of the stomach becomes considerable; and during this interval the salivary diastase continues active, and has time to accomplish a good deal of work. But we must remember that our farinaceous food is, for the most part, not in the most favourable condition for rapid digestion. It is not generally in a state of mucilage, but in the form of a solid paste, as in bread, puddings, and pastry. A good deal of it, too, is imperfectly cooked. Consequently, the larger part of our starchy food reaches the duodenum still unchanged, or only partly changed; and this larger part of the work is consummated by the pancreatic juice in the alkaline medium of the small intestine. I shall have to return to this point in speaking of gastric digestion.

It has been noted as curious, that the saliva of man possesses more diastatic power than that of almost any other animal. Among the herbivora, which are large consumers of starch, the saliva has comparatively little diastatic power; and in some, as in the horse, it is almost or altogether wanting. I apprehend that this is due to the fact that man alone has learnt to cook his starchy food, and that the diastatic power of his saliva has become developed with the opportunity for its exercise. Diastatic power would be thrown away in the saliva of the horse, because he eats his food in the raw or uncooked state, and saliva is without action on raw starch.

When can Starch be said to be fully Digested?—Seeing that in the digestion of starch a number of intermediate products are evolved, the question arises, when can the digestion of starch be said to be accomplished? Is maltose the only product absorbed, or are not the dextrines, especially the achroo-dextrines, also absorbed? The dextrines, even those coloured by iodine, are highly diffusible, and pass freely through parchment-paper in dialysis. In this respect, they contrast strongly with starch-jelly, and even with liquefied (or soluble) starch, both of which are undialysable. It seems not improbable that the lower dextrines are largely absorbed. Because, if we follow the history of starch after it has been transformed by digestion and absorbed, we are confronted with the remarkable fact that, after absorption, the products of starch digestion, or at least a large portion of them, undergo a reconversion in the liver into a substance closely resembling undigested starch. Glycogen, in its essential features, is an exact counterpart of soluble starch. It forms an opalescent solution in water; it is undialysable; and it is transformed by diastase into dextrine and sugar.

It appears reasonable to suppose that it would be an advantage to the economy, if that portion of our starchy food which is destined to be stocked in the liver as glycogen should be absorbed at an early period of

* Maly's *Jahresbericht für Thier-Chemie* for 1878, p. 40.

digestion, because, the less removed the digested product is from starch at the moment of absorption, the fewer steps it will have to retrace in recovering the amylaceous state after absorption.

It is not necessary to suppose that the ascending steps of the re-conversion are identical with the descending steps of digestion; but it is probable that they are fundamentally alike, seeing the close similarity of the products at the two ends of the journey. At any rate, there is no warrant in the present state of knowledge for the opinion that sugar is the only absorbable product of starch digestion.

Absolute Energy of Diastase.—The notion that the energy of diastase is not consumed in action seems, on *à priori* grounds, to be quite untenable; such a notion contravenes a general principle in physics, that energy in performing work is expended and finally exhausted. It is easy to show experimentally that diastase is no exception to this rule. Payen and Persoz estimated that malt-diastase was able to convert two thousand times its weight of starch into sugar. My own experiments with extract of pancreas indicate a much higher power than this. The following experiment illustrates at the same time the enormous diastatic power of pancreatic diastase, and the fact that this power is strictly limited.

A quantity of starch mucilage was prepared, containing one per cent. of pure potato-starch; one hundred cubic centimètres of this mucilage contained exactly one gramme of dry starch. The pancreatic extract employed was prepared in the following manner. Fresh pig's pancreas, freed from fat, was rubbed up with an equal weight of fine sand until it became a smooth uniform pulp. This pulp was spread out very thinly on sheets of glass, and allowed to dry in the open air for a fortnight. It was then scraped off with a knife, and formed a rough shreddy sort of powder. One hundred and twenty-five grammes of this mixture of pancreas and sand were infused, at the temperature of the room, in one thousand cubic centimètres of saturated chloroform-water, with a little more chloroform added to ensure against decomposition. The mixture was allowed to stand for four days with occasional agitation, and the product was then filtered clear through paper. The extract of pancreas thus prepared proved a very serviceable preparation, and most of my observations on pancreatic digestion were made with it.

This extract was found to be so extremely active, that it was necessary to dilute it largely in order to bring the quantities of starch operated on within due compass. Accordingly, a dilution was made of one cubic centimètre of the extract in one thousand cubic centimètres of water. Five numbered phials were then severally charged with one hundred cubic centimètres of the prepared starch-mucilage, so that each phial contained exactly one gramme of dry starch. One cubic centimètre of the diluted pancreatic extract was added to phial No. 1; two cubic centimètres to No. 2; four cubic centimètres to No. 3; six cubic centimètres to No. 4; and eight cubic centimètres of the same diluted extract to phial No. 5. The phials were then corked and placed in a warm chamber, where the temperature was steadily maintained by a Page's regulator at 100° F. (38° C.)

At the end of twenty hours, the contents of the phials were examined. All of them were perfectly transparent, and had entirely lost the opalescent appearance of the original starch-mucilage, and not a vestige of sediment existed in any of them. The following reactions indicated the progress of the transformation.

No. 1 gave an intense blue coloration with iodine, and, when the blue solution was largely diluted and more iodine added, it developed a violet tint which showed the presence of erythro-dextrine; it also reduced the cupro-potassic solution freely.

No. 2 gave a strong blue reaction with iodine, and, by diluting and adding more iodine, the colour changed to a deep claret-red, indicative of abundance of erythro-dextrine. This and all the rest gave a strong sugar reaction with Fehling's solution.

No. 3 yielded no blue reaction with iodine, but an intense port-wine coloration of erythro-dextrine.

No. 4 gave no blue reaction with iodine, and only the faintest possible brown coloration with that reagent, showing only traces of erythro-dextrine.

No. 5 exhibited not a vestige of reaction with iodine. It contained neither starch nor erythro-dextrine, but it yielded a strong sugar reaction.

The transformation of No. 5 might be regarded as complete, but the rest still contained starch or erythro-dextrine, or both. Nos. 1, 2, 3, and 4 were restored to the warm chamber and re-examined at the expiration of seven hours. No. 4 no longer gave the slightest reaction with iodine; but Nos. 1, 2, and 3 showed only slight signs of further alteration, and were returned to the warm chamber.

At the end of forty-eight hours from the commencement of the experiment, Nos. 1, 2, and 3 were examined again.

No. 1 showed a strong blue coloration with iodine, and also a strong reaction of erythro-dextrine.

No. 2 no longer gave any blue tint with iodine, but it exhibited an intense erythro-dextrine reaction.

No. 3 only gave a yellowish-brown reaction with iodine of moderate intensity.

After a further sojourn of seventy hours in the warm chamber, the contents of the three phials were not found to be sensibly altered; they gave exactly the same reactions as before. It was evident that in these phials the diastatic action had run its course to an end within the period of forty-eight hours, and that the solutions had then come to a state of rest, the ferment had liberated all its energy, the limits of its power had been reached, and the task allotted to it was left unfinished. Nevertheless, it had accomplished an amount of work which, considering its infinitesimally minute mass, appears marvellous. We shall now endeavour to measure approximately the amount of this work as indicated by the above experiments.

The original pancreatic extract, when evaporated to dryness in a water-bath, was found to leave a residue of 1.5 per cent. of organic matter. This organic matter included, besides diastase, a quantity of proteolytic ferment (trypsin) and a certain quantity of the milk-curdling ferment. It also included a certain quantity of digested proteid matter; for, in making an extract of the pancreas, there is always accomplished some self-digestion of the glandular tissue. Taking into account these various admixtures, it would appear a very liberal allowance to estimate the diastatic ferment as amounting to one-fourth of the total organic matter. This would give us for the original extract a proportion of diastase, in round numbers, of 0.4 per cent., and for the diluted extract, of 0.0004 per cent.

The proportion of diastase added to phial No. 4 seems to have hit off with precision the limit of quantity required to transform one gramme (15.5 grains) of starch in forty-eight hours at a temperature of 100° F. (38° C.). The amount of diluted extract added to this phial was six cubic centimètres; and, on the basis of the above estimate, this represents a quantity of nett diastase amounting to 0.000024 gramme. This yields us, by an easy calculation, the astounding result that pancreatic diastase is able to transform into sugar and dextrine no less than forty thousand times its own weight of starch.

The speed at which a given quantity of starch is transformed by diastase depends essentially on the proportion of ferment brought to act upon it. In the above experiments, the proportion of diastase was very minute in comparison with the amount of starch, and the action went on slowly for forty-eight hours. But if we reverse these proportions, and mix a small amount of starch with a large amount of diastase, the transformation is instantaneously accomplished.

If a test-tube be half filled with an active extract of pancreas, and a few drops of starch-mucilage be quickly shaken therewith, you cannot detect the reaction of starch or dextrine in the mixture, however prompt you may be with the testing; the transformation has followed on the admixture as instantaneously as the explosion of the charge follows the fall of the trigger. Between these extremes there are all gradations. This mode of action differs entirely from what is seen in the operation of ordinary chemical affinity. If you add a drop of acid to an excess of alkali, the acid is instantly neutralised and the action comes to an end; and conversely, if you add a drop of alkali to an excess of acid, the action is equally instantaneous; the affinity of the two bodies for each other is a mutual affinity. But this is not the case with the action of diastase on starch. The starch appears entirely passive in the process; all the energy is on the side of the diastase, and this energy can only be liberated gradually. There is something in this strikingly suggestive or reminiscent of the action of living organisms. To illustrate my meaning, let us compare the particles of the ferment to a band of living workmen, whose function is to scatter little heaps of stones. If the heaps be few and the workmen many, all the heaps will be scattered at once, and the energy of the workmen will still remain sensibly unimpaired. But if the heaps be millions and the workmen hundreds, and if the workmen be doomed to labour on until they fall exhausted at their task, the scattering of the heaps will go on for a comparatively long time, and the process of exhaustion will be a gradual one.

I may here mention that the diastatic ferment does not exist in the saliva and pancreatic juice of young suckling animals, except in minute proportions. Its quantity increases when the teeth are cut. In the human infant, diastase does not appear to exist in sufficient abundance to digest starchy matters effectively until about the sixth or seventh month. Until this period, it is, therefore, not advisable to administer farinaceous food to infants.

DIGESTION OF CANE-SUGAR: INVERSIVE FERMENT.

* Bernard* first called attention to the fact, already mentioned, that

* Claude Bernard—*Leçons sur les Phénomènes de la Vie*, tome ii, p. 36, Paris, 1879.

cane-sugar (saccharose) required digestion both in animals and plants before it could be utilised in nutrition. The cane-sugar stored up in beet-root and in the sugar-cane is changed by ferment-action into invert sugar before it is permitted to circulate in the sap, and take part in the nutritive operations of the plant. He found also that an analogous transformation was requisite before cane-sugar could be assimilated by animals. He states that, when cane-sugar is injected into the blood, it circulates therein as an inert body, and is in no degree used as nutriment by the tissues, but is eventually entirely removed unchanged with the urine. Cane-sugar is, however, an important article of food, and is consumed by us in large quantities every day; and we know that, when thus consumed, it does not behave like an inert matter, circulating awhile in the blood, and then being eliminated by the kidneys as a waste product. It is evidently absorbed and assimilated, and must, therefore, somewhere or other, be transformed or digested in animals as it is in plants. Reasoning this way, Bernard sought for an inversive ferment for cane-sugar in the alimentary tract; and after searching in the saliva, in the stomach, and in the pancreas in vain, he at length discovered it in the small intestine. In the small intestine, he found that cane-sugar was transformed into invert-sugar, and by a similar ferment with that destined for analogous purposes in yeast, in beet-root, and in the sugar-cane.

The transformation of cane-sugar into invert-sugar is represented by a very simple equation:—

The inversive ferment was detected by Bernard in the small intestine of dogs, rabbits, birds, and frogs. Balbiani found it in the intestine of the silkworm. It was recognised by myself in the small intestine of the pig, the fowl, and the hare. It does not exist in the large intestine.

But although my observations on this subject coincided in the main with those of Bernard, I noted two points which I think merit further attention. The first was, that, while a piece of small intestine infused in water yielded a mixture which was capable of inverting cane-sugar, the same infusion when filtered through paper until it was perfectly clear had no such power. It seemed as if the inversive ferment did not pass freely, if at all, into true solution, but remained attached to some of the formed elements contained in the intestine. The second point which I noted was the extreme slowness of the action. When cane-sugar was added to the unfiltered infusion of intestine, and the mixture maintained at blood-heat, it generally took a couple of hours before a reducing effect with the copper test could be obtained. Both these circumstances reminded one of the action of formed ferments, and I could not help thinking that there was here something which required clearing up at some future time.

TOXIC ACTION OF OXALIC ACID.—Drs. Kobert and Kiessner describe in Virchow's *Archiv*, Band 78, the result of experiments made by them on nearly sixty animals, mostly dogs, cats, and rabbits, and in rare instances porpoises, hamsters, rats, and hedgehogs. They state that the symptoms of poisoning by oxalic acid have in many points a strong resemblance to those of poisoning by fungi, and suggest the possibility of a part of the phenomena of the latter being due to oxalic acid contained in the fungi. The authors thus sum up the results of their researches. Oxalic acid is not a cardiac poison, but its action is in the first place on the nervous system. In this way are explained the lowering of the blood-pressure, the loss of rhythm and the retardation of the pulse, and also the slow breathing. Further indications of the same effect are phenomena of irritation and of depression (the latter predominating) in the motor, sensory, and reflex nerves. These phenomena are most distinctly marked in rapidly acute poisoning, but are by no means wanting in subacute or even in chronic cases. Their mode of onset, and the manner in which the symptoms are combined, are not constant, and therefore not pathognomonic. There are, however, other signs which are typical of poisoning with oxalic acid. These are the changes in the urine during life, and those found in the kidneys after death. These changes are the only characteristic phenomena produced; they are present both in acute and in chronic poisoning, and only gradually disappear. The principal sign—one which has hitherto been quite unrecognised—is the appearance in the urine of a powerful reducing substance, the nature of which cannot as yet be described. The urine also almost always contains albumen; and microscopic examination reveals, besides numerous cylinders and a few blood-corpuscles, crystals of oxalate in very various forms. These crystals are found—and this is the special characteristic phenomenon—in the uriniferous tubules; sometimes only in the convoluted, occasionally also in the straight tubes.

THE CROONIAN LECTURES

SOME POINTS IN THE PATHOLOGY AND TREATMENT OF TYPHOID FEVER.

Delivered before the Royal College of Physicians of London.

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LECTURE II.*

WE have next to consider what is the relation which these different processes bear to one another and to the symptoms of the disease. According to the views of many pathologists, the phenomena of typhoid fever are produced in the following manner. The poison is swallowed, and enters the system through the lymph-follicles of the ileum, on which it produces its primary effects; it then passes into the mesenteric glands, where it goes through a stage of latency or incubation, and at last enters the circulation and is deposited in other lymphatic organs and the spleen, and causes a rapid hyperplasia of their cells, and so produces the characteristic local lesions. The poison also acts on the heat-regulating centres, and produces the febrile temperature. The high temperature, in its turn, causes all the other morbid phenomena: the albuminous infiltration and softening of the heart and other organs, the vitreous degeneration of the muscles, the acceleration of the circulation and respiration, the febrile consumption of the body, and especially the disturbances of the nervous system, the delirium and stupor of the typhoid condition. The correctness or not of this view is, I need hardly say, of the utmost importance in the treatment of the disease. It is, therefore, very necessary that we should examine the arguments by which it is supported.

In the first place, it is urged that these phenomena occur in many febrile diseases which have nothing in common but the high temperature. Secondly, it is possible to produce many of them by artificially raising the temperature. Thus, the experiments of Dr. Wickham Legg show that, by raising the temperature of animals to 112° Fahr., albuminous infiltration of the liver and other organs is produced. Max Schultze, by means of his microscopic warming apparatus, directly demonstrated the injurious effects of high temperatures on living cells. We have, too, distinct evidence that raising the temperature of the body increases metabolism. By means of a vapour-bath, it is quite easy to raise the temperature many degrees, as the evaporation from the skin, and so the compensatory dispersion of heat, is prevented. Bärtsels found that sufficiently prolonged vapour-baths raised the temperature, accelerated the pulse and respiration, increased the discharge of urea 16 per cent., and diminished the weight of the body. It is interesting to observe that the discharge of urea was greater in the second twenty-four hours after the bath, when the temperature was again normal, than during the time the temperature was raised. This is analogous to the epicritical discharge of urea which takes place in those fevers which terminate by crisis. In both cases, it is probably due to its partial retention and accumulation during the febrile period, in consequence of the unfavourable conditions for its elimination during this time. Similar results were obtained by Naunyn in experimenting on dogs.

Lastly, in support of this view, may be adduced the effects of treatment. If a patient in the typhoid state—*i.e.*, in a condition of delirium or stupor, with a dry brown tongue, tremulous muscles, greatly accelerated pulse, and other symptoms which are liable to occur in severe fever—be placed in a cold bath and the temperature reduced to below 100°, a remarkable improvement usually takes place in his symptoms: the stupor passes off, the delirium ceases, the tongue becomes moister, the pulse less frequent, and commonly he falls into a quiet sleep; the symptoms recurring in the course of a few hours, when the temperature has again risen to its former height. The effects of a cold bath in cases of hyperpyrexia, as in rheumatic fever, are still more striking, and are well known to all who have employed this mode of treatment. Hence there can be little doubt that the pathological changes and injurious effects of fever are largely due to the high temperature. But, notwithstanding these and other arguments which may

* Concluded from page 507 of last number.