

CHAPTER VI

SECRETION AND GLANDULAR MECHANISMS

Correlation of Secretion, Absorption, and Excretion, and their Relationship to Osmotic Energy.—The processes of secretion, absorption, and excretion are distinguished from one another only by their object or physiological function, and not by anything intrinsically different in their nature or in the mechanism by which these processes are carried out in the body. The purpose of secretion is to prepare an active substance in solution for use in assisting a process which is of service to the organism in some other part, such as a digestive secretion; a secretion of a substance which has a guiding influence upon chemical change in other tissues, and hence affects the state of activity of those tissues, as, for example, the internal secretions, adrenalin, secretin, &c.; or a secretion which acts by mechanical means, such as the secretion of the tears in the lachrymal gland, the mucous secretions on the mucous surfaces, and the serous and synovial secretions of the serous and synovial cavities. The purpose of absorption is to take up for the service of the body generally and of the absorbing cells the materials in solution which have been prepared and modified by the secretions. Lastly, the purpose of excretion is to remove from the body materials which have passed through, or been formed in, the cycle of metabolism in the body, and have become waste products for which the body has no further use. In addition, the purpose of excretion is to maintain in normal amount and concentration in the circulating fluid of the body, the blood, those products which *are* of service, for in abnormal concentrations these useful bodies become as injurious to the living cells as effete products of metabolism, or foreign substances of actively poisonous nature.

Respiration also is essentially identical in its nature with these three processes, being a combination of absorption, secretion, and excretion, the only difference being that the products concerned in respiration exist in the form of gases before being taken

into the body and after being removed from it, but in the process of respiration itself the substances concerned, oxygen and carbon-dioxide, are as truly in aqueous solution as are the substances involved in secretion, absorption, and excretion. It is clear, then, that the purposes served in the processes of secretion, absorption, excretion, and respiration differ, but we shall see that in so far as the intrinsic nature of these processes and the mechanisms by which they are carried out are concerned, they are closely similar or identical, and are governed by the same laws.

At the outset it may be pointed out that not only in respiration, where the differentiation of the process into two parts—an external respiration and an internal or tissue respiration—has been clearly recognised, but also in the other processes of secretion, absorption, and excretion, there are two parts to the process, viz. (1) an internal or cellular part, in which chemical changes, and processes involving energy changes within the cells active in the process, occur, and (2) an external or mechanical part in which the products acted upon are brought to or carried away from the cell and transferred to other parts of the organism, and by means of which, through the activity of mechanisms external to the cells concerned in the active process, the internal or cellular part is modified and regulated.

Thus, in the case of secretion, we may point out as the internal or cellular part of the process: (1) the formation and storage in the cell of the intrinsic organic constituents of the secretion, as zymogens, &c., in which process the cell acts as an energy-transformer upon the chemical energy supplied by the organic constituents of the plasma, and builds up its own special products from these constituents; (2) the formation from the inorganic constituents of the plasma of the inorganic constituents of the secretion against the laws of diffusion and osmosis, so that the osmotic energy is increased by the separation of a secretion containing substances in greater concentration than they possess in the plasma, the cell here again acting as a transformer, and converting chemical energy derived from its absorbed and oxidised food into osmotic energy.

But we have also in secretion the external part of the process in which agencies outside the secreting cell come into operation, and either modify the action of the cell, or produce an effect apart from the cell entirely.

The agents which come into operation in the external part of secretion may be classified as follows:—

(1) The alteration in the supply of fluid or solvent and of dissolved and nutrient matter to the cell, such as variations of the blood supply to the secreting cells; or alterations in the concentration of the dissolved substances in the blood supply, for example, alteration of percentage of glucose in the blood which influences the glycogen-secreting power of the liver cells.

(2) Alterations in the secretory activity of the cells due to external causes, when the supply of solvent and nutrient remain constant or do not change proportionately to the change in secretory activity, such as the stimulation of the special secretory nervous mechanism of the secretory cells, or the effects upon secretion of chemical substances—for example, *secretin* upon the pancreatic cells, or *gastrin* upon the gastric cells, or drugs such as pilocarpin or atropin upon secretory cells in general.

(3) Most external in character of all are the mechanisms by which the secretions in certain cases are carried away from the secreting cells, diverted into different channels so as to be carried away to different parts of the body, or by certain muscular arrangements in the different ducts, are retained ready and already secreted for use at intermittent periods. Examples of such external mechanisms of secretion are found in the ducts of secreting glands, often, when of an appreciable length, supplied with muscular walls which by means of peristaltic contractions pass on the secretion, or by sphincters at definite parts along their course, provide for its retention until a reflex stimulus causes it to be discharged when there is physiological occasion for its use. Storage sacs for the secretion are found in the gall-bladder, in the organs of generation, in the dilated ducts of the mammary gland, and in the poison glands, &c., of many animals.

Exactly the same division into an intrinsic indispensable cellular or internal part is seen in the processes of excretion and absorption, together with a more or less expanded and varying accessory or external part.

Thus, in absorption, we have in the intestinal columnar cells an active cellular absorption, with accompanying chemical change, and work done against osmotic pressure, and the external part of carriage of the products to the tissues, where again cellular

processes of absorption occur modified by the operation of the nervous system, and new products are given out which are carried by an extra cellular process to other cells. Similarly in excretion, we have cellular activity in which the excretory products are formed in the various cells; external processes by which these are carried to the liver; cellular processes, again, in which the excretory products are chemically modified; external processes by which the products are carried to the excretory organ, such as the kidney; and, lastly, in the special excretory organ itself, we have cellular processes again in which the excreting cell provides energy for work to be done against osmotic pressure with corresponding increase in osmotic energy, at the expense of chemical energy obtained from oxidation of nutrient matter. Throughout the processes, in addition to external carriage in the blood stream, there is also the play from without upon the active cells of the external agencies (*a*) of the nervous system directly, or indirectly through the vaso-motors, and (*b*) the stimulus of chemical substances in the circulation, which may also act upon the cells, or intermediately through varying the blood supply.

It is in the external parts of the processes that the chief differences in their mechanisms are to be found, and this statement holds not only in contrasting the processes of respiration, secretion, absorption, and excretion with one another, but in regard to the variations between one type or case of secretion, &c., and another. The variations in the external mechanisms are manifold between one process and another, and from one animal species to another with regard to how the same fundamental process is carried out; but in all cases the essential cellular process is very much alike, and the same types of phenomena are to be found. There is in every case a living cell involved in the process, and by this living cell the processes of diffusion and osmosis are profoundly modified. Substances are separated often at higher concentrations than in the bathing fluid, which can only take place on the condition that energy is transformed by the cell and converted into osmotic energy. New substances are produced in many cases which are typical of the action of the cell involved, and can only be produced as a result of energy transformations induced by the cell. Even where the concentrations of every single instance in the secretion may be less than in the bathing fluid, and no new substance is

produced in the passage through the cell,¹ the rate of secretion or transmission is so much subject to variation apart from purely physical factors, that the cell must be regarded as something more than simply an inert membrane, because its permeability for different dissolved substances, and for the solvent, vary from time to time as the cell is acted upon either by the nervous system or by substances in solution in the plasma. Such specific substances dissolved in the plasma possess the power of affecting permeability for other and quite different substances in a manner never seen in the case of non-living membranes or apart from living cells.

The consideration of the mechanism of secretion may accordingly be divided into two parts, viz. (1) the intrinsic activity of the cells concerned in secretion, and (2) the accessory mechanisms by which the rate of secretion is varied and controlled.

INTRINSIC ACTIVITY OF SECRETING CELLS

That secreting cells do not act in a passive inert manner as filtering mechanisms, or as membranes possessing different and constant permeabilities for different dissolved substances in the plasma, or as media in which different substances possess different solubilities, is proven by many experimental observations. Thus that the rate of secretion is not merely passively dependent upon blood pressure and blood supply (although under normal conditions it is subject to variations corresponding to changes in these physical factors) is shown by the observation of Ludwig that the secretion pressure in the submaxillary salivary gland, when the outflow is resisted by fluid in a manometer, may rise much above the arterial pressure; and also by the observation that after administration of a drug, such as atropin, the blood supply may be increased as much as before administration of the drug on stimulation of the secretory nerve, without however calling forth any flow of secretion. In other cases, such as the kidney, where the secretion pressure cannot be raised above arterial pressure, this is due to the nature of the minute anatomical structure, as a result of which all supply of fluid is cut off from the secreting cells

¹ It is improbable that this condition ever is completely realised in the action of living cells.

before the pressure in the ductules can exceed that in the blood-vessels, and so the stoppage of secretion is a purely mechanical effect.

These experiments prove that, although secretion under normal conditions may be aided by filtration, yet the process in its nature is not one of passive filtration.

That it is not passively dependent upon osmotic pressure is shown (1) by the fact that the total osmotic pressure of the secretion, as shown by depression of freezing-point, is in many cases greater than that of the plasma; (2) that even in cases, such, for example, as the saliva, where the total osmotic pressure is less than that of the plasma, the osmotic pressure of certain constituents is higher than their pressure in the plasma—for example, in the saliva, the pressure of dissolved carbon-dioxide, of calcium salts, and of the sulphocyanide; (3) that new constituents appear in the secretion as a result of chemical activity in the cell which are entirely absent in the plasma, and are not sent into the plasma, but into the gland duct, by means of cellular activity and in opposition to the operation of osmotic energy; (4) the alteration in many cases of chemical reaction by concentration of hydrogen or of hydroxyl ions in the secretion high above the concentration which they possess in the plasma, may be quoted as an example of cellular activity producing an effect in opposition to osmotic pressure.

Now it is clear that while the source of energy residing in the blood pressure might separate a secretion, with concentration possessing any value up to that of the same dissolved constituent in the plasma, it cannot produce a concentration in even a single constituent exceeding the value of the concentration of that same constituent in the plasma, and certainly cannot produce a new constituent not present in the plasma. When the results of experiment are taken in conjunction with this statement, it is found that in every secretion in the body cellular activity must be brought into action, in other words, the secreting cell must furnish energy in the process of secretion, and this not only holds obviously for the new constituents, but also for all those crystallised and inorganic constituents which are found in the secretion at a higher concentration than in the plasma, and hence possess more osmotic energy.

Not only does the increase in concentration of certain constituents in the secretion above their concentration in the plasma

rule out, as far as these constituents are concerned, the operation of filtration and osmosis, but it also rules out any passive view of the secretion whatever, which does not involve work done by the cell as an active energy-transformer.

If any single substance is increased in concentration in a secretion above the concentration which it possesses in the plasma, then such increase in concentration involves the performance of work against osmotic pressure,¹ and in consequence the expenditure of energy by the secreting cell, and the secretion of such substance cannot be explained by any theory which does not take into account the work of the cell as an energy-transformer.

A recognition of this principle would have saved much error in not recognising the limitations of certain theories which have been put forward in explanation of absorption and secretion by the cell.

In the first place may be mentioned the selective absorption theory of Overton, for the explanation of the selective uptake by the cell of different ions, salts, crystalloids, and nutrient matter, and the retention of certain salts or ions in the cell, such, for example, as potassium salts, in greater concentration than in the plasma.

Overton supposes that there exists, enclosing the cell or separating off in some manner its protoplasmic constituents from the plasma, a thin envelope or layer of lipöid substances, chiefly lecithin, which possesses selective permeabilities for different substances and ions in solution, being impermeable entirely for some, easily permeable for others, and in other cases permeable with difficulty. This lipöid membrane or "plasma haut" is supposed in this way to determine the uptake and output of the cell, and its osmotic behaviour with regard to different substances, and has also been applied in explanation of the toxicity or otherwise of different substances for the cell, and of the effects of anæsthetics.

Taking the theory first from the experimental point of view, although it must be admitted that "lipöids" (if by this term is meant merely substances soluble in ether) are present in all cells, and lecithin in all of those in which it has been experimentally sought, although often only in small traces; yet it has never been shown experimentally that this forms a separating membrane

¹ This does not mean that the osmotic pressure is balanced or overcome by hydrostatic pressure in the cell, but that osmotic or volume energy must be replaced by energy in another form by the agency of the cell. (See p. 164.)

between plasma and cell protoplasm, as has been assumed by Overton. Further, it has never been shown that this hypothetical membrane possesses for different ions and crystalloids the permeabilities and impermeabilities ascribed to it.

In order to attempt to test the Overton theory with regard to salt solutions, the writer has prepared a lecithin membrane by thoroughly impregnating a membrane of parchment paper with lecithin, so that the pores of the paper were thoroughly soaked with the lecithin, and there was a continuous layer of lecithin on both sides of the paper, and using this as a membrane between sodium chloride solution and water, or between two sodium chloride solutions of different strengths, so as to avoid action of the water upon the lecithin.

According to Overton's view, the lecithin membrane, like the cell, ought to be impermeable to the sodium chloride, and in solutions of different strength an osmotic pressure effect ought to have been obtainable with such a membrane.

It was found, however, when the membrane was used in an osmometer (1) that no osmotic pressure whatever developed on the sodium chloride solution side, or on the side of the stronger solution, and (2) that sodium chloride did pass through the membrane.

Accordingly, the presence of a lecithin membrane, even were such shown experimentally to exist, would not explain the osmotic phenomena of the cell or the impermeability of the cell for the sodium ion.

Taking next the membrane hypothesis from the theoretical point of view, the following arguments may be urged, which apply not only to the lipoid membrane but to any other conceivable membrane by which an attempt may be made to explain upon such a passive basis the active work of the cell in maintaining a different composition and concentration of the crystalloids and ions within it to that which obtains in the medium in which the cell lives. It is on account of this general applicability against an explanation by any passive membrane theory that the arguments are here given at length.

Take, first of all, the position that the cells are *entirely* impermeable to certain ions (and to other non-dissociated organic crystalloids), and that it is on account of such perfect impermeability that these are found only within or only without the cell,

or in such very different and fixed concentrations within and without the cell. For example, that potassium salts are found in the cell in excess, and sodium salts in the plasma in excess, and that this is due to a membrane refusing passage entirely to sodium and potassium ions. Then this excludes all exchange of such ions between cells and plasma, and there is neither any explanation on such a basis of how the present state of affairs with such an unequal distribution of potassium and sodium ions occurred in the first instance when the cells were formed and growing; nor any explanation of how more potassium ion is taken in and sodium ion excluded when cell division takes place and new cells are growing and causing increased volume of cellular tissue without any drop in potassium ion concentration. The explanation on the ground of complete impermeability can obviously only hold so long as the cell is in complete equilibrium with the plasma as regards the inner and outer level in potassium and sodium salts. But there is no explanation whatever of how that equilibrium was attained initially, nor how it is maintained when the cell volume increases as cell multiplication occurs. Are we to suppose that the original fertilised ovum contained all the potassium salts of the adult organism? Obviously such a conclusion is absurd, and it must be admitted that the cells must have at some time taken up potassium and continued to reject sodium ions.

In fact, it is quite clear that so far from being impermeable to potassium ions, up to the period at which the cell attained its maximum saturation, it must have greedily taken up potassium ions, from an exceedingly low concentration in the plasma, by an *active* process of selective absorption against osmotic pressure¹ and with corresponding expenditure of energy by the cell, in the same fashion as a diatom concentrates the silica for its skeleton from the trace present in sea-water, or as the bone-forming cells take up the calcium salts from the circulating plasma. Once the cell has attained its normal level of potassium ion concentration this action ceases and equilibrium is attained; but this condition is preserved only so long as the cell is resting in size. There is no evidence that there is an impermeable membrane formed, or that the cell is really impermeable to potassium salts, because it does not give them out or take them up any more in appreci-

¹ See footnote on p. 145, and also p. 164.

able quantity; all this means is, that there is a balance being maintained dependent upon the nature and active properties of the particular cell protoplasm involved. When such a cell is immersed in a solution of a potassium salt it takes practically none up, because it has already attained its balance in potassium ions, and *actively* preserves this. Did it behave as an inert membrane, as when it is killed, it would take up more potassium ions in a strong solution; but the living cell does not do so to any appreciable extent; it actively preserves itself against osmotic invasion. On the other hand, when such a cell is placed in a solution not containing potassium salts, such as a solution of sodium chloride, it does not part with its potassium salts in appreciable amount; but this need not be because it is surrounded by a membrane impermeable to potassium ions but because it actively retains its potassium ions on account of that affinity or activity by which it originally took them up when they were present in traces only in the plasma.

Thus the balance of concentration for each individual ion and salt and dissolved substance within and without the cell is maintained, and readjusted when it changes, not by means of any hypothetical inert impassable membrane stopping any reaction between the cell contents and the constituents in solution within and without, but by the play of the cell's activities upon the medium in which it lives.

This, it may be remarked, is not theory but experimental fact; we see that the growing cell takes up certain definite constituents from the medium and rejects others, that the constituents taken up are often taken up in opposition to osmotic pressure, and hence only possible by the expenditure of energy by the cell. Why, then, when the cell comes into a position of *labile* equilibrium with its medium should the basis of explanation be changed, and it be supposed that instead of those forms of energy which brought the cell to that state, being still active in maintaining it in that state, the mechanism of a hypothetical membrane or permeability be invoked?

The condition is analogous to that of a chemical reaction which has come into equilibrium; here we do not suppose that the reaction is frozen rigid, so to speak, at the equilibrium point, or that membranes of an impermeable type are formed around the molecules which keep them from reacting. No, the reaction is pre-

served by the balance of opposing factors, reactions still occur between the molecules, but these are equal and opposite.

So also in the case of the living cell in equilibrium, the case is not that of an impenetrable membrane through which an ion of potassium or sodium never passes, but a labile equilibrium with both potassium and sodium ions passing in and out all the time, but the numbers passing in and out are equal, so that the concentrations are preserved unaltered.

That this is the true state of affairs there is abundant experimental proof. For let the resting cell divide, and the two daughter cells commence to grow, then the supposed impermeable membrane for potassium ions quits the scene of action, and the growing cell readily takes up potassium ions.

Further proof of the existence of a labile balance of equilibrium is seen in the physiological behaviour of the cell when the appropriate ions are absent from its circulating fluids.

As we have seen in the preceding chapter in describing the effects of inorganic salts upon living cells, in order that the physiological properties of tissues may be maintained in a normal condition, it is necessary that normal amounts of different ions shall be present in the circulating medium. Thus the normal heart-beat cannot be retained unless a certain definite low concentration of potassium ion is maintained in the perfusing fluid. What explanation of this can be given on the basis that the active cells are impermeable to potassium ions? If the cells of the heart muscle are impermeable to potassium ions, how can the presence, or absence, or variation in concentration, of such ions in the circulating fluid affect the physiological activity of the cells? Obviously the cells *are* permeable to the potassium ions and in both directions; for when there is no potassium ion in the circulating fluid, the balance, for potassium ion between circulating fluid and cell contents, becomes upset and corresponding to the low pressure in potassium ion in the circulating fluid, potassium ion must be given out by the cell until a new equilibrium is reached. On the other hand, if potassium ion is present in the circulating fluid at the proper concentration to correspond to and balance the concentration in the cell, then exchange will be equal, the concentration of potassium ion in the cell will not change, and the cell will preserve its normal activities. Finally, if the concentration of the potassium ion in the circulating fluid be greater

than that required to balance the concentration within the cell, then more potassium ion must enter the cell than leaves it, and the effect becomes evident in a change in the action of the cell.

But how, it may be asked, is such a statement to be correlated with that upon which the supposed impermeability of the cell for potassium ions is based, with the fact, namely, that the cell does not appear, as far as chemical investigations go, to take up, for example, potassium ion from a solution of a potassium salt in which it is immersed? The correlation of the two sets of experimental facts is not, however, a difficult task. The explanation lies in the fact that the cell possesses different affinities for the different ions and other dissolved constituents of its circulating fluids, so that at the equilibrium point for normal conditions, the concentrations for each constituent within and without the cell are never equal but bear a definite ratio to each other, and further that these constituents enter into unstable physical or chemical relations with the protoplasm, so that there is a more or less definite minimal concentration for each constituent ion or dissolved substance in the plasma, which might be termed the "dissociation pressure or concentration" for that particular ion or substance at which the protoplasm becomes combined with it. There is an unstable chemical or physical combination formed between the protoplasm and each of the active constituents of the plasma, the existence of which depends upon the osmotic pressure or concentration of the particular constituent in the plasma; just as the existence of the compound oxy-hæmoglobin in the red blood-corpuscles depends upon the partial osmotic pressure of oxygen in the plasma.

Just as in the case of oxy-hæmoglobin but little oxygen is given off until the pressure of oxygen in the plasma has fallen to the level of commencing dissociation of oxy-hæmoglobin, so in the case of the tissue cells in general but little potassium ion is given off until the osmotic pressure of that ion has fallen in the plasma below a certain limit, when the range of dissociation of potassium ion commences.¹ Accordingly it is only at this limit that the change in physiological action of the cell due to diminution of potassium ionic pressure in the plasma begins to become evident.

¹ The concentration of potassium ion in Ringer's solution lies above this limit.

On the other hand, with increasing osmotic pressure of oxygen in the plasma above the point at which oxy-hæmoglobin has been completely formed, there is but little further uptake of oxygen by the red blood-corpuscule; and similarly in the case of the potassium ion, or any other active ion, in the plasma above the concentration at which the protoplasm of the tissue cell has been saturated, the uptake of potassium ion by the cell will be small and inappreciable to chemical investigation, so that even in an isotonic or somewhat hypertonic solution of *potassium salt alone* the amount of potassium ion taken up by the cell will not be appreciably greater to ordinary chemical analysis than that taken up from normal plasma where the osmotic pressure of potassium ion is many times lower, but still sufficiently high to cause almost complete association between the protoplasm and the potassium ion. Although the difference in uptake of either oxygen or potassium ion is so small as to escape chemical determination, it may, however, produce in both cases profound physiological effects, probably from the rapid increase in osmotic pressure of the constituent concerned in the cell after the saturation point has been passed. Thus, although at two atmospheres of oxygen pressure the amount of oxygen dissolved in corpuscles, plasma, and tissue cells is not very appreciably higher than when the oxygen pressure is about 100 mm., yet the activities of the cells become affected and the animal dies in convulsions. So although the uptake of potassium ion by the cell may not be appreciably affected quantitatively when the concentration in the plasma is increased compared to the uptake at a lower concentration, yet the physiological action of the small additional amount upon the cell may be enormous.

It must be remembered that just as in the case of oxy-hæmoglobin there is no absolutely definite pressure which can be spoken of as the dissociation *point*, but rather a short range of pressure, during which association of the oxygen and hæmoglobin occurs, so in the case of other dissolved constituents (ions, organic crystalloids, and anæsthetics) and the tissue cells, there will not be a sharp point, but a range of association with increasing pressure, and the curve of osmotic pressure and association will also vary with each dissolved constituent and each type of tissue cell.

In the case of every active drug, and every active constituent

of the plasma, some such association must occur as the pressure of such constituent in the plasma rises, and dissociation (with recovery in the case of a drug) take place as the pressure falls. No drug or other substance can be active unless it either enters the cell, and forms some combination with the protoplasm, or else prevents in some manner association and dissociation of a like type in the case of some other important constituent necessary to normal protoplasmic activity.

The action of different drugs, their rapidity of action and their dosage, will depend on the nature and extent of the association between them and the cell protoplasm. If the saturation point of the drug and protoplasm is attained at a low pressure and with a low amount of drug, then the amount of the drug necessary to produce the full effect will be small, and in all probability the cell will take up but little of the drug, so that to chemical analysis the uptake may appear to be zero, and yet physiological methods of examination may show that the effect is very profound.

For example, in the case of salts of iron, the saturation pressure must be excessively low, and a proteid substance fully combined with iron contains but a very low percentage of iron, hence the physiological effect of iron may be very large, although the uptake is infinitesimal, and the time required for uptake is large. Thus, in an individual weighing, say, 60 kilograms, the weight of blood would be approximately 4 kilos, that of hæmoglobin about 500 grm., and in this the iron would be about 0.4 per cent., or 2 grm. Therefore in a course of iron treatment lasting over some weeks the amount of iron necessary to be taken up in order to produce a marked effect would be so small as to be entirely beyond the bounds of determination under the conditions of experiment.

Nor does the view of varying permeability of the cell to different dissolved substances, of high permeability for some and low permeability for others, give any better solution to the real problems of secretion and absorption than that of complete impermeability. For the simple reason that variations in permeability form a passive factor like the variation of a resistance, and hence can at most alter the time relations of the process, and not the end results, and so there can on such a basis be no explanation of the fact that work is done by the secreting cell in the process, as when a constituent dissolved substance is secreted at higher concentration

and pressure than in the plasma. Thus if a cell is immersed in a fluid containing any given constituent in solution, it will, if it possesses any degree of permeability whatever for that constituent, become ultimately saturated to the equilibrium point with the constituent, and the point of equilibrium will not vary with the permeability, the only thing which will vary with the permeability will be the time in which equilibrium is attained. In considering the effects of change in permeability upon the time relationships of absorption and secretion, the factors to be borne in mind are the thickness of the layer through which diffusion has to occur, the difference in concentration of the diffusing dissolved substance or ion at the two surfaces bounding the layer through which diffusion is taking place, and the coefficient of diffusion for the particular substance through the layer. The rate of diffusion, regarded as a purely physical process unaided by the cellular activity (and dependent only upon the difference in osmotic pressure at the two sides of the layer or membrane, the thickness and the coefficient of permeability or diffusion), may be said to be directly proportional to the difference in osmotic pressure and to the coefficient of permeability, and inversely proportional to the thickness of the layer or membrane, that is, the length of the absorbing or secreting cell. Hence diffusion can only occur so long as there is a fall in osmotic pressure in the direction in which diffusion is taking place; when the two pressures become equal diffusion must stop, and if by any chance the pressure became greater in the direction in which diffusion had been taking place, then the purely physical process of diffusion would carry out or tend to carry out the process in the opposite direction. Accordingly any separation of a constituent at a higher osmotic pressure must be carried out against diffusion, with increase in osmotic energy, and heaping up of difference in osmotic pressure or increase in the potential factor of osmotic energy.

It is, then, only when the concentration of a substance, either secreted or passing through as an absorption product to the other side of the active cell, is diminished that diffusion due to osmotic pressure can be regarded as a factor in the process, and it is here only that we have to consider the possible effects of changes in the permeability of the cell. If the secreted or absorbed product is carried rapidly away from the other side of the cell after having passed through, so that it does not tend to approach in concentration, as a

result of stagnation, that concentration it possesses in the fluid from which secretion or absorption is occurring, then the rapidity of secretion or absorption of the substance will be greater the thinner the secreting or absorbing cell and the higher its coefficient of permeability. In other words, accordingly, as the cell grows thinner and more permeable, the more nearly will the secretion approach in concentration of its constituents to the fluid from which the secretion has been formed.

In so far as the cell has a lower permeability than the plasma or lymph, it will form a resistance of varying amount upon the rate of secretion, and in so far as the cell has a greater permeability than these fluids it will form a less resistance than a layer of equal thickness of these fluids, and to this extent the increased permeability will aid the rate of secretion. But it must clearly be pointed out that change in permeability can only act as a variation in resistance, and hence the concentration can never be increased, nor the dissolved substance be expedited through the cell at a greater rate than if the cell did not exist on the path, that is, than if the resistance for the length of the cell were zero—in other words, as far as diffusion is concerned the cell can have no positive effect, such as is seen for some constituent or other in every secretion.

Further, it may be pointed out that the extent of the secreting or absorbing surface is in all cases so large, and the thickness of the layer so small, amounting to the length of a single cell, that increase in permeability *above* the value for a layer of lymph or plasma of equal thickness can possess but a very secondary value in determining rate of secretion or absorption. If we imagine the layer of secreting or absorbing cells spread out so as to form a huge plane lamina, the thickness of which is that of a single secreting cell, and the area of the side that of the total secreting area of cells, and that this lamina forms a membrane between lymph upon the one side and secretion upon the other. Then if this lamina were supposed to have the same resistance to diffusion through it as a lamina of lymph of equal thickness, such resistance would be excessively low, and with a rapid removal of fluid from the secretion side the concentration of each constituent upon the secretion side would be practically the same as upon the lymph side of the lamina. Hence the supposition of a higher permeability or selective permeability of the secreting cell above that of the lymph (or water) can have but an infinitesimal effect,

since it cannot increase, as we have seen, the concentration above the value in the lymph, and if it had the value of the lymph (or water) in permeability, the concentrations would be practically the same. It is when the permeability changes in the opposite direction, and the degree of permeability of the secreting or absorbing cell becomes progressively less and less than that of a layer of lymph or water of equal thickness, that the only and indeed an important effect of cell permeability becomes obvious, in slowing, never in hastening, the rate of secretion of constituents. For as the permeability of our imaginary secreting or absorbing lamina to any constituent becomes less and less, its resistance to the passage of that constituent becomes greater and greater, and the concentration of the constituent in the secretion or absorbed fluid less and less, until in the limit none may pass through at all.

It is in such a resisting action that the value of differences in permeability comes in, by causing the retention of substances in the lymph, and not in a high degree of permeability causing increased rate of passage, and increased concentration of substances in secretion. Examples are the retention of the plasma proteids in the glomerular secretion or filtration, and the prevention of ingress of poisonous substances in many cases to the tissue cells. But the greater concentration of substances and ions in the secretions cannot be explained by the application of the principle of altered permeability. Diffusion and permeability can accordingly explain the passage of such substances as are already contained in the plasma up to the concentrations at which they are contained in the plasma, but furnish no means for obtaining substances not present in the plasma, or for concentrating crystalloids or ions in solution to osmotic pressure higher than in the plasma. The latter effects, which are universal in processes of secretion and absorption, can only be obtained from expenditure of energy by the cell.

An attempt has recently been made by Overton and Meyer and by Friedenthal to explain the secretion and absorption of substances by the cell on the basis of varying solvent powers of the cell or certain of its constituents for such substances.

Thus Overton would explain the effects of anæsthetics as arising from the high solubility of the anæsthetic in the *lipoids* or lecithin of the cell, and also the absorption or non-absorption of other substances by the cell as dependent upon whether they dissolve

or not in the lipoid membrane, and hence can obtain ingress to the cell. The author does not state in the case of the anæsthetics whether the action is to be ascribed to the physical action upon the lipoids themselves, or whether it is due to a passage through the lipoids afterwards to the cell protoplasm.

Friedenthal has evolved a similar theory for the absorption of fats in the intestine, which he ascribes to the high solubility of the fats in the protoplasm of the absorbing cells. The theory is also extended to other substances taken up in solution for absorption or secretion, so that these processes are placed in dependence upon the peculiar and selective properties of the cell as a solvent.

The two theories of the lipoid membrane acting as a selective solvent and of the cell protoplasm playing a similar rôle may be taken together, as the same arguments apply to both views.

Neither of these theories furnish any basis of explanation of how energy is expended in concentrating any secreted or absorbed substance. For the fact that a substance, such as the lipoids or cell protoplasm, is a good solvent for a given constituent does not give any power to the solvent to pass that substance through the cell in more concentrated solution, or indeed to alter the concentration of the dissolved substance anywhere *save in the solvent itself*. Further, increased concentration in the solvent has no effect whatever upon rate of passage of the substance through the solvent or through the cell, and will indeed delay passage through the cell until the lipoid or cell protoplasm has become saturated with the dissolved substance, and after that will behave in an inert manner, without any effect either upon uptake of dissolved substance, rate of passage of dissolved substance through the cell, or output of dissolved substance at the other side.

In the statement of the two theories there is a complete confusion of solubility and permeability, which are quite distinct processes.

The matter may perhaps be most easily made clear by means of a diagram.

Suppose we have a sphere of fluid C, surrounded by a continuous layer of a different fluid B, and immersed in a vessel containing a quantity of fluid A, and that A contains a substance x in solution. Further, that the substance is also soluble in the fluids B and C,

and that the coefficient of distribution of the substance x is such between the three fluids, that the concentrations of βx in B and of γx in C correspond to the concentration αx in A, so that there is equilibrium when the ratio of concentrations is $\alpha x : \beta x : \gamma x$ in the three fluids A, B, and C. Now if at the commencement there is none of x in B or C but x is present in A, diffusion into B will take place, and as soon as the concentration of x in B commences to rise there will be diffusion from B into C. Also, the higher the value of the ratio $\beta : \alpha$, the more rapid, other things being equal, will be the rate of entry of x into B; *but* if β be increased so as to increase the ratio $\beta : \alpha$, the ratio of $\gamma : \beta$ which determines the rate of output into C will be correspondingly

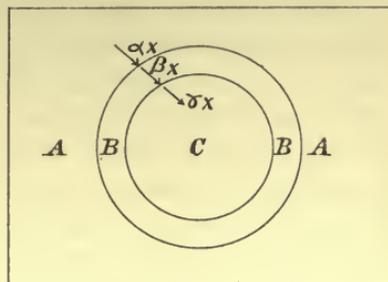


FIG. 4

diminished, and hence the rate of passage from A to C is entirely independent of the solubility in B, and depends only upon the rate of *transmission* or diffusion through B.¹ Also the final condition of equilibrium is independent of the solubility in B, for A and C are each in equilibrium with B, and hence are in equilibrium with one another, so that when the final concentrations are attained the ratio of concentrations in A and C must be the same as if B were left out and A and C had been placed in contact and allowed to come into equilibrium. The only factor which affects the result apart from equilibrium is the rate of diffusion of the substance x through the layer B, and this may not bear any constant relationship to the solubility of x in B. If the solubility in B is very low, so also in all probability will be the rate of diffusion through B; but here, as pointed out above, the extreme thinness of the layer B, in the case of the cell or any cell membrane, and the extent of surface, renders any such factor in most cases of but secondary importance. Certainly, however, solubility in B is not the determining factor with regard to the distribution of the substance *except in B itself*, and in no case can a high solubility in B determine a higher concentration in C than is given by the coefficient of distribution between A and C.

¹ The matter may also be put thus—the rate of solution from A into B is given by $k_1 \frac{\beta}{\alpha}$, that of solution from B into C by $k_2 \frac{\gamma}{\beta}$, therefore that from A into C is given by $k_1 \frac{\beta}{\alpha} \cdot k_2 \frac{\gamma}{\beta}$, or $K \frac{\gamma}{\alpha}$.

We see, therefore, that a high solubility of any dissolved substance in a supposed lipöid membrane or in the cell protoplasm, will cause a corresponding accumulation of that substance in the lipöid membrane or in the cell protoplasm, but cannot act as an engine or energy producer for sending the substance through the cell as a secretion or an absorbed product.

The substance taken up as a result of higher solubility, such as an anæsthetic absorbed by lipöids, or by fat in ordinary adipose tissue, is hence imprisoned to that same extent in the fat or lipöid, and kept from attacking or combining with the protoplasm; and accordingly the presence of such bodies, instead of aiding or causing anæsthesia, act in the opposite sense by forming a reservoir for the anæsthetic where it is inert so far as the cell protoplasm is concerned, which is its real objective so far as production of anæsthesia is concerned.

The view expressed above, that those substances which are actively absorbed and retained by the tissue cells form unstable physical or chemical compounds with the cell protoplasm dependent upon the osmotic pressure of such substances, cannot any more than the others which have been criticised be put forward as an explanation of the active work of the cell in secretion and absorption, when the product is not to be retained in the cell, but is to be turned out in greater concentration than that at which it entered. For substances in such unstable combination, although subject to different laws of relationship between concentration and osmotic pressure, obviously come into equilibrium also at a given point of concentration and osmotic pressure, and hence their formation cannot be turned into a continuous source of energy for the performance of work by the cell, such as is required to fit the case of secretion.

The formation of such unstable compounds is capable of explaining the selective uptake and retention of constituents by the cell, just as the different solubilities of different constituents by the cell protoplasm or lipöids may explain such uptake or retention, but neither view can explain more than this. Before passing on to a consideration of the energy changes involved in secretion, and the possible explanation of such changes, it may be well, however, to point out that the view of formation of unstable chemical combinations between cell protoplasm and selectively absorbed and retained constituents, fits the observed facts much

better than the alternative view of solution in cell protoplasm or in cell lipoids. For if the explanation were solution, then the osmotic pressure and amount of substance taken up must be in simple ratio to each other. On doubling the osmotic pressure of any constituent in the lymph, the amount taken up or secreted by the cell ought to be doubled, since for simple solution the coefficient of distribution between cell and lymph must be constant, or, in other words, the relationship between osmotic pressure and amount absorbed by the cell should be a linear one.

This is not found, however, experimentally to be the case; the absorption at first rises very rapidly with increasing osmotic pressure, then later the rise in amount absorbed for equal increments of osmotic pressure is much decreased, an almost maximum value is later reached, after which there is hardly any appreciable absorption. This sequence of events is precisely what would occur if formation of an unstable or reversible chemical combination took place at a certain range of pressure, and is seen, for example, typically in the combination between hæmoglobin and oxygen. Hence it is most probable that such a type of combination exists in the case of those ions and other cell constituents which are selectively absorbed and retained.

THE ENERGY CHANGES INVOLVED IN SECRETION

The work done by the secreting cell in the process of secretion may be considered as divided into two fractions, viz. (1) the work done in increasing the volume energy, or work done against osmotic pressure in increasing the concentration of dissolved substances already present in the lymph, and (2) the work done in increasing chemical energy by the formation in the cell of new substances not present in the lymph from other substances and by means of the chemical energy supplied by other substances present in the lymph.

It is only for the first of these types of energy production by the cell that accurate quantitative estimations can be made; because for the second type the chemical energy and amounts of the organic substances formed in the cell, and the chemical energy and amounts of substances used by the cell in their formation, are at present unknown to us.

Method of Estimating the Work done against Osmotic Pressure in separating each Constituent of a Secretion.—The amount of work done in separating each constituent of a secretion can easily be deduced when the pressure of the substance in the lymph and in the secretion are known, and the total volume of the secretion. But such estimation must be made for each constituent of the secretion separately, and the total work done is the sum of the work done in the separation of each constituent. It leads to quite a fallacious result to merely take the two depressions of freezing point of the lymph and secretion respectively, calculate the total osmotic pressure of lymph and secretion from these two values, and then assume that the work done is the product of the volume of the solution and the difference in pressure. For the amount of volume energy change, as has been pointed out in a previous chapter, depends upon the two pressures for each constituent between which pressure has varied for that particular constituent, and since in the formation of a secretion the same ratio is not preserved between the pressures of the various constituents as exists in the lymph, but one constituent is far more compressed or concentrated than another, it cannot be taken that the lymph is compressed or concentrated as a whole as it were by a piston impermeable to all the dissolved constituents, and the work done obtained from the total initial and final osmotic pressures and the change in volume, but instead the work done upon each pressure giving constituent must be taken separately, and the total work calculated as the sum of all these fractions.

As demonstrated in a previous chapter, the work done when a gram. molecule of substance is compressed from pressure p_1 to pressure p_2 is given by the expression $RT \log \frac{p_2}{p_1}$, and if Q be any other weight in gram. of the substance and M the molecular weight, then the number of gram. molecules will be $\frac{Q}{M}$, and the expression for the amount of work done in changing the pressure of the quantity Q gram. in solution at pressure p_1 to pressure p_2 will be $RT \frac{Q}{M} \log \frac{p_2}{p_1}$.

If now there are any number of substances A, B, C.....N in solution in the secretion in quantities $Q_a, Q_b, Q_c.....Q_n$, and the molecular weights of the substances be $M_a, M_b, M_c.....M_n$,

and the pressures of the substances in the lymph be represented by $p_a, p_b, p_c, \dots, p_n$, and the corresponding pressures in the secretion by $p'_a, p'_b, p'_c, \dots, p'_n$; then the expression for the work done upon each substance in its production from the pressure in the lymph to the pressure in the plasma will be the same as that given above for a single substance; for example, for substance A the expression will be $\frac{Q_a}{M_a} RT \log \frac{p'_a}{p_a}$. Accordingly the value of the total amount of work done against osmotic pressure (W) will be given by:—

$$W = RT \left(\frac{Q_a}{M_a} \log \frac{p'_a}{p_a} + \frac{Q_b}{M_b} \log \frac{p'_b}{p_b} + \frac{Q_c}{M_c} \log \frac{p'_c}{p_c} \dots \frac{Q_n}{M_n} \log \frac{p'_n}{p_n} \right)$$

or

$$W = RT \Sigma \frac{Q_a}{M_a} \log \frac{p'_a}{p_a}$$

If any of the constituents is electrolytically dissociated, then Q in the expression for the work done in separating it must be multiplied by the dissociation factor, because the osmotic pressure will be higher on account of the dissociation, and correspondingly more work will be done in the separation; thus in the case of the sodium chloride of the urine, for example, at the concentration at which that salt is there separated, it is almost completely dissociated, and Q must be multiplied by the factor 1.9 approximately in order to obtain the amount of work done.

The above investigation of an expression for the amount of work done against osmotic energy in separating a secretion is entirely different from that usually given, which is quite erroneous in that it supposes all the constituents of the secretion to be equally concentrated in the process of separation from the plasma. Such a supposition is wrong in fact, and leads to quite a wrong expression for the total amount of work done, as well as for the work done upon each constituent. For example, while the concentrations of urea in plasma and urine are respectively 0.04 and 2.0 per cent. respectively in human urine, the similar concentrations of sodium chloride are 0.55 and 1.10 per cent.; and hence in the expressions for the work done in secreting urea and sodium chloride respectively the factor $\log_e \frac{p_2}{p_1}$ has quite a different value in the two cases, being $\log_e 50$ in the case of the urea and $\log_e 2$ in

the case of the sodium chloride. As a result, taking the average daily quantities to be 30 gm. in the case of urea, and 16 gm. in the case of sodium chloride, and correcting for the almost complete dissociation of the sodium chloride, a calculation of the work done in the separation in the two cases shows that the amount of work done in separating the urea is nearly six times as great as that done in separating the sodium chloride.

This is quite different from the usual type of treatment, in which it is taken in calculating the work done merely from the lowerings of freezing point of serum and of urine respectively, that the calculation may be based on the supposition that the secretion may roughly be regarded as a concentration of sodium chloride.

The reason of the fallacy is not far to seek, the urea solution is, roughly speaking, concentrated 50 times in the process of secretion, while the concentration of the sodium chloride is barely doubled. If then we imagine the urea and sodium chloride as being separately removed from the plasma by the action of a semi-permeable piston, in the first case impermeable to urea and in the second case impermeable to sodium and chlorine ions and to sodium chloride; then to separate in each case 1500 c.c. of secretion containing in one case 2 per cent. of urea, and in the other case 1.1 per cent. of sodium chloride, from a plasma containing 0.04 per cent. of urea and 0.55 per cent. of sodium chloride, we should require to take in the case of the urea $1500 \times \frac{2}{0.04} = 75,000$ c.c. of plasma and compress down to 1500 c.c., while in the case of the sodium chloride we should only have to take $1500 \times \frac{1.1}{0.55} = 3000$ c.c. of plasma and compress down to 1500 c.c.

Hence to get the true expression for the work done against osmotic pressure in secretion, each constituent must be treated separately, and the work done depends in large degree upon the pressures of the separated constituent in plasma and secretion respectively, and the total molecular amount separated. So that as a result, for example, in the case of the urine, the separation of the urea involves more work than the separation of all the other constituents combined.

As an example of the method of calculating the work done in secretion against osmotic pressure, we may give the calculation of the amount done in secreting the normal daily amount of urea,

viz. 30 grm. in a 2 per cent. solution, measuring accordingly 1500 c.c. The molecular weight of urea is 60, and it is not dissociated, so that there is no correction for dissociation, also the usual figure of 0.04 per cent. may be taken for the concentration in the plasma.

The expression for the work done is

$$W = RT \frac{Q}{M} \log_e \frac{p'}{p}$$

If we express this amount of work as heat energy in small calories the value of the constant R becomes 1.98, if T be taken at 40° C., the value of T in absolute scale becomes 273 + 40 = 313, and hence the value of RT is 620 at this temperature;¹ Q is 30 grm., and the value of M, the molecular weight in grm., is 60, so that $\frac{Q}{M}$ becomes 0.5; the value of the ratio of $\frac{p'}{p}$ is the same as that of the two concentrations of the urea in secretion and plasma respectively = $\frac{2}{0.04} = 50$, and for $\log_e 50$, we can substitute $\log_{10} 50$, on dividing by the Briggs modulus for transference from Napierian to common logarithms, the value of $\log_{10} 50$ is very closely 1.7, and the value of the modulus is 0.434; so that we finally get on making all these substitutions in the above equation, for the value of the work done expressed in small calories:—

$$W = 620 \times 0.5 \times 1.7 \div 0.434 = 1214 \text{ cal.}$$

This amount of energy may be expressed as mechanical work by remembering that the small calory is approximately equivalent

¹ The value of 5.8 rational calories or 580 small calories, given in a previous chapter, was the usual value based on a temperature of 15° C., the value 620 small calories used above is that which the expression RT has at a temperature of 40° C., the approximate temperature of secretion of the urine. The value of 1.98 for R is obtained by using the formula PV = RT, or $R = \frac{PV}{T}$, and then substituting the values for P, V, and T for a grm. molecule at any given values of pressure, volume, and temperature corresponding to one another. Thus a grm. molecule at 0° C. has a volume of 22,330 c.c., a pressure of 76 c.m. of mercury = 76 × 13.4 × 981 dynes, and T is 273 on absolute scale. Also 1 small calory = 42 × 10⁶ dynes, and on substituting these values in the above equation we obtain for the value of R in small calories:—

$$R = \frac{22330 \times 76 \times 13.4 \times 981}{273 \times 42 \times 10^6} = 1.98.$$

to 0.042 kilogram-metres, and multiplying by this factor, we obtain $1214 \times 0.042 = 50.9$ kilogram-metres as the work done by the kidneys in secreting the urea against osmotic pressure. The work done in similarly secreting the sodium chloride is less than 10 kilogram-metres, as can be shown by a similar calculation, and these two form the chief amount of the work done against osmotic pressure, because the amount of the other constituents is comparatively low.

The estimate of 100 kilogram-metres would therefore be certainly above the amount of total work done by the kidneys in the twenty-four hours, and it must be pointed out that this amount is by no means large. Expressed as heat it would only, if it were all taken as heat from the urine secreted, lower the temperature between 1° and 2° C.

The osmotic pressure of a secretion expressed as a hydrostatic pressure may give a very high value; thus Dreser found in the morning urine of man a lowering of the freezing point amounting to 2.3° C., which corresponds to an osmotic pressure of 282 metres of water, or over 30 atmospheres of pressure.

In the urine of other animals still higher osmotic pressures are obtained; thus in the cat an osmotic pressure of 49,800 gm. per square centimetre was calculated by Dreser, and the statement is made that if the work of concentration were carried out by the cells of the kidney tubules, these results would imply that these cells can exert a force six times greater than the absolute force of human muscle (8000 gm. per square centimetre).

Such a statement and such a view as to the action of the cells of the tubules is, however, a highly absurd one. The kidney cells do carry out the work of concentration, but we have no evidence that they exert or resist the least possible pressure in the process. Although the osmotic pressure is so high, the amount of energy change, as is shown by the calculation given above, is comparatively very small, and the work of the kidney cell consists in supplying this small amount of energy, from energy in another form, by transformation of a corresponding small amount of the energy which it takes up as nutrient matter from the plasma. That anything approximating to the osmotic pressure of the separated urine develops in this process of energy transformation, or indeed that there is any pressure developed whatever, we possess not the smallest fraction of experimental evidence. All that is known

is that there is a small increase in osmotic energy, provided by the expenditure of energy by the secreting kidney cell. The view that the kidney cell is something in the nature of a semi-permeable membrane with a difference in pressure upon its two ends of many atmospheres of pressure is an entirely erroneous one; no cell in the body could withstand such a difference in pressure for a moment; there is no evidence that such a pressure exists in the kidney tubules; in fact, it most certainly does not exist. Finally, no arrangement in the nature of a semi-permeable membrane, could form the secretion with accompanying concentration of dissolved substances. In the first instance, because for such an operation, as has already been pointed out, energy is required which a semi-permeable membrane cannot yield. Since an energy machine such as the cell must be utilised for producing the secretion, we at once lose on the introduction of such a machine all necessity for the maintenance of hydrostatic pressure in opposition to osmotic pressure, and there is no more reason why the kidney cells should be supposed exposed to the osmotic pressure than there is to suppose that the walls of the bladder should have to withstand the osmotic pressure of the urine after it has been secreted and passed into the bladder.

In an exactly similar manner, the work done in the secretion of any constituent of any secretion can be calculated if the pressures or concentrations in plasma and secretion, and the amount of secreted substance and volume of secretion are known.

As to the mechanism or type of energy transformation by which the cell does its work nothing is known; similar phenomena of concentration of ions and of dissolved colloids by means of movement in the electric field have long been known, and it is probable that it may be the case that the living secreting cell, by developing differences in electrical potential at its two ends, or by developing differences in energy potential of some other form of energy such as that which intrinsically belongs to the living cell, may establish a directive influence upon substances in solution, as a result of which, and of energy potentials upon the dissolved molecules themselves, they may be caused to move in a definite direction and at a definite speed through the cell, different from that of the water in which they are dissolved. A similar directive movement, in fact, to that seen in the case of dissolved ions and colloidal molecules in the electric field may occur.

Or the energy changes may be brought about by chemical combinations and dissociations in the cell.

But whatever view be taken as to the mode of operation, it is clear from the experimental study of the selective rates of passage of dissolved substances through the cell that what might be termed "polar" properties must be ascribed to the cell in its phenomena of secretion and absorption. This is not theory but experimental fact. It is seen that many substances pass through the cell several times more rapidly than the solvent, while others pass through more slowly. In the case of those which pass through more rapidly, work in giving velocity to these molecules or ions and in increasing osmotic energy must be done by the cell. It is clear from this that the amount of solvent in which any given quantity of a constituent is dissolved need never enter the cell, but instead the dissolved substance be attracted and moved through the solvent toward and into the cell by the energy of the cell; just as independent velocities are given to the ions towards the electrodes by the electric potentials on the electrodes without the solvent between the electrodes moving at the same rate towards either electrode. Thus there may only be a slow current of water through the cell, with a slow uptake of water from the lymph, and a much more rapid current of dissolved substances and corresponding increase in concentration of these in the secretion or absorbed fluid.

If the water containing the dissolved substances were taken up at the same rate by the secreting cell, then in order that the secretion could become more concentrated in any constituent it would be necessary that at intervals water should be returned or pressed out again at the side of the cell at which it entered, containing the constituent which was to be concentrated in more dilute solution. It hence appears more probable that instead of such a to and fro movement of water, the dissolved substances are taken up upon the entrance side of the cell more rapidly than if they passively moved in with a corresponding amount of water.

That this view is probable is seen from the enormous amount of water which would have to pass into and out of the cell alternately if only passive absorption of water and its dissolved substances formed the first stage in the process of secretion. Thus in the secretion of hydrochloric acid in the gastric juice, the con-

centration of the hydrogen ion has to be increased from an almost immeasurably low concentration in the plasma up to about the strength of a deci-normal solution, and to do this by passive absorption an enormous amount of water must enter the secreting cell and be again rejected at the same side at which it entered. Again, in the secretion of urea in the urine 75 kilograms would have to enter and pass through the kidney cells and be reabsorbed in order to concentrate and separate the daily output of urea. Also, in absorption from the intestine, to take up a meal of 150 gm. of carbohydrate or fat in one per cent. solution, which is probably in excess of the concentration at which these food-stuffs are normally absorbed, it would be necessary for 15 kilograms of water to be taken up by the absorbing cells, and either returned by alternating back streams into the intestine free from carbohydrate or fat, or else poured into the blood stream. Such an amount is probably much in excess of the sum of the water taken with the food and the combined digestive secretions.

Hence we must suppose that the cell, whether absorbing or secreting, does not undergo passive infiltration by the fluids in contact with it, and allow these, or even the water, to stream through passively, but is an active energy machine, and takes up the various constituents and their solvent in definite and well-regulated proportions.

For the reason stated at the outset, the amounts of energy involved in the formation by the cell of the new organic constituents of the secretion not present in the plasma cannot at present be estimated, and so we pass to a consideration of the extrinsic mechanisms of secretion.

THE EXTRINSIC MECHANISMS OF SECRETION

Alterations in the Blood Supply to the Secreting Gland.—Accompanying the increased amount of physiological work which the secreting cells have to perform, there is always during secretion an increase in the amount of blood supplied. This increase was estimated by Chauveau and Kaufmann in the case of the sub-maxillary salivary gland as amounting to three times the blood supply in the resting condition of that gland, but according to more recent experiments by Barcroft, it may in the dog be set

down as amounting to more nearly six times the blood supply in the resting condition.

Comparative analyses of the blood gases in the arterial blood, and the venous blood passing from the gland show also, according to Barcroft's experiments, that the amount of oxygen used by the gland, and also the amount of carbon-dioxide formed, as shown by the sum of the increase in the venous blood and the amount in the saliva formed, both increase during activity much above the amounts similarly determined in the case of the resting gland, pointing to increased chemical activity during secretion.

Thus, Barcroft found that during secretion of saliva by the submaxillary gland, induced by stimulation of the chorda tympani, the oxygen taken from the blood was increased to an amount which was three to four times that taken up by the resting gland. The carbon-dioxide given out by the gland was also increased under the same circumstances to an equal or even greater amount. While after an injection of atropin sufficient to cause paralysis of the secretion the intake of oxygen was not increased by stimulation of the chorda tympani, on the other hand the output of carbon-dioxide was increased, at least for a time.

In the case of the pancreas Barcroft and Starling found that the secretion was also accompanied by an increased oxygen absorption from the blood, and that this increased oxidation took place irrespective of increased blood flow through the organ. These observers also found that the normal oxidation in the pancreas was much greater than in the body generally, and about the same as that of the submaxillary gland.

In experiments upon the metabolism in the kidney, Barcroft and Brodie found that the production of diuresis was accompanied by a marked increase in the absorption of oxygen, although there was no direct proportionality in oxygen absorption and degree of diuresis. The authors found no definite relation between the oxygen taken in and the carbon-dioxide given out, and also that the onset of diuresis was not necessarily accompanied by an increase in the rate of blood flow through the kidney, and even where an increased flow was found it was never proportional to the acceleration of the urinary flow.

INFLUENCE OF THE NERVOUS SYSTEM UPON SECRETION

The profound influence of the nervous system upon secretion is in the case of certain glandular structures a matter of common experience. Thus it is well known to us that the sight or smell of food often provokes salivary secretion, or causes the mouth to water, in every-day parlance; but the effect of the nervous system is in the case of other glands most difficult to prove, and may be said in certain cases not even yet to have been unequivocally demonstrated. Certain it is in some cases from the recent experiments of Bayliss and Starling that this nervous stimulation cannot be regarded as the sole, if indeed the most fundamental and important factor; and we shall see in the next section that it must be regarded as supplemented or replaced by the important action of chemical stimulation and the production of specific secretory substances which act upon the secreting cells after having been absorbed by the circulating blood.

As has been well pointed out by Pawlow, it is dangerous, in the case of the nervous mechanisms of secretion, to generalise from the somewhat simple mechanism of salivary secretion, for the secretory innervation of the whole secreting system of glands, for in the case of other glands, such as the gastric glands and probably the pancreas, the influence of inhibitory nervous mechanisms comes into play and complicates the problem. Hence we are forced to consider the nervous mechanisms in the case of each important secreting gland separately.

Before proceeding to the separate accounts, however, it may be well to point out the general resemblances.

In each case where an influence of the nervous system upon secretion has been clearly demonstrated, it has been shown that a complete reflex arc exists. The nervous stimulation is excited at the peripheral endings of afferent fibres, which excite nerve-cells in the central nervous system and cause stimuli to be discharged along efferent paths to the secreting cells. In the case of the salivary glands the afferent channels are nerves of special sense, either the optic or ophthalmic nerves, or the endings of the gustatory nerves in the mucous membrane of the mouth. In the case of the gastric secretion the afferent impulses arise at the mucous membrane of the stomach by the stimulation of peripheral

nerve-endings through the medium of digestible substances present in the stomach, or through nerves of special sense by the sight of appetising food, as has been shown by the experiments of Pawlow.

In all cases, the efferent nervous impulses by which secretion is excited pass along one of two paths, one coming directly from the central nervous system and the other indirectly through the sympathetic nervous system.

In the case of the salivary glands, our knowledge of the efferent paths belongs to classical and well-established physiological history, while in the case of the gastric and pancreatic secretions the efferent channels may be said still to be in dispute, and indeed in the case of the pancreatic secretion the influence of the nervous system at all must be regarded as *sub judice*.

The Innervation of the Salivary Glands.—Each of the important paired salivary glands receives efferent fibres from two sources, viz., directly from a cephalic nerve, and indirectly from the sympathetic system. Over fifty years ago Carl Ludwig showed in the case of the submaxillary gland that the gland possessed a special secretory nerve, the *chorda tympani*, which on stimulation called into activity a copious secretion of saliva. The flow of saliva was large in quantity but poor in organic constituents and in the specific ferment. About twenty-five years later Heidenhain demonstrated that the gland also received secretory fibres from the cervical sympathetic, which evoked a flow of saliva small in total quantity but rich in organic constituents and in the specific ferment produced by the gland.

As a result of his experiments, Heidenhain evolved the theory that the salivary glands possessed two sets of secretory fibres, one obtained from the cephalic nerve and possessing the property of evoking a flow of water and saline, and the other obtained from the sympathetic system and responsible for stimulating the secretion of organic substances and the specific ferment which he termed the "trophic" or "anabolic" nerve.

This view of Heidenhain's was subsequently generalised for secretion in general without adequate experimental proof. In the case of the submaxillary gland, however, it must be admitted, from the clear experimental evidence, that of the two efferent sets of fibres which govern the secretion of the gland, one induces a free flow of dilute saliva poor in organic constituents, while the other causes a scanty flow of a richer saliva. Also, as shown by

Langley, alternate stimulation of the two nerves causes an increase in the amount of saliva which would arise from stimulation of the sympathetic only, and indicates that in normal secretion there is a conjoint action of the two efferent nerves, giving rise to the usual secretion. Hence we must regard the chorda tympani as largely responsible for the flow of water and saline constituents, and the sympathetic as responsible for the stimulation of the gland cells to the production of the organic constituents and ferment.

The Innervation of the Gastric Glands.—The gastric glands, like all the other digestive glands, are supplied by two sets of nerve-fibres, one cerebro-spinal and the other sympathetic. In the case of the stomach the cerebro-spinal fibres are supplied by the vagus and the sympathetic fibres are derived from the solar plexus.

The proof that these fibres possess an effect upon the process of secretion by the gastric glands has, however, been exceedingly difficult to obtain unequivocally by experiment, mainly on account of the important nerve supplies to other organs and regions which accompany the gastric nerve-fibres in the vagus. As a result of this, section or stimulation of the vagus gives rise to profound effects other than those upon the secreting cells of the gastric mucous membrane, which obscure and mask, or interfere with, the effects upon secretion, and hence it was only by ingenious methods of avoiding such results that Pawlow and his co-workers were able to demonstrate that the vagus contained excitatory fibres for the secreting cells. Several of the earlier workers upon the subject found that section of both vagi in the neck led to suppression of the gastric secretion; but this double operation performed at one time leads to such profound disturbances that, as Pawlow points out, it had little effect in encouraging a belief in a causal connection between the vagus-fibres and gastric secretion, since it is not to be wondered at that an operation which in a short time brings the whole functions of the organism to a standstill should amongst other things disturb the action of the gastric glands. An attitude of caution towards the results of an experiment with such drastic consequence was suggested by the further experiment of Schiff, of dividing the vagi beneath the diaphragm in dogs, when, especially in young animals, there was good recovery and the animals lived in excellent health after the operation. Also Rutherford found that gastric secretion could be formed after section of both vagi, or of both splanchnics. Similarly Pawlow

found much more recently that even after double vagotomy the stomach is capable of preparing its specific secretion in the absence of vagal influence.

But, as Pawlow points out, this does not settle the problem as to whether the vagus contains fibres which influence the secretion, and he adduces evidence going to show that the vagus probably contains both excitatory and inhibitory fibres for the secreting cells of the stomach.

It is only by careful comparison of the secretory activity of the stomach before and after vagotomy, and by stimulation of the peripheral end of the nerve in such a manner, or after such procedures, that other effects upon the heart, &c., are not excited, that we can judge as to any possible effect upon secretion.

Previous to Pawlow's more detailed experiments as to the paths along which efferent stimuli pass to the secreting cells, it had been shown fairly clearly that the gastric secretion could be called forth by reflex nervous mechanism. Thus Richet showed in the case of a boy with an inoperable and complete stricture of the œsophagus occasioned by swallowing caustic alkali, upon whom a gastrotomy had been performed, that soon after taking anything sweet or acid into the mouth a secretion of pure gastric juice occurred, which could accordingly only be excited by a reflex nervous stimulus. Bidder and Schmidt also showed that the sight of food in a dog with a gastric fistula led to a flow of gastric juice. The experiment of Richet was, however, an isolated one, and in those of Bidder and Schmidt the stimulus might have been a direct one due to swallowed saliva.

To Pawlow belongs the credit of having devised most ingenious methods for studying the secretion of the gastric juice; the reflex influence of the nervous system upon the secretion, and the efferent path by which the reflex travelled; as also the effects of different forms of food upon the amount and properties of the secretion.

A method for studying the secretion, apart from any influence of the contact of saliva or swallowed food, was obtained by making a fistula of the œsophagus in the neck in addition to the usual gastric fistula. After the double operation the effect of "*psychical*" stimulation could be studied by *showing* appetising food to the animal but not allowing it to chew or swallow it, when a copious flow of gastric juice resulted after a latent period of about five minutes. Also the effect of *sham* feeding was investigated, in which

the animal, in addition to being shown the food, was allowed to chew and swallow it; but the food dropped out at the œsophageal fistula, and did not enter the stomach and so excite it by direct contact. In this method of sham feeding the flow of gastric juice was somewhat greater in most cases than where the afferent stimulus occurred from the sight of food only; but the increase was never very marked, and in the case of some foods which greatly excited the appetite, the psychical juice or "appetite juice" was as great or even exceeded slightly that from sham feeding.

Again, Pawlow was able to study by this method the effect of stimulation of the gastric mucous membrane by means of direct contact of the food, which was introduced into the stomach through the gastric fistula without the knowledge of the animal, when it was asleep, or when its attention was strongly excited in some other direction. In this case there is an absence of the ordinary excitants of appetite in the sight and smell of food, and in the operations of chewing and tasting it. Here it was found that the effect upon secretion varied with the character of the food, and that contrary to what might perhaps have been expected, digestible proteid food did not always prove to be a strong excitant to a flow of gastric juice. Thus milk or a solution of white of egg introduced into the stomach gave rise to scarcely any secretion, not any more than a quantity of water or dilute saline solution. But meat broth, meat juice, or solutions of meat extracts gave rise in all cases after a latent period of a few minutes to a considerable flow of gastric juice. The number of such direct excitants of a flow of juice was, however, found by Pawlow to be small, being almost confined to certain constituents of flesh food, which are also found in meat extracts. Thus, fats, carbohydrates, and ordinary proteids were without any effect.

In the case of flesh food, Pawlow showed that the amounts of secretion obtained by sham feeding and by direct introduction of the flesh into the stomach, when added together approximately, equalled the amount of secretion when the animal ate the food, and the food which dropped out at the œsophageal fistula was placed in the stomach.

Accordingly the excitation to secretion through the nervous system may be divided into three fractions: viz. (1) that due to the sight and smell of the food; (2) that due to the taste, mastication, and swallowing of the food; and (3) that due to the contact

of the food with the stomach. And of these three the first, according to Pawlow's experiments, is responsible for the greater portion of the flow of secretion.

The statement that mere mechanical irritation of the gastric mucous membrane by contact with foreign bodies is an efficient stimulus to provoke a flow of gastric juice is so often made in physiological text-books, that it may be well to state that Pawlow entirely denies such an influence, and states that the most thorough and prolonged irritation of the mucous surface, with a glass rod or feather, or by the blowing of sand into the stomach, is incapable of causing a single drop of secretion.

Another experimental method of great importance devised by Pawlow, both for investigating the effect upon secretion of various forms of foods and for studying the innervation of the glands, was that of forming a miniature stomach completely lined by mucous membrane, and possessing its nerve supply intact, yet completely shut off from the main stomach.¹ Different foods could be introduced into the main stomach by the usual process of feeding, or, in certain other animals in which the method of operation above described of œsophagotomy and ordinary gastrotomy had been performed in addition to the formation of the miniature stomach, the food could be introduced directly, into the stomach, or psychical or sham feeding could be carried on.

Since the mucous membrane is not injured in the operation, and the nerve supply is left intact, the small pouch of mucous membrane isolated becomes a faithful mirror or index of what is occurring in the main stomach. Accordingly the rate of secretion and the quality of the secretion can be studied throughout the whole process of digestion of a meal of any type, and also the innervation of the glands can be tested by observing the effects of section and stimulation of the nerves supplying the stomach.

We may now return, after the above short sketch of the methods by which Pawlow prepared the stomach for experimentation, and observed the reflex effects of the nervous system upon gastric secretion, to the experiments by which the same observer studied the efferent path in the vagus of the reflex excitation of the secretion.

¹ For the details of this ingenious operation the reader is referred to that most interesting book, "The Work of the Digestive Glands," by J. F. Pawlow, English translation by W. H. Thompson; Griffin, London, 1902.

As has already been stated, the other functions of the vagus are so important that the effects of the nerve upon gastric secretion cannot be observed by the usual simple methods of section and of stimulation of the nerve, without certain preliminary operations which allow of section and stimulation without calling forth an interference at the same time with other important functions. The procedures differ somewhat according to whether the effects of section or of stimulation of the vagus are to be tested, and hence it is better to describe each experiment separately.

Effects upon Gastric Secretion of Section of the Vagal Fibres.—The operation is carried out upon a dog in two stages. In the first stage an ordinary permanent gastric fistula fitted with a metallic cannula is made, and in addition an œsophageal fistula, so that the mouth is cut off from all communication with the cavity of the stomach. At the same operation the right vagus nerve is divided below the point of exit of the recurrent laryngeal and cardiac branches, so that on any subsequent section at a later stage of the left vagus the vagal control of the larynx and heart will still be left in action. If at some time after recovery from the operation food is offered to the animal and is eaten, it of course drops out by the œsophageal fistula and nothing reaches the stomach. Under such circumstances, however, and although the gastric fibres of the vagus on the right side have been completely severed, a copious flow of gastric juice is obtained which starts about five minutes after the commencement of the sham feeding. If now the left vagus be dissected out and severed there is no profound general disturbance of functions, because, although the pulmonary and abdominal vagal fibres on both sides are paralysed, the laryngeal and cardiac fibres on the right side are still intact. If a process of sham feeding be now commenced, although the dog takes and swallows the food greedily, no secretion of gastric juice is evoked by the process, not a single drop flowing from the gastric fistula.

In the same animal in which the above procedures had been carried out the right vagus was at a later period divided *in the neck*, yet the animal continued in perfect health and enjoyed its life to the full, although both cervical vagi were now severed. Double cervical vagotomy was also carried out in similar fashion upon a second dog, which survived the double operation for months. In both these animals after the severance of the second vagus,

sham feeding was found never to give rise to a secretion, although often tested.

In addition to demonstrating that the vagus is at any rate the most important efferent channel for reflex stimulation of the gastric secretion, these experiments clearly demonstrate that the profound and fatal effects of double cervical vagotomy carried out at one operation are due to the sudden shock of complete removal of vagal control from the heart, respiratory, and alimentary systems, and that compensation can occur and prevent the fatal result, if the operation be carried out piecemeal.

Although sham feeding calls forth reflexly no flow of secretion after the vagal fibres have been completely severed, it must not, however, be hastily assumed that no secretion can occur under any circumstances after the vagal fibres have been so thrown out of action, for both Pawlow and other observers, as already mentioned, have observed secretion under such conditions. Whether such secretion is due to stimulation through other nervous channels such as the sympathetic fibres, or to absorption of chemical substances which cause direct chemical stimulation of the gland cells, is still doubtful, but recent work goes to show that such direct chemical action upon the cells is a very probable cause of secretion.

Effects on Gastric Secretion of Stimulation of the Peripheral End of the Severed Cervical Vagus.—The experiment of vagus stimulation yields results entirely confirmatory of those obtained by section of the nerve, but similar preliminary precautions are necessary.

After gastrotomy and œsophagotomy have been previously carried out as before described, one vagus (the right) is cut through as before below the cardiac and laryngeal branches, then the other vagus is cut through in the neck, and after a length has been dissected out and attached to a ligature it is left *in situ*, and the wound closed up for a period of three to four days. The stitches are then carefully removed, exposing the nerve for stimulation, and this is stimulated with slow rhythmic induction shocks at intervals of one to two seconds. A secretion of juice is invariably obtained from the empty stomach as a result of such stimulation. The object of waiting for three or four days after section of the vagus is to allow time for the cardiac fibres to degenerate, which process appears to occur earlier than the degeneration of the secretory fibres to the stomach.

After obtaining positive results regarding the efferent function

of the vagus in gastric secretion by this so-called "chronic" method, Pawlow and his co-workers returned to the attempt to obtain evidence by the so-called "acute" method of stimulation of the peripheral vagus immediately after section. The experimental procedure was to perform tracheotomy, so that artificial respiration could be carried on, to cut the spinal cord beneath the medulla so as to throw out reflex action upon the gastric glands, to sever the vagi, keeping the peripheral ends attached to ligatures for stimulation, to establish an ordinary gastric fistula, and to ligature off the stomach from the œsophagus and pylorus. The results of stimulation of the vagus in these acute experiments were not, however, invariably the same; in more than half of the experiments a flow of secretion was obtained, but the latent period was prolonged from the usual five minutes to from fifteen minutes to an hour or more, and the causal connection of a secretion occurring an hour after stimulation has commenced is, to say the least of it, very doubtful. After the nerve had once commenced to work, however, the dependence of the secretion upon the stimulus became more apparent, for on removal of the stimulus the process of secretion gradually stopped, and on renewal of the stimulus, secretion now appeared with greater rapidity. Administration of atropin stopped the secretion. Pawlow explains the long latent period on the assumption that the vagus contains inhibitory fibres as well as excitatory fibres for the gastric glands.

Nothing is known worth recording regarding the action upon the secretion of the sympathetic fibres which run to the stomach. It is almost impossible to find and stimulate these after they leave the solar plexus. It has been stated that gastric secretion still persists after section of the splanchnics; but this fact alone proves nothing as to the possible effect of these nerves in initiating, inhibiting, or controlling gastric secretion.

Innervation of the Pancreas.—The study of the influence of its nerve supply upon the secretory activity of the pancreas has proved one of the most difficult and perplexing of the problems of gland innervation, and we cannot yet be said to be in possession of clear and complete information as to the influence of its nerves upon the physiological activity of this most important gland. But the study of the subject has indirectly led to most important results in the discovery of the fact that gland activity may be called out,

apart from nervous activity, by the chemical action directly upon the gland cells of substances which are formed in cells in other regions away from the gland, and are carried by the blood stream directly to the gland cells.

The subject of chemical stimulation will be treated in a subsequent section, and we shall here deal with the subject of pancreatic innervation which properly leads up to it.

The nerve supply of the pancreas is similar in plan to that of the stomach, being provided by cerebro-spinal fibres coming from the vagi, and sympathetic fibres derived from the solar plexus.

The methods for studying the effect of these nerves upon the secretion of pancreatic juice devised by Pawlow and his co-workers closely resemble those employed in the case of the gastric secretion, with one important exception, namely, that no means was devised similar to the œsophageal fistula for preventing escape of material from the stomach into the duodenum, as a result of, or accompanying, the stimulation of the nerves. This difference is of importance, because it was shown by the workers of the St. Petersburg school themselves that the application of dilute acid solutions or of acid chyme to the duodenal wall gives rise to a copious and long-continued flow of pancreatic juice. This flow was ascribed by these experimenters to a stimulation by the acid of afferent nerve-endings of a local reflex nervous mechanism in the duodenal wall; but it was later shown by Bayliss and Starling, as we shall see in detail in the next section, that the flow of pancreatic juice so obtained was not due to a direct action of the acid upon afferent nerve-endings in the duodenum, nor indeed to nervous mechanism at all, but to a chemical action of the acid upon a substance formed in the duodenal mucous membrane cells which they named *pro-secretin*. This *pro-secretin* is formed during rest in the duodenal cells, and when acid arrives from the stomach is converted into an active substance called *secretin*, which enters the blood stream, is carried to the pancreatic cells, and excites these cells to secretion by acting as a direct chemical stimulus.

For the present, what concerns us here as a preliminary to the description of the experiments of the Pawlow school upon the effect of stimulation of the vagus and sympathetic nerves on the process of pancreatic secretion, is the experimental fact that passage of acid chyme from the stomach to the duodenum

is capable of calling forth a secretion of pancreatic juice. It is accordingly just as important, in experimenting upon the effects of nerve stimulation upon secretion by the pancreas, to make certain that no chyme passes from the stomach to the duodenum, as it is in similar experiments upon gastric secretion to make certain that no food or saliva passes from the mouth to the stomach, upon the importance of which Pawlow himself lays great stress and against which the œsophageal fistula was intended to guard.

The absence of such a precautionary measure seriously invalidates the result of many of the earlier experiments of Pawlow and his collaborators on the effects of vagal stimulation upon pancreatic secretion. Thus, while Pawlow invariably obtained a positive effect upon pancreatic secretion as a result of vagus stimulation after certain preliminary procedures, which will presently be described, had been carried out, Bayliss and Starling were quite unable to find any result upon pancreatic secretion from stimulation of the peripheral end of the vagus. It must hence be regarded as a possibility that in Pawlow's experiments, as a result perhaps of stimulation of movement of the stomach by the vagal excitation, that acid which had escaped from the stomach set free secretin from the duodenal mucous membrane, and this in turn directly stimulated the pancreatic cells. Bayliss and Starling, while not explicitly denying a control of secretion by the vagus, state that they have not in several experiments been able experimentally to demonstrate the fact, and certainly regard the chemical stimulus as the adequate and efficient one.

Hence judgment must be reserved regarding the control of the pancreatic secretion upon the nervous side, and it must be remembered that this serious defect exists in the experiments hitherto made; still the methods used may here be described from their interest as leading up to the discovery of the chemical control, and as the experimental basis of any future attempts at a study of the influence of the gland nerves, when the additional safeguard has been provided of a fistula between pylorus and duodenum, or the separation of these by ligation.

In preparing the permanent pancreatic fistula in the dogs used for the experiments, Pawlow employed a slight modification of the method used by Heidenhain. Heidenhain, in preparing his fistulæ, had completely resected the intestine in order to obtain

a short piece of the intestine into which the pancreatic duct opened, and which was then, after splitting open, attached to the abdominal wall, the continuity of the intestine having of course been restored by suturing together the two ends of the intestine after the removal of the short piece containing the opening of the pancreatic duct. Pawlow improved upon this by merely cutting out a small oval patch of the intestinal wall around the entrance of the pancreatic duct, and then reclosing the intestine, which was only slightly narrowed by this procedure. The small oval patch so removed was then implanted on the outside of the muscular abdominal wall, so that the pancreatic secretion was now poured out to the exterior.

By careful nursing, adaptation of the food, and administration of sodium bicarbonate so as to make good the loss of alkali due to the flowing away of the secretion to the exterior, dogs with such fistulæ could be preserved alive and in good health for a long time, and after recovery could be used for the study of the effect of alterations in the nature of the food upon the amount and quality of the pancreatic secretion, and for the investigation of the effects of the gland nerves upon the process of secretion.

In such an animal, the preliminary procedure to studying the effect of stimulation of the vagus upon the secretory process is to dissect out a portion of the nerve in the neck and cut it, attaching a ligature to the peripheral end. The nerve is then preserved under the skin for a period of four days, in order to allow time for the cardiac fibres to degenerate. After the lapse of this time, the stitches are removed and the nerve stimulated with slow induction shocks. As a result of stimulating, it is found that after a latent period of about three minutes a flow of pancreatic juice commences and gradually increases in quantity. On stopping the stimulus the flow does not instantly stop, but continues in decreasing quantity for a period of four or five minutes from the cessation of the stimulus. Positive results were also obtained by Pawlow by the use of the so-called "acute" method, provided the spinal cord was cut to avoid reflex inhibition from the operative procedures, and the vagus was stimulated below the cardiac nerves so as not to produce disturbance of the heart and circulation. The order of procedure being tracheotomy, severance of cervical spinal cord below medulla, artificial respiration, opening of thorax

and preparation of vagus below the heart, insertion of pancreatic cannula, and slow rhythmic excitation of the nerve.

In using the acute method, evidence of the presence of inhibitory fibres was obtained similar to that mentioned above in the case of the gastric secretion. Thus it was found that after a steady flow of secretion had been set up by stimulation of one vagus, similar and simultaneous excitation of the other vagus often led after a latent period to a suppression of the flow.

An inhibitory influence of the sympathetic fibres was also demonstrated in the case of the acute experiment. The first effect of stimulation of the sympathetic by an induced current was a slight increase in flow; this, however, lasted only for a few seconds, and was followed later, and especially after stopping the stimulus, by a suppression of the secretion. Similar inhibitory results were obtained as a result of mechanical stimulation with the tetanometer, and in a nerve in which degeneration had been allowed to proceed for three or four days a purely inhibitory effect was obtained as a result of electrical stimulation.

The presence of inhibitory fibres in the vagus was also shown by Popielski, by the employment of another method. This observer caused a continuous flow of pancreatic secretion by injection of dilute hydrochloric acid into the duodenum, and then strongly stimulated the vagus, when a slowing of the secretion was always obtained, often to a complete standstill. Excitation of the sympathetic under like circumstances did not produce such a marked effect, but usually gave rise to decrease in rate of secretion after a long latent period.

The important fact that the presence of acids in the duodenum gives rise to a copious and long-continued flow of pancreatic juice was established by Dolinski in Pawlow's laboratory in 1894. The whole mental aspect of the workers in Pawlow's laboratory at that period was directed towards the discovery of the innervation of the pancreas, and hence naturally the flow of pancreatic secretion caused by the presence of the acid in the duodenum was looked upon as a reflex act in which the stimulation of the acid upon peripheral nerve-endings in the duodenal mucous membrane give rise to the afferent impulses.

The secretion set up by the presence of acid in the duodenum was further studied by Popielski and by Wertheimer and Lepage, who showed that secretion was still evoked by the introduction

of acid into the duodenum even after section of both vagi and splanchnics, or destruction of the spinal cord, or after complete extirpation of the solar plexus.

These experiments clearly shut out the central nervous system from participation in the supposed reflex, but the observers, still clinging to the belief that the phenomena before them arose from nervous activity, accommodated their views to the additional experimental facts, by receding to the conclusion that the secretion arose from a *peripheral* reflex act. Popielski concluded, from finding that the secretion occurred after removal of the solar plexus, and also after separating the duodenum with the pylorus from the stomach, but not if the duodenum were cut across a short distance below the pylorus, that the centres for the supposed peripheral reflex were in the scattered ganglia of the pancreas of which the most important were to be found near the pylorus, and were cut off when the duodenum was cut across near to the pylorus. Wertheimer and Lepage accepted the peripheral reflex explanation, but as they found that injection of acid into the jejunum also called out a secretion diminishing in intensity as the distance from the duodenum increased, they came to the conclusion that the centre for the supposed reflex varied according to the region of intestine stimulated by the acid, and that while the secretion in the case of the duodenum might result from stimulation of pancreatic ganglia, that from the jejunum probably was set up by stimulation of the solar plexus. The experiment of injection of acid into a loop of jejunum, after extirpation of the solar plexus, or after severance of the mesenteric nerves of the loop, was not performed by these observers. They found that the secretory effect was not abolished by administration of atropin, but instead of arousing any suspicion that the secretion might not after all be of nervous origin, this fact was only correlated to the absence of effect of this drug upon the sympathetic salivary secretion.

The possibility of the secretion induced by acid in the duodenum being due to chemical action was not unthought of entirely, however, by the St. Petersburg school, and is discussed by Pawlow in his book, in which he states that the acid works either locally by exciting the peripheral end-apparatus of the centripetal nerves in the mucous membrane, or else it is absorbed into the blood and stimulates either the secretory centre or the gland cells

directly. The view that the acid produces its effect by absorption into the blood is then negatived by Pawlow, from theoretical considerations, as well as from the fact that injection of acid into the rectum was without effect upon pancreatic secretion.

It did not occur, however, to the discoverers of the secretion of the pancreas as a specific result of the presence of acids in the duodenum, that there was a third hypothesis, namely, that the acid might awaken an internal secretion in the duodenal cells, and that the substance so secreted might travel in the blood stream to the pancreatic cells and set them in activity.

This view did occur to Bayliss and Starling, who, on testing it experimentally, found it to be the correct one, and so not only brilliantly supplemented the work of the St. Petersburg school on pancreatic secretion, but made a new departure in our knowledge regarding secretory processes, and opened up a new field to research which is now being explored for other secretions.

THE CHEMICAL MECHANISMS OF SECRETION—CHEMICAL EXCITANTS OF SECRETION OR HORMONES

Pancreatic Secretion and Secretin.—The apparently local character of the reaction when acid was placed in the intestine, described in the preceding section, led Bayliss and Starling to experimentation upon the subject, from the view that there might here be an extension of the local reflexes, the action of which in movements of the intestinal wall these observers had already investigated. It was soon found, however, that the phenomenon was one of an entirely different order, and that the secretion of the pancreas is normally called into action not by nervous agency at all, but by a chemical substance formed in the mucous membrane of the upper parts of the small intestine under the influence of acid, and carried thence by the blood stream to the gland cells of the pancreas. To the active substance the name *secretin* has been given by the authors.

In the earlier experiments of Bayliss and Starling, dogs were used, but in a later research other animals were used (rabbit, cat, and monkey), and it was demonstrated that the reaction is a general one for all vertebrates.

The animals received an injection of morphia previous to the

experiment, and during its course were anæsthetised with A.C.E. mixture. In order to keep the condition of the animals constant during the experiment, artificial respiration was resorted to, and a constant depth of anæsthesia was attained by placing the anæsthetising bottle in the air circuit; this procedure is especially necessary when the vagi have been cut. The animals in the earlier experiments had not been fed for a period of eighteen to twenty-four hours, but in later experiments it was shown that secretin is active no matter what may be the state of digestion. In order to avoid shock and to keep up the temperature, the animal was immersed in a bath of warm physiological saline throughout the experiment, the level of the fluid was above that of the abdominal wound, so that the intestine was bathed with the warm fluid. The arterial pressure was always recorded by means of a mercurial manometer connected with the carotid artery in the usual way. The pancreatic juice was obtained by placing a cannula in the larger duct which enters the duodenum on a level with the lower border of the pancreas. To the cannula was connected a long glass tube filled at first with physiological saline; the end of this tube projected over the edge of the bath, so that the drops of the secretion fell upon a mica disc cemented to the lever of a Marey's tambour; this was in connection by means of rubber tubing with another tambour which marked each drop upon the smoked paper of the kymograph. A time tracing was taken showing intervals of ten seconds, and an injection signal was arranged to indicate the point at which acid was injected into the intestine, or a preparation of secretin into a vein, in which a venous cannula had been placed in the usual way.

The authors first confirmed the results of previous experimenters as to the effects of injection of acid into the duodenum or jejunum, and found that the result of injecting from 30 to 50 c.c. of 0.4 per cent. hydrochloric acid into the lumen of the duodenum or jejunum is to produce, after a latent period of about two minutes, a marked flow of pancreatic juice. This effect is still produced after section of both vagi, section of the spinal cord at the level of the foramen magnum, destruction of the spinal cord, section of the splanchnic nerves, extirpation of the solar plexus, or any combination of these operations.

The next step in the chain of evidence was to test the effect of injection of acid into a loop of the upper part of the intestine

after severing the mesenteric nerves. Such a procedure was impossible for anatomical reasons in the duodenum, but was successfully carried out with a positive result on a loop of jejunum.

In this crucial experiment the loop of intestine was completely cut off from all nervous connection with the pancreas, and hence the conclusion is an inevitable one that the effect must be produced by some chemical substance finding its way into the circulation, and then either directly or indirectly stimulating the pancreatic cells.

It must be admitted here that the process of severing all the network of sympathetic nerve-fibres surrounding the blood-vessels passing to the intestinal loop is a difficult one, and it is hard to make certain that it has been effectually carried out, so that it would have been well to insert in this experiment small cannulae into the completely severed artery and vein of the loop. But, as Bayliss and Starling point out, the experiment was that which led to the discovery of *secretin*, the specific chemical excitant, or *hormone*, of the pancreatic secretion. Also the effects about to be described of injection of extracts of the duodenal or jejunal mucous membrane prepared by the action of dilute acid clearly demonstrate a local action of the secretin upon the pancreas.

The positive result obtained in the experiment with the enervated loop of intestine, taken in conjunction with the result obtained by Wertheimer and Lepage, that acid itself introduced into the circulation has no effect upon the pancreatic secretion, led Bayliss and Starling to the view that the acid must give rise to some active substance in the cells of the mucosa which is taken into the circulation and produces the specific effect. This view was then abundantly confirmed by the results of experiment. The loop of jejunum from which the positive result was obtained was cut out, the mucous membrane scraped off, rubbed up with sand and 0.4 per cent. hydrochloric acid in a mortar, filtered through cotton wool, and the extract injected into a vein. The result was a flow of pancreatic juice at more than twice the rate produced at the beginning of the experiment by introduction of acid into the duodenum. Two further results were obtained in the same experiment: first, it was shown that the acid extract could be boiled without losing its activity, so that the active substance (*secretin*) was shown not to be a ferment; and secondly, it was shown that the activity of extracts of portions of the small

intestine taken at different levels showed a decreasing amount of activity as the intestine was descended, corresponding to the known effects upon the pancreatic secretion of injection of acid

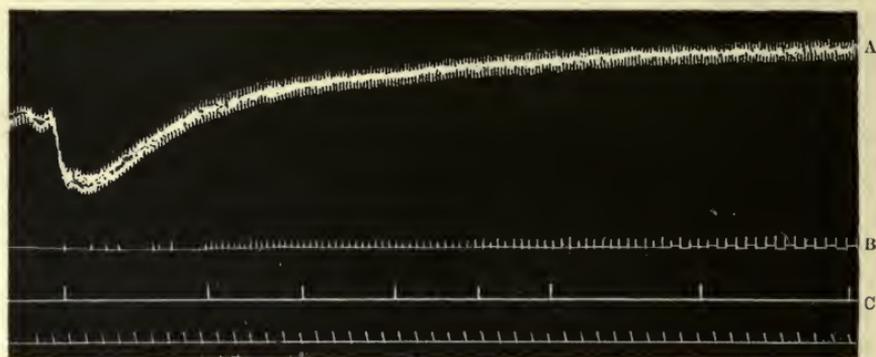


FIG. 5.—Action of Acid Extract of boiled and washed Mucous Membrane of Duodenum. A, Blood Pressure; B, Drops of Pancreatic Juice; C, Drops of Bile. (*Bayliss and Starling.*)

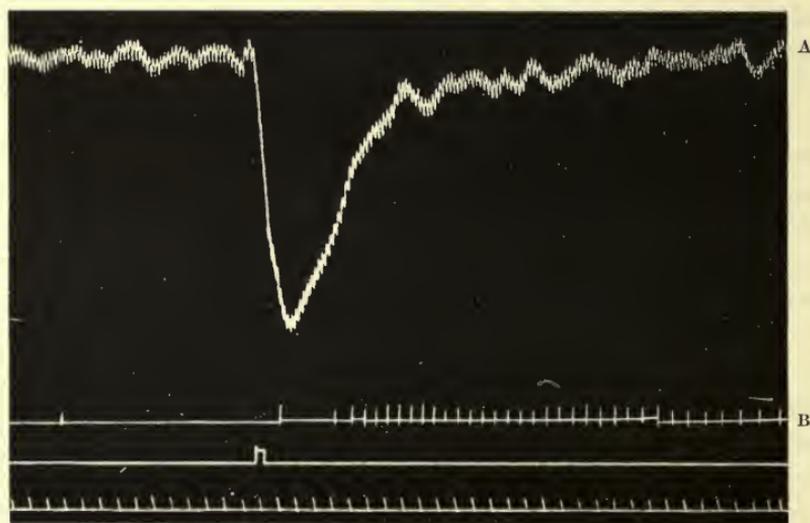


FIG. 6.—Action of Acid Extract of Mucous Membrane of Duodenum which had been dried after Dehydration by Alcohol. A, Blood Pressure; B, Drops of Pancreatic Juice. (*Bayliss and Starling.*)

into these various portions. Thus injection of acid into a loop from the lower end of the ileum gives rise to no pancreatic secretion, and corresponding to this, an acid extract from the mucous

membrane of the lower end of the ileum possesses when intravenously injected no exciting effect upon the pancreatic secretion.

With regard to the seat of action of secretin, Bayliss and Starling have traced it as far as possible towards the periphery, and conclude that it acts in all probability directly as a chemical excitant upon the secreting cells of the pancreas. It is impossible with our present experimental methods to exclude a possible action upon the nerve cells and fibres in the pancreas itself; just as it is impossible to do so in the case of tracing towards the periphery the seat of action of any drug or other active substance—for example, to exclude an action of adrenalin upon nerve cells or endings upon the muscular walls of small arteries rather than upon the muscle cells directly. But it has been shown that the excitatory effect upon the pancreatic secretion is still obtained after the gland has been cut off, as far as is experimentally possible from the anatomical relationships, from connection with nervous mechanisms, both central and peripheral. The sensitiveness of the pancreas renders practically impossible the experiment of perfusion of whipped blood containing secretin through the excised gland.

Certain physical and chemical properties of secretin solution have also been investigated by Bayliss and Starling and W. A. Osborne, as well as the properties of the pancreatic juice secreted as a result of the action of secretin; the results are summarised in the following conclusions, taken from Bayliss and Starling's paper:—

1. The secretion of the pancreatic juice is normally evoked by the entrance of acid chyme into the duodenum, and is proportional to the amount of acid entering (Pawlow). This secretion does not depend on a nervous reflex, and occurs when all the nervous connections of the intestine are destroyed.

2. The contact of the acid with the epithelial cells of the duodenum causes in them the production of a body (secretin), which is absorbed from the cells by the blood current, and is carried to the pancreas, where it acts as a specific stimulus to the pancreatic cells, exciting a secretion of pancreatic juice proportional to the amount of secretin present.

3. This substance, secretin, is produced probably by a process of hydrolysis from a precursor (prosecretin) present in the cells,

which is insoluble in water and alkalies and is not destroyed by boiling alcohol.

4. Secretin is not a ferment. It withstands boiling in acid, neutral, or alkaline solutions, but is easily destroyed by active pancreatic juice or by oxidising agents. It is not precipitated from its watery solutions by tannic acid, or alcohol and ether. It is destroyed by most metallic salts. It is slightly diffusible through parchment paper.

5. The pancreatic juice obtained by secretin injection has no actions on proteids until "enterokinase" is added. It acts on starch and to some extent on fats, the action on fats being increased by the addition of succus entericus. It is, in fact, normal pancreatic juice.

6. Secretin rapidly disappears from the tissues, but cannot be detected in any of the secretions. It is apparently not absorbed from the lumen of the intestine.

7. It is not possible to obtain a body resembling secretin from any tissues of the body other than the mucous membrane of the duodenum and jejunum.

8. Secretin solutions, free from bile salts, cause some increase in the secretion of bile. They have no action on any other glands.

9. Acid extracts of the mucous membrane normally contain a body which causes a fall of blood pressure. This body is not secretin, and the latter may be prepared free from the depressor substance by acting on desquamated epithelial cells with acid.

The Chemical Mechanism of Gastric Secretion—Gastrin.—It has long been known that the introduction of certain substances into the stomach provokes a secretion of gastric juice, and the effect has been ascribed to a nervous mechanism stimulated by the effect of absorbed substances upon peripheral nerve-endings in the gastric mucosa. Quite recently, however, it has been shown by Edkins, that intravenous injection of extracts prepared in special manner from certain parts of the gastric mucous membrane leads to a flow of gastric juice. Edkins considers this action to be due to a substance which he has named *gastrin*, and which acts as a chemical excitant or "hormone" for the gastric secretion, in a similar fashion to secretin in the case of the pancreatic juice. It is hence possible that those substances shown by Pawlow to excite the gastric secretion when introduced into the stomach so as not

to call forth a psychical flow, as by the use of a sound, or better, through a gastric fistula without attracting the animal's attention, produce their effect not by exciting peripheral nerve-endings in the gastric mucosa, but by means of a chemical action upon the secreting cells. This action may either be a direct one of the substances themselves or more probably, according to Edkins's observations, an indirect action in which these substances, similarly to hydrochloric acid in the case of the duodenal mucosa, set free an active substance chiefly from the pyloric portion of the gastric mucosa. This substance, after being absorbed by the blood stream, is carried to the secreting cells lying deeper in the mucosa, and also to the secreting cells of the fundus, where it acts as a chemical stimulant, and calls forth secretion.

Edkins has studied the effects of intravenous injection of extracts made from different parts of the gastric mucosa. He placed a certain amount of saline in the stomach, and then determined the amount of acid formed in the stomach after the injection of each extract to be tested into a vein by titrating this saline for total acidity.

The results obtained were as follows :—

“ If an extract in 5 per cent. dextrin of the fundus mucous membrane be injected into the jugular vein, there is no evidence of secretion of gastric juice. If the extract be made with the pyloric mucous membrane, there is evidence of a small quantity of secretion. With dextrin by itself there is no secretion.

“ Extracts of fundus mucous membrane in dextrose or maltose give no secretion; extracts of pyloric mucous membrane give marked secretion; dextrose or maltose alone bring about no secretion.

“ If extracts be made with commercial peptone, it is found that no secretion occurs with the fundus mucous membrane, a marked secretion with the pyloric mucous membrane; the peptone alone gives a slight secretion.

“ If the extracts be made by boiling the mucous membrane in the different media, the effect is just the same, that is to say, the active principle, which may be called ‘gastrin,’ is not destroyed by boiling.

“ Finally, it may be pointed out that such absorption as occurs in the stomach apparently takes place at the pyloric end. In the pig's stomach, in which the cardiac region differs from the

ordinary type in only having simple glands as in the pyloric, extracts of the cardiac region in general have the same efficiency in promoting secretion as do pyloric."

The media most powerful in calling forth secretion in these experiments are hence those containing the products of advanced salivary digestion, or of peptic digestion, viz. glucose, maltose and commercial peptone, and the region from which active preparations can be prepared being the pyloric mucous membrane, which also is the region in which any slight absorption in the stomach occurs, the indication of the experiments is that the precursor of the active gastrin is formed in the pyloric mucosa, and is activated by the absorption of these digestive products, and discharged into the blood stream, whence it reaches the gastric secreting cells.

The earlier experiments of Pawlow upon those substances which excite gastric secretion on introduction into the stomach are of interest in the light of these later experiments on intravenous injection. Thus introduction of water into the stomach, *even after section of both vagi*, always gave rise to a secretion, although not a very copious one; here there is a good deal cut off from central control, as the vagi are clearly, from Pawlow's other experiments, the most important efferent nerves for gastric secretion, and it would be most interesting to know if this secretion on the introduction of water also occurred after more profound interference with the central nervous system connections, *e.g.* if it still took place after destruction of the spinal cord and extirpation of the solar plexus.

Alkaline solutions, such as sodium bicarbonate, were found by Pawlow to exercise an inhibitory effect upon gastric secretion. Fresh meat and meat extracts were found to be the most powerful excitants, and research is required to test whether this action is nervous or chemical in origin. Starch and fat were found by Pawlow not to excite secretion on direct introduction without psychical stimulation. Bread and solution of egg-albumin also were found to be non-excitants, but the fluid digestive products from the stomach of another dog which had eaten egg-albumin, when introduced without psychical effect directly into the main stomach, gave a stronger and more constant effect than a like quantity of water.

The above experiments upon the effects of chemical stimulants

formed in the cells of the body itself upon the activity of the secreting cells of pancreas and stomach open up to physiological research a field of great importance, and one with practical bearing for medicine and organo-therapy. Doubtless similar actions occur elsewhere in the body which will in the future be brought to light. Bayliss and Starling in their paper briefly draw attention to what they term the *chemical sympathies* between uterus and mammary gland, and to the modifications in the composition of the pancreatic juice accompanying long-continued change in the diet, such, for example, as the production of a laccase as the result of milk feeding, and call attention to the advisability of a renewed investigation of these facts from the point of view of the production in such cases of bodies allied to secretin. There is no doubt that in many cases the stimulus to seasonal functional activity of organs may be a chemical one. In this connection also might be mentioned the occurrence of menstruation, and the seasonal recurrence of rut in cattle, also the absence of these during pregnancy accompanying the changed chemical metabolism at such a period, and the chemical changes going on in the corpus luteum of the ovary.

Thus the field of "internal secretion," which first began to be explored in the case of the ductless glands, the thyroid and suprarenal, goes on widening in scope, and we learn afresh that an organ or cell, in addition to its most conspicuous function, may possess other and no less important chemical activities.

Effects of Food upon the Production of the Digestive Secretions.—A number of most interesting and valuable observations have been published from the Pawlow school, upon the effects of different foods on the rate of secretion, and variations in this during the period of digestion, and on the alterations in the quality of the secretion resulting from the intake of different foods, and continuance upon different diets for more prolonged periods. The series of experiments upon these points are very extensive, and only a summary of results can be included in this article; a good account of the matter is contained in Pawlow's book on "The Work of the Digestive Glands" (translated by W. H. Thompson).

1. Secretion under normal conditions only commences as a result of food being taken into the alimentary canal. The miniature

stomach does not secrete during inanition, but commences a few minutes after a meal. The quantity of juice from a pancreatic fistula during hunger amounts to only two or three c.c. per hour, but some time after a meal increases to many times that amount.

2. The quantity of juice secreted in the case of the same food is directly proportional to the quantity of food taken. Thus for raw meat, for 100 gm., 26 c.c. of gastric juice were secreted; for 200 gm., 40 c.c. of juice, and for 400 gm., 106 c.c. On a mixed diet of meat (50 gm.), bread (50 gm.), and milk (300 c.c.) 42 c.c. of gastric juice were secreted, for double these quantities 83.2 c.c. were secreted.

3. The secretion is not all poured out rapidly at the beginning, but is distributed throughout the period of digestion, and the curve of quantity secreted and time varies for the different types of food. Each food possesses a modifying effect both upon the quantity and quality of the secretion. Also the presence of one food has a modifying power upon the secretion called forth by another, and on the whole course of digestion.

Thus in the case of gastric secretion of a meal of flesh, bread, or milk respectively. Each separate food corresponds to a definite hourly rate of secretion, and calls forth a characteristic alteration of the properties of the juice. Flesh and bread diet produces a maximum rate during the first hour of digestion, while milk gives the maximum rate during the second or third hour. Tested as to maximum content in ferment during the period of digestion, the greatest activity is found with flesh diet in the beginning; with bread in the second and third hours; and with milk in the last (or sixth) hour. Contrasting the digestive power of the juices for proteid at corresponding periods of digestion in the case of the three foods, the greatest power is found in the case of the flesh diet, the bread comes second, and, in the earlier stages at least, close to the meat, while that on the milk diet is much feebler in proteolytic power.

In the case of the pancreatic secretion, a similar adaptation of the secretion to the nature of the food is seen, and here the changes become more striking, because there is a ferment for each class of food-stuff, and relative variations can be contrasted.

The following table of results by Walther, quoted by Pawlow, gives the variation in secretion (quantity and ferments) of pan-

creatic juice on milk, bread, and flesh respectively. The quantities of each food given are based on the percentages of nitrogen contained in each variety :—

Diet.	Quantity of Pancreatic Juice.	Proteoclastic Strength.	Amyloclastic Strength.	Steatoclastic Strength.
Milk, 600 c.c.	48	22·6	9	90·3
Bread, 250 grm.	151	13·1	10·6	5·3
Flesh, 100 grm.	144	10·6	4·5	25·0

The adaptation of the secretion to the nature of the food requires no comment. Attention may be drawn to the high proteoclastic power of the secretion called forth by the milk, and to a contrast of this with the low proteoclastic power produced by milk in the case of the gastric secretion. In the case of flesh there is the reverse effect. It looks from the figures as if the proteid of the flesh were digested chiefly in the stomach and that of the milk in the intestine.

Similar variation in the curve of rate of secretion and time are found in the case of the pancreas as in the stomach, the curve being characteristic for each food. The form of this curve is altered by the simultaneous presence of different food-stuffs; thus the curve of gastric secretion for lean meat consisting chiefly of proteid, becomes profoundly modified if a small amount of fat or oil be also given: the rate of secretion and amount of pepsin being reduced, and the maximum point of secretion being pushed back to a later point in the period of digestion. Similarly the curve of secretion for flesh is modified by the addition of starch to the flesh meal, so as to come to resemble fairly closely that of a bread meal.

4. When an animal is kept for a long period (some weeks) upon a definite and constant diet, the ferment content of the pancreatic juice becomes adapted to the character of the food. If, for example, an animal which has been fed for some weeks entirely upon bread and milk is brought on to an exclusively meat diet, which in contrast with the other diet contains more proteid but scarcely any carbohydrate, it is found that the power of the pancreatic juice for digesting proteid increases from day to day, while the digestive power for starch progressively diminishes. On reversing the diet

again to bread and milk, similar but inverse changes are observed. The moral from this for practical medicine, which experience had already indicated, is that a sudden change from one régime to another may have a disastrous effect upon the digestive process, by subjecting the glands to a strain to which they have not been adapted. Hence changes in dietary should be brought about slowly and progressively wherever possible, and not by a sudden and sweeping change.

The physiological causes and mechanisms of this interesting adaptation in quantity and quality of the digestive fluids to the nature of the food are as yet obscure to us.

Pawlow, their chief discoverer, ascribed them to a differentiated peripheral nerve supply in the mucous membrane of the alimentary canal, whereby the absorption of different digested food-stuffs stimulated different nerve endings, fibres, and cells, and caused a discharge of correspondingly different efferent stimuli to the gland cells, as also to the variation in amount and kind of psychical stimulation by the variation to sight and smell of different sorts of food.

This explanation was given, however, before the days of Bayliss and Starling's discovery of the chemical excitants to secretion, and the question now remains an open one whether the nervous system has anything, and if so how much, to do with the adaptation of secretion to food, and with the characteristic variations above described of rate and progress of secretion with the nature of the food.

In the light of our new knowledge the whole subject of secretion stands ripe for investigation, and is rich in promise of new additions to our knowledge, of the highest value to physiology and to medicine.

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