flame. Special directions were given to the glass blower about this, because the effect of it would be the production of considerable tension in that part of the glass. Notwithstanding my directions, some of the tubes were rounded off in the lamp and the effect was as I had foreseen. The only one of these ends which I used burst. In the case of ends which have been cut off and not heated, the fracture is confined to the part of the tube outside the apparatus. In the case of the end with rounded edges the outside part was fractured in the ordinary way, and in addition the rounded portion, which was exposed to no difference of pressure, exploded out of sympathy, much after the fashion of a Prince Rupert's drop.

I am continuing this investigation, and I hope shortly to be in a position to be able to communicate further results to the Society.

Croonian Lecture.—"The Chemical Regulation of the Secretory Process." By W. M. Bayliss, F.R.S., and E. H. Starling, F.R.S. Received March 21,—Read March 24, 1904.

In the complex reactions which make up the life of an individual, and the evolution of which has been the determining factor in the individual's existence, we may distinguish two main types; though, as in all attempts at classification of biological processes, the line of division between the two types must be more or less indistinct.

In the first place we have those reactions which depend for their production on some special structural arrangement, and are therefore determinant factors in the evolution of form. In some cases the adaptive production of organs or protective mechanisms may be associated with a direct chemical reaction, as in the formation of protective tissues. In most cases, in higher animals at any rate, such an adaptation will be intimately associated with the development of the central nervous system, of which the peripheral parts of the body must be regarded as the executive mechanisms. In general, however, we may say that this type of adaptation is dependent on the adaptive *growth* of cells.

The second type, the more primitive of the two, involves, in the first place, not so much a change in the growth or arrangement of cells, as a change in the metabolism of pre-formed cells or structures. It may, perhaps, be looked upon as a preliminary to the first type, namely, structural change. It is, however, of special interest, since its mechanism is subject to analysis by physiological methods. Instances of chemical adaptation may again be divided into two groups. In the first place we have the chemical adaptation to the

environment, which is found in all living organisms from the lowest to the highest. This adaptation may be conditioned by changes in the food, or may arise as a reaction to the presence of harmful substances in the surrounding medium. As an example may be mentioned the mould *Penicillium glaucum*, which, as shown by Duclaux,* when grown on calcium lactate forms invertase only; on starch, however, it produces amylase in addition, while on milk it produces a proteolytic ferment and rennet. In the higher animals we have all the complex processes by which an animal reacts to the introduction of living or dead poisons, and which result in the production of an acquired immunity. As part of the same process, if we accept Ehrlich's views, we must include the process of assimilation of food, and the adaptation of an animal to profound changes in its diet.

But in all the higher animals the reaction of any part of the body to external changes involves alterations in its relations to other parts, and there is evolved a complex system of internal correlation of the activities of organs, effected partly by the action of the central nervous system, and therefore determinant of changes in form, partly through means of the internal medium—the blood or similar fluid. This latter mechanism of internal correlation has only recently entered the domain of exact investigation. Thus the profound influence exercised by the thyroid gland on the nutrition of the whole body, specially of the central nervous system, and the production of a substance by the suprarenal bodies which maintains the tone of all contractile tissues in the body, have been disclosed to us during the last 15 years. When chemical adaptation occurs in response to changes either in the environment or in definite organs of the body, the adaptive reaction may affect all cells of the body, or may be specific in the case of certain cells. Only in the latter case will the results be apparent to the morphologist as determinant of form.

The researches which we wish to bring briefly before the Royal Society have reference entirely to the last two groups we have mentioned, and deal with the mechanism of adaptation to changes in the food and the chemical correlation of the activities of different organs engaged in the digestion and assimilation of the food.

As we proceed down the alimentary tract, we find that each cavity has its own set of reactive mechanisms arranged so as to pour on the ingested food a juice which shall dissolve one or more of the constituents of the food. In the mouth, as has been shown by the researches of Ludwig, Heidenhain, Langley, and Pawlow, the mechanism for the secretion of saliva is entirely nervous. The mucous membrane is endowed with distinct sensibilities for different classes of food, and the activity of the salivary glands is excited reflexly according to the nature of the substance present in the mouth. In

* 'Microbiologie,' vol. 2, p. 86.

the stomach, the researches of Heidenhain, and especially of Pawlow,* have shown that the secretion of the gastric juice is, in the first place, controlled by the nervous system, and is excited by appetite, or by reflex impulses arising in the mouth. Only later on, in gastric digestion, does a secretion come on, determined, in some way or other, by the presence and nature of the food in the stomach. This secondary secretion is independent of the central nervous system; but whether it is to be looked upon as a local reflex, or as a chemical excitation, directly or indirectly from the gastric contents, has not yet been determined. As the strongly acid fluid containing the products of gastric digestion leaves the stomach to enter the duodenum, it comes in contact with two other secretions, the bile and the pancreatic juice, which are secreted in such an amount that the duodenal contents become practically neutral. According to Pawlow, the secretion of the pancreatic juice is exactly comparable to the secretion of saliva, and is effected by a nervous reflex. The starting point of this reflex is the stimulation of the duodenal mucous membrane by the chyme, or by substances such as oil, ether, or oil of mustard. Not only is the pancreatic juice turned out into the intestine just at the time when it is required, but, according to Pawlow, the composition of the juice varies according to the food, the proteolytic ferment being increased by a diet of meat, while the amylolytic ferment is increased by a starchy diet. This adaptation of the glandular activity was ascribed by him to a species of "taste" in the mucous membrane. It was imagined that the different constituents of the food excited different nerve endings, which, in their turn, caused reflex activity of different mechanisms in the pancreas itself. The field of these assumed reflexes was considerably narrowed by the researches of Popielski† and Wertheimer,‡ who showed that the introduction of acid into the duodenum was productive of secretion even after destruction of all nerve connections of the pancreas and alimentary canal with the central nervous system, and even after extirpation of the sympathetic ganglia of the solar plexus. It was with a view to determine the mechanisms of this reflex secretion of the pancreas, as well as of the adaptation of the pancreatic secretion to variations in the food of the animal, that we began our researches.

The last-named authors had also shown that the secretion occurred, but in smaller quantities, if the acid was inserted in any part of the small intestine, with the exception of the lower end of the ileum. It was thus easy to examine the effects of the introduction of acid into a loop of ileum in which all nerve connections with the pancreas, or with the rest of the body, had been destroyed. This crucial experi-

* 'Le Travail des Glandes Digestives,' Paris, 1901.

† 'Gazette Clinique de Botkin,' 1900.

‡ 'Journal de Physiologie,' vol. 3, p. 335, 1901.

ment had, curiously, not been performed by previous workers in the subject. On carrying it out, we found that destruction of all nerve connections made no difference to the result of introducing the acid. The pancreatic secretion occurred as in a normal animal. It was therefore evident that we had to do here with a chemical rather than a nervous mechanism. Previous work had narrowed the question down to such a degree that the further steps were obvious. We knew already that the introduction of acid into the blood-stream had no influence on the pancreas; hence the acid introduced into the intestine must be changed in its passage to the blood-vessels through the epithelial cells, or must produce in these cells some substance which, on access to the blood stream, evoked in the pancreas a secretion. This was found to be the case. On rubbing up the mucous membrane with acid, and injecting the mixture into the blood-stream, a copious secretion of pancreatic juice was produced. It was then found that the active substance, which we call *secretin*, was produced by the action of acid from a precursor in the mucous membrane, probably in the epithelial cells themselves. Once formed by the action of acid, it could be boiled, neutralised, or made alkaline, without undergoing destruction. The precursor of the substance (*pro-secretin*) cannot be extracted by any means that we have tried from the mucous membrane. Even after coagulation of the mucous membrane by heat or alcohol, however, secretin can still be extracted from the coagulated mass by the action of warm dilute acid.

The question then arose whether this chemical mechanism represented the normal mode in which secretion of the pancreatic juice was excited by the presence of food in the gut. It had already been shown by Wertheimer that the secretion evoked by the presence of acid diminished as the acid was placed further down in the small intestine, and was absent when the acid was placed in the lowermost section of the ileum or in the large intestine. We found a corresponding distribution of pro-secretin. The most active extracts of secretin were to be obtained from the duodenum. The extracts from the jejunum were less powerful, while those from the lower 6 inches of ileum or from the large intestine were practically inert. The proof that secretin is really carried by the blood to the gland has been furnished by Wertheimer,* who has shown that the blood coming from a loop of intestine into which acid has been introduced, when injected into another dog, evokes in the latter a secretion of pancreatic juice. All authors who have investigated the matter since our first publication on the subject have confirmed our results; but many of them are still loth to give up the idea of a nervous connection between the gut and the pancreas. Pawlow had obtained evidence of the existence of secretory nerves to the pancreas in the vagus as well

* 'C. R. Soc. de Biologie,' 1902, p. 475.

as in the splanchnics. In all his experiments, however, it was difficult to exclude the possibility of the secretion having been excited by the contraction of the stomach or relaxation of the pylorus, causing the passage of some acid contents of the stomach into the duodenum, since both these results may occur on stimulation of the vagus. We have been unable to obtain secretion from stimulation of any nerves in any case where this possibility was excluded, and we are inclined to believe that the chemical mechanism we have described is the *only* method by which the pancreas is awaken to secrete. The inhibition of secretion obtained by some authors in an unanæsthetised animal on stimulation of the vagus is, we believe, a secondary phenomenon due to interference with the blood supply or more probably with the flow of acid chyme from the stomach, or perhaps to the rapid emptying of the upper part of the gut of its acid contents.

Secretin can be split off from its precursor in the mucous membrane by the action of acids or boiling water. Many acids are able to effect this conversion, their power being roughly proportional to their ionic concentration. We have, therefore, concluded that the process is one of hydrolysis. According to Fleig,* a secretin can also be prepared from mucous membrane by the action of soaps, and secretin has been detected in the blood flowing from the loop of intestine into which oil of mustard had been introduced. Fleig regards the secretin produced by the action of soaps as different from that produced by the action of acids; but it is difficult to see on what grounds he makes this distinction, since the action of the secretin prepared in the two ways is identical. The production of secretin by the action of oil of mustard as well as the well-known secretion of pancreatic juice evoked by the introduction of ether into the duodenum, suggests that the hydrolytic dissociation which gives rise to secretin may occur in the living cells as a result of stimulation or severe lesion, since neither of these two substances will produce secretin from an excised and dead mucous membrane.

We have not yet succeeded in determining the chemical nature of secretin, though we have obtained chemical evidence which will serve to exclude certain classes of substances. Thus the fact that it will stand boiling shows that it is neither a coagulable proteid nor a ferment. It is soluble in 90 per cent. alcohol in the presence of ether, but it is insoluble in absolute alcohol and ether. It is slightly diffusible through animal membranes. It can be filtered through a gelatinised Chamberland filter. It is not precipitated by tannic acid, thus excluding bodies of alkaloid nature as well as di-amido compounds. This evidence, slight though it is, points to secretin being a body of relatively small molecular weight and not a colloid. It may be compared to the active principle of the suprarenal glands, adrenalin,

* 'C. R. Soc. de Biologie,' 1903.

which has been obtained in a crystalline form and the chemical constitution of which has been approximately determined. This is, indeed, what one would expect of a substance which has to be turned out into the blood at repeated intervals in order to produce in some distant organ or organs a physiological response proportional to the dose. The bodies of higher molecular weight, such as the toxins, which owe their activity, according to Ehrlich, to the fact that they can be directly assimilated by the cells of the body, and built up into the protoplasmic molecule, always give rise to the production of anti-bodies, a process which, while not preventing necessarily their utilisation in the body, would prevent their acting as a physiological stimulus to certain definite cells. Adrenalin and secretin on the other hand belong to the class of drugs which act by their physico-chemical properties, and whose physiological effect is determined by the total configuration of their molecule. It was suggested to us early in our experiments that the secretion of pancreatic juice, evoked by secretin, was essentially a sudden production of an anti-body; such a sudden production is unknown in the animal body, and the anti-character of the secretion is at once negatived by the fact that secretin can be mixed with a freshly secreted juice without in any way destroying its efficiency.

Like adrenalin, secretin is extremely easily oxidised, and it is probable that it is got rid of in this way from the body, since, even after repeated injections of secretin, it is impossible to find this substance or any precursor of it either in the pancreas, the urine, or other tissues of the body. Just as in the case of adrenalin, so we find that secretin is not specific for the individual or species. An extract of the mucous membrane of the dog will evoke secretion in the pancreas of the frog, the bird, rabbit, cat, or monkey. In the same way the pancreatic secretion of the dog can be excited by injection of secretin prepared from the intestine of man, cat, monkey, rabbit, fowl, salmon, skate, frog, or tortoise. The evolution of this mechanism is, therefore, to be sought at some time anterior to the development of vertebrates.

The action of secretin is not confined to the pancreas. It has long been known that the pancreatic juice, in order to exert its full activity on the food stuffs, needs the simultaneous presence of bile, and the fact that in many cases the two fluids are poured into the duodenum by a common orifice shows the close connection which must exist between them. Digestion of fats is impossible unless both fluids have access to the gut, and even in the digestion of carbo-hydrates, as was shown by S. Martin and Dawson Williams many years ago, the presence of bile greatly hastens the digestive powers of the pancreatic juice. Whenever, therefore, a secretion of pancreatic juice is required, a simultaneous secretion of bile is also necessary. It is

interesting to note that this simultaneous secretion is provided for by the same mechanism by which the secretion of pancreatic juice is evoked. If the flow of bile be determined by measuring the outflow from a cannula placed in the bile duct, it will be found that introduction of acid into the duodenum causes a quickened secretion of this fluid. The same increase in the secretion of bile can be produced by injecting solutions of secretin into the blood stream. This influence of secretin on the liver has been fully confirmed by Falloise. This observer has shown that acid extracts of the intestinal mucous membrane cause an increase in the bile secretion most marked when the extract is made from the duodenum and diminishing as the extract is taken from the lower parts of the gut, that from the lower section of the ileum being quite ineffective.

In some cases the injection of secretin is followed by a secretion of glairy saliva, but this is at once abolished on section of the nerves going to the salivary glands, and is simply a result of the lowering of blood pressure which occurs when any extract of the intestinal mucous membrane is injected into the blood stream. On no other glands of the body has secretin the slightest influence. We must, therefore, regard secretin as a drug-like body having a specific excitatory effect on the secreting cells of the liver and pancreas.

The discovery of secretin has placed in the hands of physiologists the power of controlling the activity of a gland by purely physiological means, and we have taken opportunity of the control thus acquired to investigate the exact character of the changes induced in the pancreas under this physiological stimulus. So far as we can tell secretin has no specific influence on any one constituent of the pancreatic juice. When injected it causes secretion of a juice which is normal in that it resembles the juice secreted on entry of food into the duodenum, and contains a precursor of trypsin, amylopsin, and steapsin. Secretin, in fact, appears to cause the pancreatic cells to turn out the whole of the mesostates which they have accumulated during rest in preparation for the act of secretion. If secretin be injected at repeated intervals until the gland will no longer respond to the injection, it is found on microscopic examination that the cells have discharged the whole of their granules. In sections stained with toluidine blue and eosin the whole of the cells stain blue in marked contrast to the normal resting gland, where one-half or two-thirds of the inner margin of the cells is taken up with brilliantly stained red granules. This effect is not produced in all cases. In some animals we have injected secretin at frequent intervals over a period of 8 hours, and obtained at the end of the experiment a secretion as vigorous as after the first injection. The pancreas in this case was evidently not fatigued, and on killing the animal and examining this organ microscopically, it was found to give the typical picture of a

resting pancreas. One may say, therefore, that under healthy conditions the activity of the pancreas is two-fold in character, and that the normal stimulus of secretin excites not only a breaking down of the protoplasm and a discharge of granules, but also a building up of the protoplasm and a new formation of granules. So marked, in fact, is this power of self-restitution that it is often advisable to diminish the resistance of the animal by bleeding or other means if it is desired to obtain a specimen of exhausted gland.

A study by Mr. Dale of the stages of exhaustion carried out in this way has brought to light a remarkable behaviour in the cells of the pancreas, to which we have no analogies in other secreting glands of the body. After the discharge of the granules the cells seem to undergo a still further involution, losing the whole of their chromophile substance, diminishing in size or undergoing vacuolation, and finally being transformed into cells undistinguishable from those which have long been known as forming the so-called "islets of Langerhans." Mr. Dale has, in fact, shown that in all probability these "islets," which are generally regarded as pre-formed structures, really represent stages in the functional activity of the secreting cells of the gland, and he is of opinion that the activity of the gland is always associated with a cycle of changes in which the islets are formed, to be afterwards regenerated into secreting tissue. Other observers have noted in the embryo a development of secreting tubules from tissue undistinguishable from the "islets of Langerhans," and it is interesting to note that the depletion of the gland caused by long starvation has a similar effect to that caused by over-excitation, namely, the conversion of a large proportion of the gland tissue into "islet" tissue.

Although secretin acts in this apparently coarse manner in turning out all the pre-formed secretory products present at the time in the pancreatic cells, the conditions of its formation determine a close adaptation of the pancreatic activity to the needs of the animal. Formation of secretin depends on the presence of acid chyme in the duodenum. This acid chyme is squirted in small quantities into the stomach at varying intervals after the taking of food. As soon as it enters the gut, secretin is formed in the mucous membrane, absorbed by the blood-vessels and carried to the pancreas, and it will continue to be formed until the secreted pancreatic juice exactly neutralises the acid of the intestinal contents. The presence of an excessive amount of acid in the duodenum is prevented by the reflex pyloric mechanism revealed by the researches of Von Mering and of Serdjunow.* These observers have shown that so long as the contents of the duodenum are acid the pylorus remains firmly closed. As soon, however, as they become neutral or alkaline the pylorus opens and allows a further

* Pawlow, 'Das Experiment,' 1900, p. 17.

quantity of acid gastric contents to enter the duodenum. By this double mechanism, which is partly nervous, partly chemical, it is provided that the acid contents of the stomach shall pass on into the gut only in such quantities as can be dealt with by the secretory mechanisms of the intestine.

One more chain in the link of adaptive reactions may be briefly mentioned. The pancreatic juice, as secreted, contains only a weak proteolytic ferment. But it contains also trypsinogen. As soon as this juice enters the gut it causes a profuse secretion of intestinal juice. This latter contains another ferment, enterokinase, which acts on the trypsinogen, converting it into a body trypsin, one of the most active proteolytic ferments with which we are acquainted.

So far we have dealt only with the correlation of the activities of the cells lining the intestinal tube with those forming the masses of the pancreas and liver, and have seen that a very large part in this correlation is played by a chemical substance which acts, so to speak, as a chemical messenger between these various organs. A striking feature, however, of the pancreas is its alleged power of adapting its secretion to the nature of the food taken in by the animal. It has been stated by Pawlow that according as the food consists chiefly of proteids, carbohydrates, or fats, so do we find a relative preponderance of the ferments acting respectively on each of these three classes of foods. The evidence on which this statement is based, although lending to it considerable support, is not absolutely convincing. Vasilieff* examined the pancreatic juice of dogs which were fed on meat, or bread and milk alternately for periods extending over several weeks for each kind of diet. This observer found that the transition from bread and milk diet to a meat diet caused a rapid rise in the proteolytic power of the juice, which reached its maximum after several days of meat feeding. A return to a diet of bread and milk caused a slower fall in the proteolytic power of the juice, but a rise in the amylolytic power. Similar results were obtained by another pupil of Pawlow—Jablonsky†—who also extended his observations to the fat-splitting ferment. At the time that these observations were made the function of enterokinase was unknown, and it is therefore impossible to say what proportion of the trypsinogen of the juice secreted in these experiments had been converted into trypsin by the small amount of intestinal mucous membrane at the mouth of the duct. While, therefore, we are unable to ascribe much importance to the results as regards the proteolytic power of the juice, there seems no reason to doubt the results obtained by these workers as regards the starch-digesting power of the juice. In 1899 Walther‡ made a series of observations

* 'Archives des Sciences Biologiques,' St. Petersburg, 1893.

† *Ibid.*, 1896.

‡ *Ibid.*, 1899, vol. 7, p. 1.

on a dog with pancreatic fistula in order to determine whether the amounts of ferments secreted were determined by the nature of the food at any given meal. He was satisfied that his results showed that, even without prolonged adherence to one diet, the composition of pancreatic juice was adapted to the nature of the meal taken. His results do not entirely bear out his contentions, as is seen by the following table, in which it will be noticed that although milk contains no starch it evokes the secretion of a large amount of amylopsin, and that meat causes a secretion of more steapsin than does milk, although this latter contains much more fat than the meat diet.

Table I.—Results of Walther's Experiments.

Diet.	Total amount of enzyme secreted.		
	Proteolytic.	Amylolytic.	Fat-splitting.
600 c.c. milk	1044	2310	4125
250 grammes bread	2360	6343	1218
100 grammes meat	1720	2498	4410

Of course Walther, as well as the other observers mentioned, regard the adaptation as determined by the stimulation of special nerve endings in the mucous membrane by each constituent of the food, a conclusion hardly borne out by the results just quoted. Another disturbing factor in these experiments is the large variation in total quantity of juice secreted with different food stuffs.

Table II.—Amount of Pancreatic Juice Secreted for different Food-stuffs (Walther).

Food.	Hours of secretion.									Total amount.
	1.	2.	3.	4.	5.	6.	7.	8.	9.	
600 c.c. milk	8·2	6·0	23·0	6·2	1·75	..	..	..	..	45 c.c.
250 grammes bread	35·5	47·0	20·5	16·5	10·0	12·0	6·5	3·0	..	151 „
100 grammes meat	45·0	52·0	35·0	9·75	..	..	..	..	..	142 „

The quantity of juice secreted will depend on the amount of secretin turned into the circulation, and this, in its turn, on the amount of acid entering the duodenum from the stomach. The

amount of juice will, therefore, be measured by the stay and resistance to digestion of the substance in the stomach rather than to any direct nervous or other influence of the duodenal contents on the pancreas. A repetition of Walther's experiments by Popielski,* working independently, has in fact led the latter to deny altogether the adaptation of the pancreatic juice to the nature of the food. Popielski concludes from his experiments that variations in the juice depend only on the intensity and duration of the stimulus, the intensity of the stimulus determining the amount of enzymes, whilst its duration determines the total quantity of juice.

In the meantime the question had been attacked from another side. It had been shown by Fischer and Niebel† as well as by Portier‡ that watery extracts of the pancreas of the cow, horse, and dog had no influence on lactose. Weinland in 1899 confirmed these results so far as concerns the pancreas of dogs on an ordinary diet free from milk. On the other hand, he found that extracts of the pancreas of dogs, which had been fed for several days on milk, sometimes with the addition of lactose, invariably contained lactase in considerable amount, and these results have been confirmed lately by Bainbridge working in our laboratory. Here then we have a definite instance of adaptation of the pancreas, the pancreatic juice or pancreatic extracts of dogs on normal diet containing no lactase, while the administration of lactose to these animals causes the appearance of lactase in both cases. Since in this case we have to determine, not simply an increase or diminution in the amounts of ferments always present in the juice, but the presence or absence of a definite substance, this was evidently the best starting point for an investigation of the mechanism by which the pancreas can adapt itself to the nature of the food, an investigation which has been carried out and completed by Dr. Bainbridge.

What are the limiting conditions? In the first place the reaction is absolutely specific. Unless the animal is taking lactose in its diet no lactase is ever found in the pancreas or in its secretion. The pancreas of new-born animals, for instance, is quite free from lactase, which, however, makes its appearance 2 or 3 days after birth as the result of the milk diet. The production of lactase is not a direct reaction of the pancreas to the presence of lactose in the blood, since subcutaneous or intravenous injection of lactose does not cause the appearance of lactase in the pancreas. The intestinal mucous membrane of all animals, whether on a milk diet or not, contains lactase and has an inverting action on lactose. It might be thought therefore that the production of lactase by the pancreas was a reaction to the

* 'Centralblatt f. Physiologie,' vol. 17, 1903.

† 'Sitzungsberichte der K. Preuss. Akad. d. Wiss.,' 1895, p. 73.

‡ 'C. R. Soc. de Biologie,' 1898, p. 387.

presence of the products of inversion of lactose in the blood. This was found not to be the case. Subcutaneous injection of galactose for several days was not followed by any appearance of lactase in the pancreas or its juice. Nor was the appearance of lactase due to the increased production of this ferment in the mucous membrane, and its escape into the blood. Injection of an extract of mucous membrane rich in lactase, repeated several days in succession, was not followed by any appearance of lactase in the pancreas. Injection of lactose into the duodenum, and the subsequent injection of secretin after an interval of 1 hour, was inefficacious in causing the appearance of lactase in the pancreatic juice. For the production of lactase in the pancreas, or its juice, it is therefore necessary that lactose should act on the intestinal mucous membrane for some time. The reaction is a slow one, like the adaptation in Vasilieff's experiments, and is certainly not due to the stimulation of certain nerve endings in the mucous membrane by the lactose.

The problem was somewhat similar to that presented by the action of acid in the duodenum, since this introduced into the duodenum produces secretion of juice, whereas, when introduced into the blood stream, it has no effect whatever on the pancreas. The question suggested itself whether, under the influence of lactose, a special secretin was formed in the intestinal mucous membrane which, on access to general circulation, evoked the formation and secretion of lactase by the pancreas. Secretin was therefore made in the usual way (*i.e.*, acidification, boiling, neutralisation, and filtering) from the mucous membrane of milk-fed dogs. The secretion evoked by the injection of this liquid resembled that obtained from the injection of ordinary secretin, and contained no lactase.

Yet it was evident from the results already obtained that lactose must act on the pancreas through the mucous membrane of the intestine. An extract was therefore made from the mucous membrane of the whole small intestine of a milk-fed dog. This was filtered through muslin, and about 10 c.c. injected subcutaneously into a biscuit-fed dog once a day for three days. The dog was then anæsthetised, a cannula placed in its pancreatic duct, and ordinary secretin injected. A flow of pancreatic juice was obtained, and this juice was found to contain lactase. This experiment was performed eight times, and in each case the juice obtained from a biscuit-fed dog which had been injected with an extract of the mucous membrane of a milk-fed dog contained lactase.

Here then at last we have some glimpse into the mechanism of the adaptation of the pancreas to the nature of the food. As the result of injection of lactose some substance which we may call x is produced in the mucous membrane of the small intestine. This substance is carried

by the blood to the pancreas, and there slowly gives rise to the formation of lactase, which is turned out in the juice when secretion is excited by the entry of acid chyme into the duodenum. We have no knowledge as yet as to the nature of this substance x. All we can say is that it is destroyed at a boiling temperature, since boiled extracts of the mucous membrane of milk-fed dogs do not, when subcutaneously injected, cause the appearance of any lactase in the pancreatic juice of biscuit-fed dogs.

Table III.—Effect on Milk Sugar of Pancreatic Juice from *Biscuit-fed* dogs, which had received Subcutaneous Injections during 3 days of Extracts of the Mucous Membrane of *Milk-fed* dogs.

The figures represent c.c. of lactose solution which reduced 50 c.c. Pavy's solution.

Exp.	Controls.		Lactose + pancreatic juice.	Percentage of inversion.
	Solution of lactose.	Lactose + pancreatic juice (boiled).		
1....	7·4	..	6·8	18·1
2....	8·2	8·2	7·6	16·5
3....	8·2	8·15	7·85	9·7
4....	7·95	7·9	7·65	8·5
5....	7·8	..	7·5	8·8
6....	7·0	7·05	6·75	8·1
7....	4·1	..	3·75	20·8
8....	9·25	..	8·2	25·9

Whether the qualitative adaptation of the juice in respect of its trypsin, amylopsin, and steapsin is carried out in a similar fashion we cannot as yet say. We hope that an investigation of the mechanism of this adaptation, which is now proceeding, may throw light, not only on the factors involved, but also on the nature of the substance which is formed in the mucous membrane, and has this marked effect on the activity of the pancreatic cells. Involving, as it does, two distinct sets of cells, this chemical adaptation is more complex than any yet investigated, and shows the intimate relation which must exist between the chemical activities of very different organs of the body.