CROONIAN LECTURES
ON
CHEMICAL CORRELATIONS

STARLING

1905


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Presented to the College by
Ernest H Starling

THE CROONIAN LECTURES

ON

THE CHEMICAL CORRELATION OF THE FUNCTIONS OF THE BODY

DELIVERED BEFORE

THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

ON JUNE 20TH, 22ND, 27TH & 29TH, 1905

BY ERNEST HENRY STARLING, M.D., LOND., F.R.S.

FELLOW OF THE COLLEGE

JODRELL PROFESSOR OF PHYSIOLOGY, UNIVERSITY COLLEGE, LONDON

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LECTURE I.

Delivered on June 20th.

THE CHEMICAL CONTROL OF THE FUNCTIONS OF THE BODY.

MR. PRESIDENT AND GENTLEMEN,—From the remotest ages the existence of a profession of medicine, the practice of its art, and its acceptance as a necessary part of every community, have been founded on a tacit assumption that the functions of the body, whether of growth or activity of organs, can be controlled by chemical means; and research by observation of accident or by experiment for such means has resulted in the huge array of drugs, which form the pharmacopœias of various civilised countries and the common armamentarium of the medical profession throughout the world. The practice of drugging rests on the supposition that the functions of the body can be influenced in a normal direction by such means. I propose in these lectures to inquire how far such a belief is consonant with our own knowledge of the physiological workings of the body; how far, that is to say, the activities and growth of the different organs of the body are determined and coördinated among themselves by chemical substances produced in the body but capable of classification with the drugs of the physician. If a mutual control, and therefore coördination, of the different functions of the body be largely determined by the production of definite chemical substances in the body, the discovery of the nature of these substances will enable us to interpose at any desired phase in these functions, and so to acquire an absolute control over the workings of the human body. Such a control is the goal of medical science. How far have we progressed towards it? How far are we justified in regarding its attainment as possible?

I hope to be able to vindicate to you the assumption which is at the basis of medical practice, and to show that the activities of, at any rate, the large majority of the organs of the body are coördinated among themselves by the production and circulation of chemical substances. The results of physiological researches up to the present justify us in the faith that, within a reasonable space of time, we shall be in the possession of chemical substances which are normal physiological products, and by means of which we shall be in a position to control not only the activities but also the growth of a large number of the organs of the body.

In man and the higher animals, the marvellous adaptations effected by means of the central nervous system are so much in evidence, that physiologists have been tempted to ascribe every nexus between distant organs to the intervention of the nervous system; the more so because by this means an adaptation to changes, internal or external, can be effected in many cases within a fraction of a second. But in the evolution of life upon this earth, this method of adaptation is of comparatively late appearance and is confined almost entirely to one division of living beings —*i.e.*, the animal kingdom. In the lowest organisms, the unicellular, such as the bacteria and protozoa, the only adaptations, into the mechanism of which we can gain any clear insight, are those to the environment of the organism, and in these cases the mechanism is almost entirely a chemical one. The organism approaches its food or flies from harmful media in consequence of chemical stimuli; it prepares its food for digestion or digests it by the formation of chemical substances, toxins or enzymes. In the lowest metazoa, such as the sponges, there is still no trace of any nervous system. The coördination between the different cells of the colony is still determined by purely chemical means. The aggregation of the phagocytic cells round a foreign body is apparently due to the attraction exerted on them by the chemical substances produced in the death of the injured tissues.

With the appearance of a central nervous system or systems in the higher metazoa, the quick motor reactions determined by this system form the most obvious vital manifestations of the animal. But the nervous system has been evolved for quick adaptations, not for the abolition of the chemical correlations which existed before a nervous system came into being. A study of the phenomena of even the highest animals shows that the development of the quick nervous adaptations involves no abrogation of the other more primitive class of reactions—*i.e.*, the chemical ones. Where the reaction is one occupying seconds or fractions of a second the nervous system is of necessity employed. Where the reaction may take minutes, hours, or even days for its accomplishment, the nexus between the organs implicated may be chemical. Already we are able, in many cases, to prove the existence of such a chemical nexus, and to employ it in artificially producing a state of growth or activity, which is in normal circumstances merely a phase in a complex series of physiological changes.

The chemical reactions or adaptations of the body, like those which are carried out through the intermediation of the central nervous system, can be divided into two main classes—(1) those which are evoked in consequence of changes impressed upon the organism as a whole from without; and (2) those which, acting entirely within the body, serve to correlate the activities, in the widest sense of the term, of the different parts and organs of the body.

The first class of adaptations includes the reactions of the body to chemical poisons produced by bacteria or higher organisms, and represents one of the most important means by which the body maintains itself in the struggle for existence. The complicated phenomena involved in the formation of antitoxins, of cytolysins, of bactericidal substances, and such like means of protection, have been the subject of much study of recent years, and their immediate interest to the practical physician renders it unnecessary for me to devote any time to their discussion,

especially as the subject is one to which I have not given any personal attention. The investigation of the second class, that of the correlation of the activities of organs, has by reason of its greater obscurity, or of the greater difficulty of its practical application in medicine, fallen largely to the province of the physiologist, and I therefore propose to deal almost exclusively with those members of this class of reactions which have so far been definitely ascertained.

Before, however, entering into details of any particular correlation, it may be profitable to consider what we may expect to be the nature of the substance which will, in any given case, act as a chemical nexus between different organs. We are dealing here with a question of general pharmacology. As Ehrlich has pointed out, the chemical substances which act on the body or parts of the body, producing physiological or pharmacological effects, can be divided largely into two main groups. Ehrlich's conception of the first group is bound up with his conception of the nature of the living protoplasmic molecule as a living nucleus with side chains of various descriptions. Assimilation of foodstuffs consists in the linking on of the food molecule as a fresh side chain to the central nucleus. The common feature among the substances of the first class is their close resemblance to an assimilable substance or foodstuff. All these substances acquire a close attachment to, or even identification with, the living protoplasm, and as a rule their effects are apparent only after sufficient time has elapsed for their building up into the protoplasmic molecule. To this class belong the numerous bodies, closely allied in their chemical character to the proteids, which are designated as toxins. All are produced by the agency of living organisms. I need only adduce as examples the various products of the pathogenic bacteria, such as diphtheria and tetanus, the poisonous toxins of higher plants, such as ricin and abrin, and those formed as a weapon of offence by higher animals, such as the active principles of the various snake venoms. According to Ehrlich, these all resemble assimilable foodstuffs in that they possess a haptophore group, by which they can anchor themselves on to the living molecule, becoming thus part of its side chains. The toxophore group thus introduced into the living molecule upsets and disorganises its reactions, leading by disorder of one or more functions to the death of the animal. In most cases the toxophore group is specific for some definite tissue or type of cell. Thus tetanotoxin exercises its effect almost entirely on the peripheral sensory neurones. It is doubtful, however, whether the haptophore group is so specific, if we are to accept Ehrlich's conception of the mode of formation of antitoxins; since we may get formation of antitoxins in animals where the toxic effect is entirely wanting.

The idea that these toxins ape the part in the protoplasmic molecule of an assimilable foodstuff does not involve as a necessary sequence the formation of antitoxins or antibodies to the normal foodstuffs. That the power of assimilation is independent of the power to produce antibodies has been shown by van Dungern in a research specially directed to determine this point. This observer found that the proteids of crabs' blood could be injected into the blood stream of the rabbit and undergo assimilation. Being proteids foreign to rabbits' blood, their injection provoked the production in the latter of a precipitin for crabs' blood plasma, but the assimilation of the proteid and the production of the precipitin were found to be absolutely independent phenomena.

The first group of pharmacological substances may be defined as substances presenting many points of resemblance to proteids, potent like enzymes in infinitesimal doses, and giving rise, as a result of their introduction into the body, to a reaction consisting in the production of an antibody.

The substances belonging to Ehrlich's second group, which includes all our common drugs, probably act on the protoplasmic molecule or part of it by reason of their chemico-physical properties or their molecular configuration. It is difficult to give a more definite expression of their mode of action. We know that in many cases slight changes in the molecule, such as the introduction or withdrawal of an ethyl, methyl, or NH_2 group into or from a drug or group of drugs, alter their physiological actions in a regular manner. We know, moreover, that substances of the most diverse constitution, such as the various anæsthetics, may have little more than their fat solvent powers in common. All these drugs, however, are more or less stable compounds, generally to be obtained in a crystalline form and not easily destroyed by heat. On introduction into the body, the incubation period of their physiological effects is generally determined only by the time necessary for their distribution to, and their diffusion into, the cells which they chiefly affect. Although repeated doses of them can set up a certain degree of tolerance, in no case is there any evidence of the formation of a physiological antidote or antitoxin to the poison.

To which of these two groups of bodies must we assign the chemical messengers which, speeding from cell to cell along the blood stream, may coördinate the activities and growth of different parts of the body? The specific character of the greater part of the toxins which are known to us (I need only instance such toxins as those of tetanus and diphtheria) would suggest that the substances produced for effecting the correlation of organs within the body, through the intermediation of the blood stream, might also belong to this class, since here also specificity of action must be a distinguishing characteristic. These chemical messengers, however, or "hormones" (from ὁρμάω, I excite or arouse), as we may call them, have to be carried from the organ where they are produced to the organ which they affect, by means of the blood stream, and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body. If they belong to the first class and are analogous to the toxins, the production of a given substance and its discharge into the blood stream must give rise to the formation of a specific antibody, which must increase in amount with each production of the substance in question and tend therefore to possesses the physiological effects. It might be supposed, though, that in case of these chronic or prolonged [illegible], the formation of an antibody was a process not limited to the organ affected and that, [illegible] physiological adjustment, secretion was scarcely a [illegible] of the antibody [illegible] of the [illegible]. But, as we shall see later, experimental evidence is entirely against this view, which, moreover, is not supported by any known instance of a similar localisation of antibody as a result of [illegible] into the [illegible] of any of the substances which belong [illegible] from them. The formation of antibodies appears to be, not a process of value in the normal physiological life of the organism, but one which has been evolved as a protective means of defence to prevent the spread of infective substances from the spot originally attacked or affected.

We are therefore forced to the conclusion that, if the processes of coordination of activities among the organs of the body are carried out under physiological conditions in any large extent by chemical agencies, i.e. by the discharge of chemical substances into the blood stream, these chemical substances must belong to [illegible] class of substances acting on the body and must fall into the same category as the drugs of our Pharmacopoeia. Among these, indeed, specificity of action is [illegible], and is the basis of their application by pharmacologists. Thus we have drugs elevating or depressing the activity of the nervous system; we can excite secretion in all the glands of the body by pilocarpine; we can stimulate and finally paralyse the preganglionic nerve endings of the sympathetic system by the injection of nicotine, or [illegible] of the heart by the administration of digitalis. In all these cases we are certainly interfering with normal processes. The methods, however, which we employ, are not [illegible] with those made use of by the body itself in [illegible] the harmonious co-ordination of its various parts.

In discussing the internal chemical relations of the body, it will be convenient to divide them into two classes, viz., those which [illegible] (1) [illegible] of other organs, and (2) [illegible] organs. In both cases [illegible] that the [illegible] stimulus [illegible], the first class [illegible] these changes which are [illegible] with activity, and the [illegible]. We might in this speak of the two classes of chemical [illegible] as [illegible] and [illegible].

[illegible] RELATION [illegible] ACTIVITY OF ORGANS.

The most striking [illegible] the [illegible] of this class of [illegible] is that which [illegible] through the [illegible] with oxygen and the removal of its chief waste product, carbonic acid. The increased depth and frequency of [illegible] muscular exertion are [illegible]

neutralise its physiological effects. It might be suggested that, in the case of these chemical messengers, the formation of an antibody was a local one and limited to the organ affected and that, in fact, their physiological effect—*e.g.*, secretion—was actually a pouring out of the antibody to the chemical messenger. But, as we shall see later, experimental evidence is entirely against this view, which, moreover, is not supported by any known instance of a similar localisation of antibody as a result of injection into the organism of any of the substances which belong definitely to the toxin class. The formation of antibodies appears to be, not a process of value in the normal physiological life of the organism, but one which has been evolved as a chemical means of defence to prevent the spread of injurious substances from the spot originally affected or attacked.

We are therefore forced to the conclusion that, if the processes of coördination of activities among the organs of the body are carried out under physiological conditions to any large extent by chemical means—*i.e.*, by the despatch of chemical messengers along the blood stream—these emissary substances must belong to Ehrlich's second order of substances acting on the body and must fall into the same category as the drugs of our Pharmacopœia. Among these, indeed, specificity is not wanting and is the basis of their classification by pharmacologists. Thus we have drugs elevating or depressing the activity of the nervous system ; we can excite secretion in all the glands of the body by pilocarpin ; we can stimulate and finally paralyse the præganglionic nerve endings of the sympathetic system by the injection of nicotine, or arouse the anabolic mechanism of the heart by the administration of digitalis. In all these cases we are certainly interfering with normal processes. The methods however, which we employ, are not at variance with those made use of by the body itself in securing the harmonious coöperation of its various parts.

In discussing the internal chemical reactions of the body, it will be convenient to divide them into two classes—*viz.*, those which involve (1) increased activity of an organ, and (2) increased growth of a tissue or organ. In both cases we must assume that the reaction to the chemical stimulus is itself chemical, the first class including those changes which are chiefly katabolic or dissimilative and are always associated with activity, and the second class involving diminished katabolism and increased building up or anabolism. We might, in fact, speak of the two classes of chemical stimulants as augmentor and inhibitor.

Reactions involving Increased Activity of Organs.

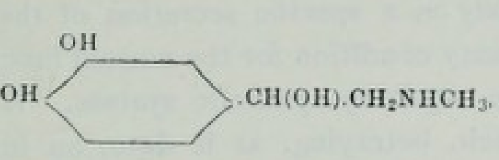
The most striking, because the simplest, of this class of reactions is that which determines in higher animals the adequate supply of a contracting muscle with oxygen and the removal of its chief waste product, carbon dioxide. The increased depth and frequency of respiration contingent on muscular exertion are familiar to everyone, and we know that the physiological object of such changes is to secure the increased ventilation rendered necessary by the enormous rise of gaseous metabolism which accompanies muscular exercise. Even moderate work may raise the gaseous exchanges to between four and eight times their amount during rest. This increase in the respiratory movements is entirely involuntary and may, in its earlier stages, when affecting chiefly depth of respiration, be absolutely unnoticed by the subject of them. How is the respiratory centre aroused to an increased activity which is absolutely proportional to the increased metabolism of the distant muscles? A nervous path is at once excluded by the fact that hyperpnœa or even dyspnœa may be excited in an animal, after division of the spinal cord, by tetanisation of the muscles of the hind limbs. Zuntz and Geppert therefore came to the conclusion that the exciting agent in this increased activity was some acid substance or substances produced by the contracting muscles and transmitted from them through the blood stream to the respiratory centre. The subject has been lately investigated in this country by Haldane and Priestley. In a series of masterly experiments these observers show conclusively that the chemical messenger in this case is none other than carbon dioxide. The contracting muscle, when properly supplied with oxygen, takes up this gas and gives out carbon dioxide in direct proportion to the energy of its contractions. The carbon dioxide diffusing rapidly into the blood stream raises its percentage and, what is still more important, its tension in this fluid. The respiratory centre differs from the other parts of the central nervous system in having developed a specific sensibility to carbon dioxide. Its normal activity is determined by the normal tension of this gas in the blood and lymph bathing the centre. Diminution of the tension of this gas depresses the activity of the centre, causing slackening of respiration or even the total cessation of respiratory movements, known as apnœa.

This work by Haldane may be regarded as finally deciding a question which has been the subject of debate for nearly half a century. The dyspnœa, caused by the circulation of venous blood through the brain or by the deprival of the respiratory centre of the means of maintaining its normal gaseous interchanges, has been variously attributed either to oxygen starvation or to carbon dioxide intoxication of the centre. Haldane shows that the centre is very little sensitive to changes in the oxygen tension of the blood. The oxygen tension in the pulmonary alveoli may be altered from 20 per cent. to 8 per cent. without any increase in the depth or frequency of the respiratory movements. In these circumstances the heart or circulatory system may feel the deprivation of oxygen before the respiratory centre has responded to it. On the other hand, a rise of only ½ per cent. in the tension of carbon dioxide in the alveolar air, and therefore in the blood circulating round the respiratory centre, will increase the volume of air respired 100 per cent.

This simplest of all examples of a coördination of two widely separate organs by chemical means may, perhaps, give us a clue to the mode in which the more complex of such correlations have been evolved. In

this case the chemical messenger is a product of activity which is common to all protoplasm and must be excreted by the cell as a condition of its further activity. The adaptation in this case therefore is not the formation of a special substance which shall exert a specific influence on some distant organ, but the development in this distant organ of a specific sensibility to the common product of excretion of the first organ. We may, perhaps, assume that the more specialised messengers, which we shall have to consider in detail later, were at first accidental by-products of the selfish activity of the organ producing them, the first step in the development of a correlation being the acquisition of a sensibility to the substance in question by some distant organ.

The only other example of such a reaction, in which we know both the source and nature of the chemical messenger and the exact nature of the effects which it produces, is the suprarenal gland. Since the time of Addison we have known that atrophy of these glands in man leads to a disease characterised by the three cardinal symptoms of bronzing, vomiting, and extreme muscular weakness. Most of the attempts to reproduce this disease in animals have failed, owing to the fact that death follows the excision of both glands within 24 hours; the extreme muscular weakness is certainly produced, and this is attended by a profound fall in the general blood pressure. In 1894 Oliver and Schäfer showed that from the medulla of the suprarenals a substance could be extracted which, on injection into the circulation, caused marked rise of blood pressure and increased strength of the heart beat. Since the publication of these observations our knowledge concerning the nature and actions of this substance has progressed rapidly. The researches of Jowett in this country, and of von Fürth in Germany, have shown that the active substance is a definite chemical compound derived from pyrocatechin and having the formula—



Takamine, by the elaboration of a method for its preparation from the gland in a state of purity, has placed in the hands of the druggist a means of supplying the substance in bulk to the medical profession for therapeutic purposes. The exact knowledge of the constitution of adrenalin thus acquired has paved the way for the actual synthetic formation of this substance. Here, again, there has been a keen international rivalry, and the credit of its synthesis must be divided between this country and Germany. It is gratifying that the only original investigation of the subject which has yet been published as a contribution to science is the admirable account by Dakin of his synthesis, not only of adrenalin but of a whole array of substances, which are closely allied to this body in their chemical structure as well as in their physiological influence on the animal organism.

In order to comprehend the point of attack of adrenalin, the specific secretion of the medullary part of the suprarenal glands, we shall do well to go back to the mode of development of these organs. It was shown by Balfour that the suprarenals have in the fœtus a two-fold origin, the cortex being derived from the mesoblastic tissue, known as the intermediate cell-mass, while the medulla is formed by a direct outgrowth from the sympathetic system, and consists at first of an aggregation of neuroblasts. In some animals—*e.g.*, teleostean fishes—the two parts of the gland thus formed remain separate throughout life, but in the higher vertebrates the sympathetic outgrowth becomes surrounded by the cortex, and the cells rapidly lose all traces of resemblance to a nerve cell. But the medulla is genetically part of the sympathetic system, and its specific secretion, adrenalin, has an action which is apparently confined to the sympathetic system. In whatever part of the body we test the effects of adrenalin, we find that they are identical with the results of stimulating the sympathetic nerve fibres which run to that part. Thus, in all the blood-vessels of the body, adrenalin causes constriction; the contraction of the heart muscle is augmented, the pupil is dilated, while the intestinal muscle, with the single exception of the small ring of muscle forming the ileo-colic sphincter, is relaxed. The action of the sympathetic on the bladder differs, as shown by Elliott, markedly in various animals; but, whatever its effect, a similar one will be produced in the same animal by the injection of adrenalin. I have already mentioned that excision of the suprarenal bodies causes a profound fall of blood pressure, which continues until the death of the animal, and it has been stated that, when this fall is well established, it is impossible to raise the blood pressure by stimulation of the splanchnic nerve, or indeed to produce any effect at all on stimulation of the sympathetic nerve. Thus, not only does adrenalin excite the whole sympathetic system in its ultimate terminations, but its presence in the body as a specific secretion of the suprarenal bodies seems to be a necessary condition for the normal functioning, by ordinary reflex means, of the whole sympathetic system. We are dealing here with a problem which, betraying, as it does, an intimate relationship between nerve excitation and excitation by chemical means, promises by its solution to throw a most interesting light on the nature of the nerve process and of excitatory processes in general.

Our knowledge of certain other members of this group of chemical reactions is so shadowy that a mere mention of them will suffice. As an antithesis to the vaso-constrictor action of adrenalin, we find that every organ, when active, is supplied with more blood in consequence of a vaso-dilatation of the vessels which supply it. In certain instances Bayliss and I have found that boiled extracts of organs, when injected into the circulation, may evoke vaso-dilatation of the same organs of the animal under investigation, and we have suggested that the normal vaso-dilatation accompanying activity is brought about in consequence of the specific sensibility of the arterial walls to the metabolites of the organ which they supply. Too much stress, however, cannot be laid upon

these experiments, since a more extended series by Swale Vincent has failed to give a general confirmation of our results.

The severe diabetes which, as shown by Minkowski, can be produced in nearly all animals by total excision of the pancreas, has been held to denote the normal production in this organ of some substance which is indispensable for the utilisation of carbohydrates in the body. All efforts to obtain a more exact idea of the nature of this pancreatic substance or influence have so far proved in vain. Ordinary sugar, when placed in contact with extracts of muscular tissues, undergoes oxidation; and Cohnheim states that this process is much accelerated if an extract of pancreas be added to the extract of muscle. A repetition of Cohnheim's experiments by other observers has shown that the effect is so small as to be almost accidental; and we must therefore regard the nature of the pancreatic influence on carbohydrate metabolism and the causation of pancreatic diabetes as problems still to be solved.

So far (except in the case of the muscle—respiratory centre reaction) we have been dealing with isolated phenomena occurring in different parts of the body, in which the reaction affects a whole series of tissues. The chemical stimulus in these cases might be considered analogous to alterations in the composition of the surrounding medium, and the reaction lack that definite and localised character, which we have learnt to regard as distinguishing the adaptations or reflex actions brought about by the intermediation of the central nervous system. We have now to discuss the mechanism of a whole series of chemical reactions where this feature of a nervous reaction is not wanting, so that the reactions, until quite recently, were regarded as undoubtedly nervous in character. I refer to the chain of processes in the alimentary canal by which the secretion of one juice succeeds that of another as the food progresses along this tube. This series of reactions may well form the subject of a separate lecture.

LECTURE II.

Delivered on June 22nd.

The Chemical Reflexes of the Alimentary Tract.

Mr. President and Gentlemen,—With the first appearance of multicellular animals and the setting apart of a distinct layer of cells, the hypoblast, for digestion and assimilation, the activity of the cells is at first largely analogous to that of the previous unicellular organisms, each cell of the alimentary epithelium seizing and ingesting the food particles which reach the cavity of which the cells are a lining. The digestion is therefore at first largely intracellular, and the ingestion of food particles must be determined partly by chemical and partly by tactile or mechanical stimuli arising in the food particles themselves. In the lowest of metazoa, however, cells are found which exercise their influence on external organisms by the production and excretion of poisonous material, and a similar mechanism is soon evolved in the alimentary tract for the production of digestive fluids. An elementary type of digestive apparatus would therefore be a cavity lined with epithelial cells, which are stimulated to the secretion of digestive juices by the chemical and mechanical stimuli arising from food introduced into the cavity. The increase in these digestive cells, necessitated by the greater bulk and greater activity of the animal arising with the elevation in type, is procured in all the higher animals by the formation of outgrowths of cells from the lumen of the alimentary canal, outgrowths which give rise to the structures which we know as glands. The cells composing these glands are no longer subject to direct stimulation by any food present in the alimentary canal. Each act of secretion of digestive juices must therefore involve the transmission of a message of some sort or other from the lining epithelium of the alimentary canal to the gland in question—a transmission which is apparently analogous in all respects to the mechanism for the production of movements in response to external stimulation. In the higher animals all the motor reactions affecting skeletal muscles are carried out by reflex actions and involve the coöperation of the central nervous system. It is natural to suppose that the similar reactions, affecting the chemical activity of glands, should be carried out in the same way, and the earliest investigations of the influence of the nervous system on glandular activity corroborated in all respects this supposition. The taking of food into the mouth, for instance, is at once followed by a flow of saliva, due to an induced activity of the various salivary glands. This reaction was studied by Ludwig in the first half of the last century, and

the experiments of this investigator showed conclusively that the normal path for the message from mucous membrane of mouth to gland lay through the central nervous system. The nerves involved in the reflex secretion of saliva were determined, as well as their central connections. In such a case as this, where all kinds of material—dry, fluid, pleasant, or harmful—may be taken into the mouth, a rapid response of the salivary glands is necessary to provide for the speedy swallowing of the food or to facilitate its expulsion from the mouth. When the food has once undergone a preliminary warming and moistening in the mouth, and has been passed, so to speak, by the critical organs of taste and smell placed at the commencement of the alimentary tract, a rapid reaction of the other glands of the alimentary canal—*i.e.*, one occupying fractions of a second—would not seem to be absolutely necessary. The predominant part, however, played by the central nervous system in all the most direct reactive phenomena of the body led physiologists to search for similar reflex nervous mechanisms of secretion through the rest of the alimentary canal, and the firm faith that such nervous mechanisms existed was in no way damped by the difficulties experienced in the attempts to determine their existence and their paths. Thus for many years the only known method of exciting gastric secretion was the introduction of irritant subtances into the stomach, apart, that is to say, from the taking of a meal which would excite in physiological fashion a secretion of gastric juice. In the case of the pancreas Heidenhain observed on a few occasions a scanty secretion from stimulation of the medulla oblongata, but could not obtain this result at will. Succus entericus was obtained by some observers from intestinal fistulæ by mechanical stimulation of the mucous membrane, and the so-called paralytic secretion of succus entericus was produced in certain circumstances in a denervated loop of intestine.

These were the sole indications of any influence of the nervous system on the secretions below the mouth until the subject was taken up by Pawlow at St. Petersburg. This observer realised that the last word could not be said on any physiological question until experiments had been made on an animal in an absolutely physiological condition, *i.e.*, with normal blood pressure, free from fear or pain, and unpoisoned by anæsthetics. To effect this aim Pawlow has enriched physiology with a new technique. By the exercise of scrupulous asepis, and aided by his great surgical skill, he has succeeded in making observations on the digestive process in animals by providing them with fistulous openings into different parts of the alimentary canal, or with culs-de-sac which were in nervous and vascular continuity with the rest of the canal, and whose activity could be taken as samples of the activity of the whole organ from which they were cut off. The results obtained by this physiologist seem at first to point to an extension throughout the alimentary canal of processes similar to those occurring in the mouth, and to prove that every gland in the canal is excited reflexly through the central nervous system by the presence of the foodstuffs in different stages of digestion at the appropriate part of the lumen of the canal.

Thus the mere sight of food or the taking of pleasant food into the mouth excites reflexly through the vagi a reflex secretion of gastric juice, and this secretion can be also evoked by artificial stimulation of the peripheral end of a cut vagus. The passage of acid chyme, of water, or oil, from the stomach into the duodenum excites the flow of pancreatic juice, the efferent channels, according to Pawlow, for the reflex being both the vagi and the splanchnic nerves, since secretion of pancreatic juice can be evoked by stimulation of either of these nerves. The secretion of succus entericus is less distinctly due to the intervention of a distant nervous system, since it occurs under two conditions—namely, (1) mechanical distension of the gut; and (2) introduction of inert pancreatic juice.

Previously to the publication of Pawlow's results, no physiologist had succeeded in obtaining an invariable secretion of either gastric or pancreatic juice as the result of stimulation of any nerves. A few years after the description by Pawlow of the production of pancreatic secretion by stimulation at some point in the long reflex path, *viz.*, from intestinal mucous membrane, through medulla and vagus or splanchnics to pancreas —it was shown by Wertheimer in France and by Popielski in Russia that the introduction of acid into the duodenum evoked a reflex flow of pancreatic juice, even after division of the vagi and splanchnics or complete destruction of the spinal cord. These observers, therefore, regarded the reaction as belonging to the type of peripheral reflexes, and located the centre for the reflex in the ganglion cells, somewhere in the wall of the intestine or in the pancreas itself. Previous observations by Bayliss and myself had shown that the normal peristaltic movement of the intestine was a peripheral reflex, the paths of which lay wholly within the walls of the alimentary canal; and we were therefore interested to determine the conditions of the similar supposed reflex affecting the glandular activity of the pancreatic outgrowth of the canal. A few experiments sufficed to show that the so-called peripheral reflex secretion of pancreatic juice, evoked by the introduction of acid into the duodenum or upper part of the small intestine, occurred absolutely independently of any nervous channels whatsoever, and that it was possible to isolate the pancreas from the duodenum, to divide all the nerves going to a loop of the small intestine, and then by injection of acid into this loop to evoke secretion of pancreatic juice. Further observations showed us that the reaction, instead of being nervous, was in reality a chemical one. The entry of acid into the duodenum or upper part of the small intestine causes the production in the mucous membrane of a chemical substance which we call secretin. Since, as I shall show later, there are other secretins, we may speak of this as the pancreatic secretin. This pancreatic secretin is rapidly absorbed into the blood and travels with the blood to the gland, the cells of which it excites to secrete.

In order to obtain secretin, the method we have always adopted has been to scrape off the mucous membrane of the duodenum and upper two feet of the small intestine, to pound this up in a mortar with sand with [illegible] the mixture [illegible] contains the [illegible]. In order further [illegible] it may be [illegible]

[illegible] which can be collected by means of a capillary tube [illegible] of the plant. [illegible]

[illegible] determined by direct experiment [illegible]

[illegible]

We may now [illegible]

[illegible]

the addition of 0·4 per cent. hydrochloric acid, and then to boil the mixture over a free flame, the liquid when boiled being neutralised with caustic potash. All the proteids of the decoction are precipitated and, if the mixture be thrown on a filter, a clear fluid filters through. This fluid contains the secretin. In order further to free it from traces of gelatin and proteid, it may be precipitated by absolute alcohol and ether; the secretin is not thrown down, and can be recovered from the alcohol-ether solution by evaporation of the latter. A few cubic centimetres of the original filtrate from the boiled mucous membrane or of a watery extract of the residue left on evaporating the alcohol-ether solution, on injection into the veins of an animal, evoke a plentiful secretion of clear pancreatic juice which can be collected by means of a cannula placed in the duct of the gland. The secretin can be obtained in this way from the upper part of the intestine of any member of the vertebrata, and a solution of secretin obtained from any animal will, on injection into any other animal, evoke a secretion in the latter of pancreatic juice. We have, therefore, in secretin a substance of the same general distribution as adrenalin, which, like this latter, is unaltered by boiling, is soluble in alcohol, and, as we have determined by direct experiments, is more or less diffusible. Although secretin has not been further isolated and we have therefore no clue as to its chemical characters, there can be little doubt that it belongs, like adrenalin, to the drug class of substances which exercise an influence on the physiological workings of the body. The limited seat of production of secretin and the definite response evoked by its injection determine a chemical reflex, which is as adapted to the needs of the organism as are the muscular reflexes carried out by the central nervous system. The acid chyme entering the duodenum excites the formation of secretin in the mucous membrane, which in its turn causes a flow of alkaline pancreatic juice. The formation and absorption of secretin will proceed until the chyme is exactly neutralised by the alkaline juice. As soon as this neutralisation occurs, the pyloric sphincter, which remains firmly closed so long as the duodenal contents are acid, opens and allows the entry of a fresh portion of acid gastric contents which, in their turn, will, through the secretin mechanism, call forth a secretion of an exactly corresponding amount of pancreatic juice. It is thus contrived that the further digestion of the foodstuffs in the small intestine will proceed in a medium which is approximately neutral, and is at any rate free from any trace of mineral acid.

We may next inquire into the manner in which the contact of acid can give rise to the production of secretin in the mucous membrane. It seems most probable that the action of acid is one of hydrolysis, since, although various acids can be used for the preparation of secretin, their efficacy is more or less proportional to their strength or rather to their acidity, a weak acid such as boracic having no influence on the production of secretin. Bayliss and I have suggested therefore that the epithelial cells lining the upper part of the small intestine contain a substance, pro-secretin, from which by hydrolytic agents secretin can be split off. This precursor of secretin is quite insoluble, since we have been unable to obtain secretin by the action of acids on filtered extracts of the mucous membrane. It is not destroyed by the death of the cell, since secretin may be obtained by the action of acids upon boiled mucous membrane or upon mucous membrane which has been repeatedly extracted with absolute alcohol and then dried. On the other hand, if the process by which secretin is formed is hydrolytic this change must be able to be effected by the living cells in the absence of such strong hydrolytic agents as dilute hydrochloric acid. Thus Fleig has shown that a secretin similar in all respects to that described can be obtained by the action of soaps on the mucous membrane; and there is no doubt that a similar substance is produced in the mucous membrane and absorbed into the blood, when such substances as ether, chloral, or oil of mustard are introduced into the lumen of the gut. It is difficult to imagine that any of these substances can exercise a direct hydrolytic effect; and it is certainly impossible by their means to extract secretin from a mucous membrane which has been already killed.

That the secretin formed in the mucous membrane actually reaches the pancreas by way of the blood stream has been shown by Wertheimer. This observer led the blood from the intestinal veins of one dog (A) into the blood stream of a second dog (B) and found that injection of dilute acid into the intestine of dog A evoked a secretion of pancreatic juice in dog B. Although the view given above as to the origin of secretin is most probably correct, our failure up to the present to isolate pro-secretin in any way from the mucous membrane forbids us to accept the theory as definitely established. Délézenne has found that the digestion of a solution of secretin with a fresh extract of intestinal mucous membrane deprives the secretin of its efficacy. He has therefore advanced the suggestion that secretin is really preformed in the wall of the gut, but is accompanied by another body, its physiological antagonist, which he denotes by the name of anti-secretin. He imagines that the action of acid is to destroy the anti-secretin, thus unmasking the action of the secretin. The fact, however, that secretin, which is extremely soluble both in water and fairly strong alcohol, is not extracted in any appreciable quantity by these fluids from the mucous membrane until acid has been added, is difficult to reconcile with Délézenne's suggestion; moreover, the general characters of secretin, its resistance to proteid-precipitating agents, and so on, point to it as belonging to a class of bodies which would not give rise to antibodies when introduced into the organism.

As to the mechanism by which secretin arouses the activity of the pancreatic cells, the expulsion of its preformed ferment or pro-ferments, together with the building up of new protoplasm and ferments, which always accompanies normal activity, we have little or no conception. Early in our researches the suggestion was made to us by Dr. A. Walker that the secretion of pancreatic juice was of the nature of the formation of an antibody to the secretin. That this explanation will not hold is shown by the fact that secretin is equally efficacious when it is mixed with a large quantity of fresh pancreatic juice. If, however, the pancreatic juice be activated by the addition of succus entericus so that its [illegible] is converted into trypsin, is [illegible] secretion. Moreover, as I [illegible] in my last lecture, [illegible] injection and [illegible] has [illegible] by [illegible] as to the [illegible] in general. We are [illegible] that the [illegible] that of a specific drug [illegible] on all the glands of the body, including the [illegible] perhaps one or two other glands which are [illegible] with the [illegible] by their [illegible]. [illegible] action is [illegible], however, [illegible] with that of [illegible]. The latter drug [illegible] juice containing from [illegible] per cent. of [illegible] by the injection of a small dose of [illegible]. On the other hand, [illegible] juice which [illegible] in every particular [illegible] with a [illegible] in any way by the previous [illegible] dose of [illegible].

The discovery of a chemical [illegible] which is [illegible] the correlation of activities between the [illegible] of the [illegible] [illegible]

[illegible]

trypsinogen is converted into trypsin, it has the power of destroying the secretin. Moreover, as I mentioned in my last lecture, such a localised formation and excretion of an antibody has no analogue among the facts hitherto brought to light by bacteriologists as to the formation of antibodies in general. We are inclined to think that the action of secretin is that of a specific drug—that just as pilocarpin acts on all the glands of the body, including the pancreas, so secretin acts on the pancreas with, perhaps, one or two other glands which are associated with the pancreas in their functions. Its action is not, however, identical with that of pilocarpin. The latter drug induces in the pancreas the secretion of a thick viscid juice containing from 7 to 8 per cent. of solids. Its action is entirely abolished by the injection of a small dose of atropin. On the other hand, secretin produces a juice containing about 3 per cent. of solids, which resembles in every particular the juice obtained from an animal with a pancreatic fistula after it has received food. Its action is not altered in any way by the previous injection of, at any rate, moderate doses of atropin.

The discovery of a chemical reflex, which is sufficient to explain the correlation of activities between the mucous membrane of the small intestine and the pancreas, must cause us to inquire how far these results are to be reconciled with the previous results obtained by Pawlow. According to Pawlow's original idea the reflex secretion of pancreatic juice was entirely nervous. The question now arises whether both mechanisms function in normal circumstances or whether it is possible to explain all Pawlow's results by the chemical mechanism which I have described. Although we cannot at the present time give a definite answer to this question, we are inclined to believe that the chemical mechanism is the only one involved in the secretion of pancreatic juice, and that in all Pawlow's experiments, where secretion was excited by the stimulation of nerves such as the vagus or splanchnics, the effect on the pancreas was really a secondary one, due to movements of the stomach arising as a result of the nerve stimulation, and squeezing some of its acid contents into the first part of the small intestine. Other workers, however, such as Fleig and Wertheimer, believe that both mechanisms are at work—namely, that through the mucous membrane of the intestine the pancreas can be excited to secrete by both nervous and chemical means. We ourselves have never been able by nervous means to obtain secretion of pancreatic juice, provided that we excluded all possibility of entry of acid into the upper part of the small intestine.

The discovery of this simple chemical nexus between alimentary canal and pancreas suggests at once the possibility of other mechanisms of the same description taking part in the complex chain of events involved in the digestion of our foodstuffs. Investigations on this point, carried out partly in my laboratory and partly by independent observers, have shown this belief to be justified, and I propose in my third lecture to deal with the facts at present ascertained which point to a whole chain of such chemical reflexes throughout the alimentary tract.

LECTURE III.

Delivered on June 27th.

The Chemical Reflexes of the Alimentary Tract.

Mr. President and Gentlemen,—It is not until the food arrives at the stomach that any use is made by the organism of the more primitive chemical method of adjusting the secretion of the digestive juices to the presence of food at various sections of the canal. We have searched in vain for evidence of the production of a secretin in the mouth or its mucous membrane, as the result of the taking of food into this cavity, which might serve as a stimulus to the salivary glands, and the processes in the first part of the alimentary canal are so closely associated with consciousness and volition that one would expect their complete subordination to the central nervous system. In the stomach, however, the researches of Pawlow have already pointed to the possibility of some chemical mechanism being involved in the secretion of gastric juice. This observer has shown that gastric secretion begins even before the entry of food into the stomach, as a result either of stimulation of the nerves of taste or of the mental reproduction of sensations of smell and taste. This immediate secretion is therefore largely psychical and is so designated by Pawlow. The efferent channel of the nervous process is represented by the vagus nerves, and Pawlow has shown that division of both vagus nerves absolutely prevents this immediate secretion of gastric juice. There can be no doubt that the psychical secretion is the more important factor in the production of gastric juice in normal circumstances. The dependence of normal digestion in the stomach upon the free play of these nervous influences is shown by the indigestion which is a familiar result of mental disturbance. Gastric secretion has, however, two stages. In the first stage there is the rapid secretion due to the psychical stimulation. Two or three hours after the taking of food into the stomach a second rise in the secretion of juice may be observed, and this second rise is apparently dependent, not on the taste of the food or mental condition of the animal, but on the nature of the stomach contents. Pawlow states that this second stage occurs even when both vagus nerves are divided, and the possibility is at once suggested that this stage is not due to nervous processes at all, but is determined by some chemical mechanism similar to that which we have studied in the case of the pancreas. Pawlow is apparently of opinion that the secondary secretion is due to local reflexes in the wall of the viscus, but recent experiments by Edkins have shown that it is unnecessary to invoke the aid of any such obscure mechanism.

The stomach consists functionally of two parts—namely, the fundus and the pyloric end. In the fundus of the stomach are found the glands which secrete an acid juice. In the pyloric end the glands are devoid of oxyntic cells and the mucous membrane is much more closely adherent to the subjacent muscular coats. After a full meal the food forms a mass lying in the fundus of the stomach, the pyloric portion being at first quite empty. The movements, which occur from 20 to 30 minutes after the taking of food, involve only the pyloric half of the stomach, the fundus gradually contracting on its mass of food, so that the portions which are already partially digested are squeezed into the pyloric mill, where thorough admixture of the food with the juices takes place. It seems that such absorption as occurs in the stomach takes place solely at its pyloric end. If, then, there be a gastric secretin, we should expect it to be formed in the cells of the pyloric mucous membrane under the influence of the acid or food passing to this end of the stomach from the fundus. Injection of an extract made by treating pyloric mucous membrane with the products of gastric digestion should provoke a secretion of gastric juice. On such lines Edkins made his observations. Extracts of the pyloric mucous membrane were made by rubbing this up with 5 per cent. dextrin, with dextrose or maltose, or with peptone. A dog's stomach, which had been previously washed out, was filled up with normal salt solution under slight pressure. No absorption of salt solution takes place through the stomach, so that at the end of an hour the salt solution could be recovered unchanged. If, however, the extracts made, as just described, were injected in repeated small doses into the veins of the animal under observation, the salt solution removed from the stomach at the end of an hour was found to contain hydrochloric acid as well as pepsine, showing that secretion had been excited in the stomach. Injections of dextrin, maltose, etc., by themselves were without effect, so that the secretory results must be due to the injection of some substance produced in the pyloric cells under the influence of these digestive products. This substance, which Edkins calls *gastrin*, but which would be better named *gastric secretin*, is produced only from the pyloric mucous membrane, extracts made by rubbing up digestive products with fundus mucous membrane being without influence on the gastric secretion. Edkins has shown that the substance is not destroyed by boiling, so that it evidently belongs to the same class of bodies as the pancreatic secretin described in my last lecture.

It is an old theory, as propounded by Schiff, that certain constituents of the food have a special influence in promoting the secretion of gastric juice. These substances, among which Schiff placed dextrin, were called by him peptogenous, and it seems from Edkins's researches that this term is justified and that our future definition of peptogenous substances will be such bodies as can by their action on the pyloric mucous membrane give rise to the production of gastric secretin.

The movements of the pyloric mill have the effect of squirting into the first part of the duodenum, at intervals of a few minutes, a small quantity of strongly acid chyme containing the products of gastric digestion of the foodstuffs. The pylorus opens to admit the passage of a few cubic centimetres of chyme at a time, and then closes and remains closed so long as the contents of the duodenum continue to be acid. As soon as the duodenal contents are neutralised, the pylorus opens again and allows the propulsion of a further portion of semi-digested chyme into the duodenum. As we have seen, the effect of this acid chyme is to give rise in the cells of the mucous membrane of the first part of the intestines to secretin which, carried by the blood-vessels to the pancreas, excites a flow of strongly alkaline pancreatic juice. We may take it that ten cubic centimetres of pancreatic juice would suffice to neutralise from 15 to 20 cubic centimetres of the acid chyme. Pancreatic juice, however, although it contains many ferments, is dependent for the full display of its digestive activity on the coöperation of the other juices which are poured into the intestines at the same time—namely, the bile and the succus entericus. Pancreatic juice contains preformed both a fat-splitting ferment and a starch-splitting ferment. The activity of both these ferments is, however, doubled or trebled if bile be simultaneously present. Moreover, the fat-splitting properties of pancreatic juice are of little avail to the organism unless bile salts are also present, which by their solvent power on fatty acids and soaps and by their effect on surface tension can enable the absorption of the products of fat digestion to take place. It is essential, then, that the secretion of bile shall take place at the same time as, and in proportion to, the flow of pancreatic juice. The simultaneous and correlated flow of these two juices is effected by one and the same mechanism. Bayliss and I observed that if a cannula were introduced into the bile duct, the cystic duct having previously been ligatured, intravenous injection of secretin evoked not only the flow of pancreatic juice but also an increased flow of bile. Most extracts of the mucous membrane of the small intestine contain small traces of bile salts which are themselves cholagogue and might, therefore, be responsible for any increase in bile secretion observed as the result of the injection of ordinary extracts of intestinal mucous membrane. The presence of bile salts in our extracts was, however, guarded against, since, in our experiments on the influence of secretin on bile, we used for the preparation of secretin only mucous membrane, which had been previously thoroughly extracted with boiling absolute alcohol and proved by special experiment to contain no trace of bile salts.

Still more important for the full display of the powers of the pancreatic juice is the coöperation of the succus entericus. It was shown in Pawlow's laboratory that the proteolytic effects of pancreatic juice obtained from a pancreatic fistula were enormously increased by the addition of a small trace of intestinal juice, and it was concluded that the pancreatic juice contains, besides a small amount of trypsin, a large amount of trypsinogen. This latter " proferment " has no action on proteids. The succus entericus contains another ferment, called by Pawlow enterokinase, which has the power of converting trypsinogen into trypsin. More lately it has been

[illegible]

[illegible]

shown by Délézenne, as well as by Bayliss and myself, that normal pancreatic juice as secreted contains no trypsin whatsoever. It has, indeed, a feeble proteolytic ferment, which is powerless to digest coagulated proteids or even solid gelatin and only slowly attacks unboiled fibrin or caseinogen. The proteolytic ferment of fresh pancreatic juice is therefore no stronger than the ferments which can be extracted from almost any tissue of the body. In the presence of succus entericus, however, the pancreatic juice speedily develops a proteolytic power more marked than that of any other proteolytic ferment we are acquainted with. It dissolves proteids, whether or not coagulated, and rapidly carries them through the stages of hydration to their end-products of amino-acids, bases, and so on, effecting in this way a thorough destruction of the proteid molecule. Certain French observers, Délézenne, Dastre, and others, have imagined that the interaction of enterokinase and trypsinogen is of the same nature as the interaction between antibody and complement, which is necessary for the destruction of red blood discs by hæmolytic sera. Experiments by Bayliss and myself have shown that this view is untenable and have confirmed Pawlow's original statement that the activating effect of succus entericus on pancreatic juice is due to the presence of a body which acts like a ferment. Our results have been fully confirmed more recently by Hekma in Holland and by Falloise in Belgium.

Enterokinase is active in such minute quantities that the presence of the minutest trace of mucous membrane in a pancreatic juice will suffice to activate the latter. It is important that the activation of the proteolytic ferment should take place as speedily as possible after the entry of pancreatic juice into the intestine, and there must therefore be some means by which a flow of succus entericus containing enterokinase is evoked in direct proportion to the amount of pancreatic juice entering the intestine. That such a mechanism is present and is of a chemical nature there can be little doubt, although some discrepancy still exists between different observers as to the exact nature of the chemical mechanism. We have commenced to study the subject, but our experiments are not yet far enough advanced to enable us to decide between the rival views. It is necessary to bear in mind that very considerable differences may exist between the mechanism of secretion of succus entericus in the upper and lower parts of the small intestine. It has long been known that there is a gradual increase in the absorbing powers of the intestine as we proceed from its upper to its lower end, and every worker with intestinal fistulæ has noticed an inverse ratio between the secreting powers of the different parts of this tube, secretion being most abundant in the duodenum and least abundant in the lower parts of the ileum. It is possible, therefore, that the various mechanisms described by different observers are really all involved, but that their importance varies according to the part of the canal under investigation. Pawlow, as the result of experiments carried out on dogs with intestinal fistulæ, came to the conclusion that two main factors were involved in the secretion of succus entericus—namely: (1) the mechanical distension of the intestinal canal; and (2) the presence of pancreatic juice. He found that a flow of succus entericus could be more easily evoked by the introduction of a small amount of fresh pancreatic juice into the intestine than by any other means, and work by his pupils seems to point to the richness of the juice in enterokinase being proportional to the amount of pancreatic juice introduced into the canal. If these observations be correct, they would point to the trypsinogen, or some associated substance in the pancreatic juice, as being itself the chemical stimulant for the glands of the intestinal wall. Whether this chemical irritant acts directly, or whether it reaches the follicles of Lieberkühn by way of the blood stream, is as yet undetermined. Since it is the trypsinogen which needs the presence of enterokinase, it would be natural to assume that this substance itself is the actual stimulant of the intestinal glands.

A somewhat different view of the exciting agent for the intestinal secretion has been put forward by Délézenne. This observer, working on dogs with intestinal fistulæ at various regions of the gut, obtained practically no secretion except from the uppermost section—namely, that including the duodenum. He finds that the secretion of what we may call duodenal juice, which must be succus entericus together with a small amount of the secretion of Brunner's glands, is excited simultaneously with the pancreatic juice and the bile by the injection of secretin into the blood stream. According to this observer, therefore, the secretion of the three coöperating juices in the upper part of the small intestine—namely, bile, pancreatic juice, and succus entericus containing enterokinase—is brought about by one and the same mechanism—namely, the production of secretin in the intestinal mucous membrane under the influence of the entry of the gastric contents. It is, however, only in the upper part of the gut that the chief *rôle* of the succus entericus can be regarded as adjuvant to the pancreatic juice, and it is only here that the intestinal juice contains any large quantity of enterokinase. Lower down in the gut a secretion of alkaline intestinal juice is still of importance in consequence of its content in (*a*) sodium carbonate for the neutralisation of the organic acids produced in the changes in foodstuffs; (*b*) the ferment erepsin which breaks down the products of gastric and pancreatic digestion of proteids, converting albumoses and peptones into the nitrogenous end-products, amino-acids, and nitrogenous bases; and (*c*) the ferments invertase and maltase which complete the digestion of the carbohydrates of the food. To these two ferments we must, in the case of milk-fed animals, add the ferment lactase, in the absence of which milk sugar is incapable of undergoing assimilation.

According to Frouin the secretion of succus entericus (apparently in the middle part of the small intestine) can be evoked by the intravenous injection of succus entericus itself or by an extract of the intestinal mucous membrane. It is difficult to see the teleological significance of such a mechanism, unless we assume that some constituent of the succus entericus, produced by the mechanical stimulation of the foodstuffs themselves, is absorbed into the blood [illegible] the secretion [illegible] juice [illegible] preparations for the reception of the oncoming mass of food.

We see that, from the entry of the food into the stomach until its passage through the ileocaecal valve, there is a continuous chain of chemical reflexes, and that the process in any section of the alimentary canal calls forth the activity of the digestive glands in the immediately following section. In the stomach this chemical mechanism is rather in association with, and probably subordinated to, a nervous reflex mechanism. In the rest of the alimentary canal the chemical mechanism seems sufficient to account for the secretion of all the digestive juices which are demanded by the food. Whether there is in addition a system of nervous processes, the evidence at present [illegible] is not sufficient to decide, though we ourselves have been unable to obtain any satisfactory evidence of their existence. The mechanisms I have described suffice to explain in large measure the adaptation of the digestive processes to variations in the quality of the food supplied. As a rule the more [illegible] the foodstuff, the longer will it remain in the stomach, the greater, therefore, will be the secretion of acid gastric juice, which is the stimulus [illegible] Increased secretion of gastric juice will be attended automatically with increased secretion of the other digestive juices.

There is, however, evidence of a more specific adaptation of certain of the digestive juices to the nature of the foodstuff. Experiments carried out in Pawlow's laboratory have shown that the saliva poured into the mouth varies in amount and other qualities according to the nature of the food or other substance introduced into the mouth. [illegible]

In the stomach the peptic ferment, which is so important in inaugurating the digestion of the food, [illegible]

is absorbed into the blood and provokes the secretion of more intestinal juice lower down in the canal, in preparation for the reception of the advancing mass of food.

We see that, from the entry of the food into the stomach until its passage through the ileo-cæcal valve, there is a continuous chain of chemical reflexes, and that the process in any section of the alimentary canal calls forth the activity of the digestive apparatus in the immediately following section. In the stomach this chemical mechanism or reflex is associated with, and probably subordinated to, a nervous reflex mechanism. In the rest of the alimentary canal the chemical mechanism seems sufficient to account for the secretion of all the digestive juices which are demanded by the food. Whether there is in addition a chain of nervous processes, the evidence at present before us is not sufficient to decide, though we ourselves have been unable to obtain any satisfactory evidence of their existence. The mechanisms I have described suffice to explain in large measure the adaptation of the digestive processes to variations in the quality of the food supplied. As a rule the more indigestible the foodstuff, the longer will it remain in the stomach; the greater, therefore, will be the secretion of acid gastric juice, which is the stimulus setting free the chain of processes below the pyloric sphincter. Increased secretion of gastric juice will be attended automatically with increased secretion of the other digestive juices.

There is, however, evidence of a more specific adaptation of certain of the digestive juices to the nature of the foodstuffs. Experiments carried out in Pawlow's laboratory have shown that the saliva poured into the mouth varies in consistence and other qualities, according to the nature of the food or other substances introduced into the mouth. Thus introduction of sand into a dog's mouth evokes profuse secretion of watery saliva; meat provokes secretion of thick, viscid saliva; bread of thin saliva, chiefly from the parotid gland, and so on. The same results can be evoked by showing the dog these substances—*i.e.*, by the psychic reproduction of previous actual stimulation of peripheral sense organs.

In the stomach the psychic secretion, which is so important in inaugurating the digestion of the food, is apparently unaffected by alterations in diet, any variations which may be caused being sufficiently explained by the different digestibilities and therefore different length of stay of the foodstuffs in the stomach. In the case of the pancreas, however, according to Walther and Vasilieff, there is an accurate adaptation of the composition of the juice to the nature of the food, the dog that has been on a bread diet secreting more amylopsin, while the dog on a proteid diet secretes a larger amount of trypsin or trypsinogen. These results have been controverted by Popielski, according to whom the composition of pancreatic juice is determined solely by the strength of the stimulus which the pancreas receives. Further experimental work is still required on the subject. If Walther's contentions are supported, it will be interesting to determine whether the adaptation of the pancreatic activity to the nature of the food is nervous in character as imagined by Pawlow, or whether the mechanism in this case also is chemical. An apparent example of adaptation of the pancreatic activity to the nature of the food was described in 1901 by Weinland, who stated that, whereas the pancreatic juice of an ordinary adult dog contains no lactase and is therefore without effect on milk sugar, it is only necessary to feed the dog for some time, a week or more, with milk or with milk sugar in order to determine the appearance of lactase in the pancreatic juice. These experiments of Weinland were confirmed and amplified more recently by Bainbridge, who endeavoured also to determine the mechanism by which the adaptation was carried out, and especially to decide the question whether it were of a nervous or of a chemical nature.

(More recent work by Bièrry has thrown doubt on this adaptation of the pancreas to lactose. Dr. Plimmer has therefore reinvestigated the whole question, using more accurate methods than either Weinland or Bainbridge, and has proved conclusively that under no circumstances does the pancreas or pancreatic juice contain lactase. I am therefore inclined to accept Popielski's view as to the absence of any qualitative adaptation of the pancreas to the nature of the food—at all events until further experimental evidence has been brought forward for such adaptation. *Note added December 1st, 1905.*)

LECTURE IV.

Delivered on June 29th.

The Chemical Correlations involving Growth of Organs.

Mr. President and Gentlemen,—The chemical adaptations of the body, which I have discussed in my first three lectures, have been almost exclusively in the direction of increased activity of the responding organ. One cannot, however, draw a sharp line between reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since under physiological circumstances the latter is always the immediate sequence or accompaniment of the former. It is a well-known fact that the best method of producing hypertrophy of any organ is by increase of its physiological activity, and a good example of the coincidence of assimilative with dissimilative changes is afforded by the action of one of the hormones—namely, secretin—on the pancreas. The most obvious result of injection of secretin is secretion of pancreatic juice. If the animal is in bad condition, so that assimilatory changes are, so to speak, handicapped, this increased activity of the pancreas is attended by a total discharge of the zymogen granules, so that after a few hours the gland on microscopic section is a typical discharged gland. The discharge may go so far, as shown by Dale, that the ordinary secreting cells of the gland lose not only their zymogen granules but also the main part of their protoplasm and acquire the aspect and arrangement of the cells which are familiar as forming part of "Langerhans' islets." If, however, we are dealing with an animal in good condition and are using a preparation of secretin free from harmful admixtures, such as the depressor substance usually present in extracts of the intestinal mucous membrane, we may succeed in exciting a continuous flow of pancreatic juice for some hours without inducing any change in the aspect of the gland, microscopic sections at the end of four or five hours' continual secretion presenting the typical aspect of a resting gland. In this case the stimulus exciting to activity has at the same time directly or indirectly called forth a corresponding building up of protoplasm and secretory granules. The division of the chemical adaptations which we have adopted must, therefore, relate solely to the primary effect of the excitation involved. In the cases hitherto studied the primary effect has been katabolic or increased activity. In the cases I shall bring before you to-day the primary effect of the chemical stimulus is anabolic. We must not, however, expect that the anabolic stimulus will diminish permanently the activity of the responding organ; rather will its ultimate effects be, by building up the responding organ, to increase its activity.

The most familiar example of a chemical correlation evoking the building up of tissues is that presented by the thyroid gland, though the effects of the chemical substance formed by the thyroid are so widespread, and differ to such an extent according to the age of the animal employed, that a physiological analysis of its results is still difficult to give. In the growing animal the chemical substance secreted by the thyroid evidently influences the growth of tissues, among others of the bones, and it is a familiar fact that injection or administration of thyroid to cretins will result in a restoration of the child towards normal, in increased growth of bones, and in development of various functions, including those of the brain and central nervous system. On the other hand, in adults, the pronounced effect of injection of thyroid is increased activity of the chemical changes of the body, as instanced by the increased nitrogenous metabolism, and disappearance of all over-growth in the subcutaneous connective tissue such as is present in myxœdema. Although, therefore, the main result of thyroid treatment is to restore normal growth where such has been previously wanting, it is difficult to say whether its primary effect should be regarded as dissimilative or assimilative. The fact that the thyroid gland can be administered by the mouth shows that the active principle is not destroyed by the gastric juice, and would, therefore, remove this from the proteid class of bodies, and would diminish very largely any probability of the hormone furnished by this gland being of the nature of a toxin. Whether it is represented by the thyroiodin, the organic iodine compound extracted from the gland by Baumann, is still doubtful, and we can only conjecture that in all probability, when isolated, it will be found to belong to the drug class rather than to the toxin class. We are still quite without knowledge as to the conditions which determine the amount of active substance produced in the thyroid gland. All we know is that the activity of the thyroid, like that of the suprarenal gland, is essential to the normal development of the functions of the body. Whether we are dealing here with a constant process, or with a chemical reflex similar to those we have studied in the alimentary canal and evoked by some event affecting directly the thyroid gland, we cannot say.

The largest group of correlations between the activity of one organ and the growth of others is formed by those widespread influences exercised by the generative organs on the body as a whole and on parts of the body. The effects of removal of the testes in the male animal on the growth and disposition of the individual have been known for centuries, and marked additions to our knowledge of this subject have been made recently by Mr. S. G. Shattock. According to Ancel and Bouin, the interstitial cells of the testis provide an internal secretion, in the absence of which the sexual characters of the male are not developed. The experiments of Shattock and Seligmann show that the formation of the so-called secondary sexual characters must be due to chemical influences from the

gland, and not to metabolic changes set up by a nervous reflex arising from the function of sperm ejaculation.

Corresponding results have been obtained in the female by extirpation of the ovaries, double oöphorectomy before puberty not only preventing the onset of puberty and the occurrence of menstruation, but modifying the future growth of the whole body in the direction of the male character. It has been shown recently by Marshall and Jolly, in a paper read before the Royal Society, that the changes in the uterus which determine menstruation are due, not to ovulation, but to an internal secretion arising from the ovary. These observers suggest that the interstitial cells of the ovary may be the seats of manufacture of this internal secretion or hormone; and it is interesting to note that, in a research recently carried out by Miss Lane-Claypon, definite evidence is brought forward of the origin of the interstitial cells of the testis from the germinal epithelium and of the complete equipotentiality of those cells with those which are forming the ova and Graafian follicles. Many observations have been made on the effect of administering by the mouth preparations of ovaries, especially in cases where the morbid symptoms were presumably due to abolition of the ovarian functions, either by disease or in consequence of the operative removal of these organs. Although in many cases favourable results are said to have been attained—results which would appear to prove the resistance of the ovarian hormone to digestion in the alimentary canal—it is difficult in this, as in most clinical evidence, to judge how far the results were due to the treatment or to the expectation of the medical man or patient. More definite evidence of a direct influence of the ovary on the growth of the uterine mucous membrane has been furnished by the experiments of Fraenckel, as well as by those of Marshall and Jolly. At the suggestion of Born, Fraenckel removed the ovaries of rabbits from one to six days after copulation, in order to decide whether the ovary exercised any influence on the growth of the mucous membrane of the uterus and its preparation for the fixation of the ovum. In every case on subsequently killing the animal it was found that the extirpation of the ovaries had prevented the fixation of the ova. On the other hand, if the ovaries were removed on or after the fourteenth day of pregnancy, which in the rabbit lasts about 30 days, the animals went on to full time and healthy fœtuses were produced. The fact that the corpus luteum of pregnancy grows enormously during the first third of pregnancy and then diminishes in size, suggests that this hypertrophy and growth of cells are for the express purpose of influencing the mucous membrane; and Fraenckel states that destruction of the corpora lutea by means of the galvano-cautery is as efficacious as total removal of the ovaries in determining the end of pregnancy. The cells which form the corpora lutea are derived, not from connective tissue cells but from the interstitial cells lying immediately outside the Graafian follicles. Their origin is, therefore, identical with that of the interstitial cells of the ovary—*viz.*, from the primitive germinal epithelium.

These experiments of Fraenckel have been confirmed by Marshall and Jolly, who conclude that the ovary is an organ providing an internal secretion, which is elaborated by the follicular epithelial cells or by the interstitial cells of the stroma. This secretion circulating in the blood induces menstruation and heat. In animals which have been deprived of their ovaries and in which the phenomena of heat are therefore absent, these phenomena can be reinduced by the injection of ovarian extracts. After ovulation the corpus luteum is formed. This organ provides a further secretion, the function of which is essential for the changes taking place during the attachment and development of the embryo in the first stages of pregnancy.

A still more striking example of growth in response to chemical stimulation from distant organs is afforded by the mammary glands. As is well known, at birth these glands are limited to a few ducts in the immediate neighbourhood of the nipple, continuous with those of the nipple and equal in extent in both sexes. At puberty in the human female there is growth of the breasts associated with some gland-growth, the main increase in size, however, being due to fat. With the occurrence of pregnancy a true hypertrophy of the gland begins at once and continues steadily up to birth. In the rabbit, in which we have studied the changes in the gland, it is extremely difficult to find in the virgin even a trace of mammary gland. The nipple is small and undeveloped and, on making serial sections through the nipple, the gland is found to be confined to a few ducts not extending more than a few millimetres outside the nipple. No trace of secreting alveoli is to be observed. With the occurrence of pregnancy a rapid growth of the gland appears to begin at once. Five days after impregnation, when it is still impossible to find the impregnated ovum with the naked eye in the enlarged uterus, the mammary glands are marked out as small pink patches about two centimetres in diameter just under each nipple. On microscopic section the gland is found to be made up chiefly of ducts, which, however, are undergoing rapid proliferation. The cells lining the ducts are about three deep and present numerous mitotic figures. At about the fourteenth day the whole of the front of the abdomen is covered with a thin layer of mammary tissue. Branching ducts with proliferating epithelium are still the predominant feature on section, but here and there, especially towards the margins of the gland, small secreting alveoli lined with a single layer of epithelium are to be seen. After this time the gland grows with ever-increasing rapidity, so that at birth, at the thirtieth day after impregnation, the mammary glands form a layer about half a centimetre thick over the whole of the abdomen. In the virgin rabbit it is impossible to obtain by expression any fluid from the nipples, but from the fifth to about the twenty-fifth day pinching the nipples results in the expression of a clear, colourless fluid. From the twenty-fifth day onwards this fluid becomes opalescent and during the second and third days immediately preceding birth the fluid obtained is typical milk. The appearance of milk is earlier in multiparous rabbits, and in animals where pregnancies succeed each other rapidly it may be possible to express milk throughout the whole

of pregnancy. In the primiparous rabbit termination of pregnancy at any time after the fifteenth day results in the appearance of milk in the mammary glands, a result which has also been observed in the human female under corresponding conditions. That this onset of lactation is not due to any stimuli, chemical or nervous, received by the mammary glands from the involuting uterus or ovaries is shown by the fact that it may be brought on by performing total extirpation of ovaries and pregnant uterus. The essential feature therefore seems to be in this case the removal of the growing fœtuses.

These facts demonstrate the intimate connection between the growth and activity of the mammary glands and the growth of the fœtus in utero. Many facts point to a close nervous connexion between the mammary glands and the uterus. I need only instance the production of uterine contractions on putting the child to the breast. and the occurrence of hypertrophy of the breast as a result of abnormal uterine conditions. It is, therefore, only natural that the growth of the mammary glands in pregnancy should have been regarded as determined reflexly through the central nervous system, and the nervous nature of the nexus between the generative organs and the mammary glands is still maintained by some writers, such as von Basch, who, however, locate the centres involved in the ganglia of the sympathetic system. There are many facts which militate against our acceptance of such a view. I need mention only some of the more striking of these. Ribbert transplanted in a guinea-pig a mammary gland to the neighbourhood of one ear. The occurrence of pregnancy in this animal was attended by enlargement of the transplanted gland, from which milk could be expressed at the termination of the pregnancy. A similar experiment was made by Pfister on the rabbit. Goltz and Ewald extirpated in the dog the whole of the lumbo-sacral cord. Pregnancy in this animal was attended by enlargement of the mammary glands, and the bitch suckled its pups normally. Von Basch suggests that in this case the nervous connexion could still be through the sympathetic system. Apart from the fact that there is no such connexion possible in the sympathetic system, which since Langley's researches is no longer the happy hunting-ground for speculative reflexes, von Basch's own experiments tell against such a hypothesis. Von Basch extirpated different portions of the abdominal sympathetic in the dog and rabbit and found that at the next pregnancy the glands showed their usual signs of activity. The only difference he observed between such animals and normal ones was a certain increase in the colustrum corpuscles, an unimportant difference which might have been occasioned by any trivial circumstance. Physiologists are therefore ready to believe that the nexus between generative organs and mammary glands is a chemical one, though opinions differ widely as to the seat of formation or origin of the chemical stimulus.

Pregnancy commences with changes in the ovary—*i.e.*, ovulation. The occurrence of fertilisation involves growth of the ovaries with their corpora lutea, growth of a fœtus which soon enters in the mammal into close relationship with the maternal circulation, and growth of the uterine mucous membrane and muscle. Moreover there is formed, partly from fœtal and partly from maternal tissues, an organ of highly complicated structure—the placenta—the express object of which is the nourishment of the growing young animal. It is evident that the chemical stimulus or hormone for the growth of the mammary gland may be manufactured in any of these four organs—the ovary, uterus, placenta, or fœtus—and that, in fact, two or more of these might coöperate in producing the effective stimulus for the mammary gland. The experimental solution of the question must therefore be a lengthy one. Even if we were certain of the seat of origin of the specific hormone, we should have to imitate the constant leakage of this substance into the maternal organism and to continue our experiments over a long period in order to produce artificially any growth of the mammary glands. It is impossible, in a short experiment, to prove the presence of a growth-compelling hormone in a fluid, as is so easily done in the case of substances, such as adrenalin or secretin, which increase the functional activity of any given tissue. There are a few clinical facts which, though not decisive, give an indication of the direction in which we may seek solution. Thus, in extra-uterine pregnancy, the growth of the mammary glands occurs as usual, although there is only a relatively slight hypertrophy of the uterus and its mucous membrane. If, under these conditions, death of the fœtus occurs, growth of the mammary glands at once ceases, although no definite change has taken place in the uterus. We shall be therefore inclined to locate the origin of the hormone either in the fœtus or in the fœtal part of the placenta. The influence of the ovary on the growth of the mucous membrane of the uterus and on the attachment of the fœtus has been already mentioned. This influence is apparently exerted by the luteal tissue. Since the corpora lutea atrophy during the latter half of pregnancy—*i.e.*, at a time at which the growth of the mammary gland is most rapid, it seems unlikely that the ovary will elaborate the specific hormone in question, though the possibility must be excluded by special experiments. For the past 12 months I have been engaged with Miss Lane-Claypon in an endeavour to determine the origin and nature of the specific stimulus which occasions the growth of the mammary glands during pregnancy. In a preliminary series of experiments one rabbit was injected every day for a fortnight subcutaneously and intraperitoneally with an emulsion prepared by grinding up the ovaries from pregnant rabbits. Another rabbit, also a virgin, received a similar emulsion prepared from the placenta and uterine mucous membrane from a series of pregnant rabbits. Each rabbit received about ten injections from as many pregnant rabbits. In no case, however, was any effect produced on the mammary glands.

These negative results caused us to try the influence of extracts made from the body of the fœtus itself. The large size of the fœtuses, however, rendered it impossible to adopt the method we had previously been using—*i.e.*, the injection of emulsions. The injection of emulsions of tissues, either subcutaneously or intraperitoneally, is, moreover, fraught with considerable risk of suppuration, even though scrupulous precautions

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are taken with regard to asepsis. A large mass of material is introduced which can have no direct bearing on the experiment and in course of absorption must give rise to a large amount of plastic exudation. Proceeding on the hypothesis that the specific stimulus in this case must resemble the other members of the class of hormones in being a body of comparatively small molecular weight, diffusible and not a colloid, we determined in subsequent experiments to inject such constituents of the tissues experimented on as could be extracted by normal salt solution and filtered through a Chamberland filter. In all our later experiments the tissue, whether placenta, ovaries, or fœtus, has been pounded for one hour with sand so as to break up all the cells, and, after the addition of a little salt solution, mixed with Kieselgur; the resultant powder, which is almost dry, is then subjected in a Buchner's press to a pressure of 300 atmospheres. The whole of the fluid of the tissues, containing their soluble constituents, is pressed out. This fluid is sterilised by passage through a Berkefeld filter into a sterilised flask and can then be injected in any quantity either into the peritoneum or subcutaneously without fear of septic trouble.

The first experiment carried out with this improved technique was on a rabbit eight months old which had lived in a cage in the laboratory since it was 14 days old. This animal received 15 injections spread over a period of 17 days. The injections consisted of the fluid parts of the whole of the viscera of 66 fœtuses, varying in age from the fourteenth to the twenty-fifth day. The day after the fifteenth injection the rabbit was killed. It was found that fluid could be expressed from the nipples, which were distinctly enlarged, and on reflecting the skin of the abdomen all the mammary glands were seen to have grown to the size found in a rabbit about eight days pregnant. On microscopic section the gland was seen to consist entirely of proliferating ducts which were lined with an epithelium about three cells deep, presenting numerous mitotic figures. The aspect, in fact, both macroscopic and microscopic, was that of a gland incited to grow by the normal stimulus of pregnancy.

The question then arose whether one could not, by increasing the number of the injections and the duration of the experiment, carry on the hypertrophy of the gland to the point of formation of secreting alveoli. As the subject of our next experiment we had a rabbit which had been in the laboratory four weeks. The general aspect of the rabbit and the undeveloped condition of its nipples showed it to be a virgin. This rabbit received 24 injections, which were spread over five and a half weeks, an interval of ten days intervening at the end of the first week, during which the animal received no injections in consequence of the temporary failure of our supply of pregnant rabbits. During this time the animal received the fluid extract of the viscera of 160 fœtuses. Towards the latter part of the experiment the animal improved considerably in condition, the growth of hair on its abdomen became very active, and the nipples enlarged and yielded a colourless fluid when pressed. On killing the animal the day after the last injection the mammary glands were found to form a thin sheet extending over almost the whole of the abdomen. Each gland was about five centimetres in diameter and consisted of branched ducts radiating from the nipple. The peripheral zone of the gland was swollen and vascular and on section was found to contain alveoli. Both in the alveoli and in the epithelium of the ducts, which was many-layered, many mitoses were seen, showing that cell proliferation was actively proceeding.

During the last 17 days of this experiment the rest of the bodies of the fœtuses after the extraction of the viscera were finely minced and ground up and boiled with normal saline solution. While boiling the mixture was rendered slightly acid to precipitate the proteids and then filtered. The filtered extract was injected intraperitoneally into a rabbit which had been in the laboratory about two months but from the size of the nipples had evidently been previously pregnant. After the injection had been repeated for 10 or 12 days it was found that milk could be obtained by squeezing the nipples. On killing the animal the abdominal wall was covered with a well-marked layer of mammary tissue which contained many alveoli. In some of the ducts there was some indication of proliferation. Both alveoli and ducts contained fluid with fat granules and colustrum corpuscles. Although our failure to obtain a virgin rabbit for this last experiment rendered it impossible to be absolutely certain that the gland tissue had undergone hypertrophy as the result of our injections, the occurrence of secretion and the appearances observed in parts of the gland rendered it probable that we were really dealing in this case with a specified stimulus to the mammary gland and suggested that the specific hormone of the gland would therefore withstand boiling.

In our next series of experiments we employed four rabbits. Two were injected with the extract of the viscera, boiled and unboiled, and two with extracts of the rest of the fœtus, also boiled and unboiled. For injection with the unboiled extract of viscera we took a rabbit which we knew to have been previously pregnant. The entire uterus had, however, been removed so as to avoid the possibility of any coöperation on the part of the uterus in the effects of our injections. For the injections of boiled viscera a rabbit was taken which, so far as we could judge, was nulliparous. Of the rest of the fœtus the boiled extract was injected into a rabbit which had certainly borne young some time previously. But for the unboiled extract we obtained a rabbit which was nulliparous. Since in this series the fœtuses were divided into four parts the injections were smaller than in the previous series. Each rabbit received 22 injections, spread over 31 days, obtained from 90 fœtuses. The fœtuses varied in age from the twentieth to the twenty-sixth day. The results of this last series were shortly as follows. In both the virgin rabbits there was hypertrophy of the mammary glands, due chiefly to duct proliferation, though not so marked as in the previous series. Towards the end of the injections a watery fluid could be obtained by squeezing the nipples of either of the two rabbits. In the two multiparous rabbits it was impossible to be certain that any actual growth of the gland had taken place.

But in each case from the ninth injection onwards typical milk could be obtained on squeezing the nipples.

During the last 17 days of this experiment two virgin rabbits were obtained and were used for trying the effects once more of placenta, uterine mucous membrane, and ovaries. The first received the fluid extract unboiled of 123 placentæ mixed with the fluid extract of the mucous membrane of 14 uteri. The other received 13 injections composed of the fluid extract of 26 pregnant ovaries. In both cases at the end of the experiment the uteri of the animals which had received the injections were found to be somewhat enlarged and congested, but in neither case was there any trace of growth of the mammary glands.

A consideration of all these results brings us to the conclusion that the specific stimulus which determines the growth of the mammary glands in pregnancy is produced in the product of conception, *i.e.*, the fertilised ovum or fœtus; that it is contained in all parts of the fœtus; that in all probability it withstands boiling; that it passes through a Berkefeld filter, and is not retained to any appreciable extent by the Kieselgur in Buchner's method for the extraction of cell juices. This mammary hormone has apparently a two-fold effect, according as the animal experimented on is multiparous or primiparous. If the animal be a virgin, the effect of its injection is to produce hyperplasia of the gland, beginning, as in normal pregnancy, with proliferation of ducts and later leading to formation of secreting alveoli. In the multiparous animal, where there is already a considerable amount of partly involuted mammary tissue, the most striking result of the injection of this hormone is the production of secretion of milk.

The question arises whether these two results are to be ascribed to two substances or whether they represent phases in the action of one substance. A little consideration will show us that in all probability the latter is the true explanation. It has already been suggested by Hildebrandt that the specific hormone for mammary growth is a substance which inhibits autolytic processes in the gland. It is highly improbable that the process of secretion can be ascribed to autolysis. But the idea of an inhibitory substance as a stimulant to growth is a valuable one and consonant with our ideas of the inhibitory process in general. The stationary condition of any given cell is not the expression of inactivity but is the result of the equilibrium between two sets of processes, one set anabolic or assimilative, causing a building up of the cell, the other set katabolic or dissimilative, causing a breaking down of the cell. During activity of a muscle or gland, dissimilative processes predominate, causing a loss of material. During the subsequent period of rest, there is a swing back in the direction of increased assimilation, resulting in the making good of the loss during activity. The continued application to any tissue of a stimulus to dissimilation will finally result in its complete destruction and death. On the other hand, the continued application of an assimilatory stimulus, if such an expression may be allowed, results in a piling up of the sources of energy of the cell, with actual growth and probably multiplication of the cells. The final result of this continued building up must be an increase in the functional capacity of the tissue, so that it will be ready to break down—*i.e.*, enter into activity, directly there is any diminution of the assimilatory stimulus. This is what happens in the case of the mammary glands. During the whole of pregnancy the mammary gland is receiving a continual inhibitory or assimilative stimulus from a substance produced in the fertilised ovum or fœtus which, diffusing through the placental villi, circulates in the maternal blood-vessels. The result of this negative stimulus is a building up of a gland, proliferation of its cells, and formation of new secretory alveoli. As soon as parturition occurs, the source of the inhibitory stimulus is removed. As the substance which has already obtained entrance in the maternal organism is used up, the cells built up to a high state of activity begin to break down; the dissimilation which is the concomitant of activity in the mammary cells resulting in the production of milk. At any time during the course of pregnancy in an animal we can remove the source of the inhibitory hormone by excision of the fœtuses or pregnant uterus. We have found that if extirpation of the pregnant uterus be carried out during the first half of pregnancy—*i.e.*, at a time when the mammary gland consists almost exclusively of proliferating duct tissue—the sole result is to bring about atrophy of the tissue already formed. After about the fifteenth day in the rabbit, extirpation of the pregnant uterus causes the appearance of milk in the gland alveoli, and this milk can be obtained within two days of the operation on squeezing the nipples. In the same way we may explain the secretion of milk which is observed on injecting multiparous rabbits with extract of fœtus. The daily injection of a small amount of extract of fœtus can be but a poor imitation of the continual leakage of the specific hormone into the maternal blood-vessels, which occurs during pregnancy. We must, in fact, imagine that, during the first few hours after the injection, we are really imitating the condition in pregnancy. The specific hormone will, however, be probably absorbed and used up long before the termination of the 24 hours which elapse between each injection. With the disappearance of the hormone the cells already built up beyond their normal point will tend to break down. There are, in fact, every day a temporary pregnancy and a parturition, and in all cases where there is a glandular epithelium present at the beginning of the experiment—*i.e.*, in all rabbits which have been previously pregnant—we shall have a tendency to formation of milk in the gland during a certain number of hours in every day of the experiment.

We must conclude, therefore, from these experiments that the growth of the mammary glands during pregnancy is due to the assimilatory or inhibitory effects of a specific hormone produced in the body of the fœtus and carried thence through the placenta by the fœtal and maternal circulations. The removal of this inhibitory stimulus at the end of pregnancy determines the spontaneous break-down of the built-up tissues—*i.e.*, activity which in those cells is expressed by the formation of milk.

Much work still remains to be done in the elucidation of various questions connected with the origin, conditions of formation, and mode of action not only of the mammary hormone but also of the other chemical messengers which I have mentioned in these Lectures. But the facts which I have been allowed to lay before you will, I trust, serve to convince you of the great part played by chemical processes in the coördination and regulation of the different functions of the body. If, as I am inclined to believe, the majority of the organs of the body are regulated in their growth and activity by chemical mechanisms similar to those I have described, an extended knowledge of the hormones and their modes of action cannot fail to render important service in the attainment of that complete control of the bodily functions which is the goal of medical science.

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