T. H. Pellow.

THE WORK OF

THE DIGESTIVE GLANDS

[*SOLE AUTHORISED ENGLISH TRANSLATION*]

THE WORK OF THE DIGESTIVE GLANDS

Lectures by

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TO

THE MEMORY OF HIS FRIEND,

THE TALENTED PHYSICIAN

NIKOLAÏ PETROWITSCH BOGOJAWLENSKY

THE AUTHOR DEDICATES THIS WORK

PREFACE TO THE ENGLISH EDITION

The great importance of the results obtained by Professor Pawlow, first published in collected form in the Russian language in 1897, was soon recognised by PHYSIOLOGICAL INVESTIGATORS all the world over. Hence the Russian edition was quickly followed by others in German and French.

But the work is of no less value to the PRACTISING PHYSICIAN. To place the matter, therefore, within easy reach of every English speaking medical man it was felt that an English edition was called for.

In carrying this into effect the translator has had the ready permission of Dr. A. Walther, and also of Mr. J. F. Bergmann, to make use of the German text, a kindness which he desires to gratefully acknowledge.

The present edition includes the later work of Pawlow on the Physiology of the Bile, Succus Entericus, and Salivary Secretion, together with more recent notes kindly supplied by the author, thus bringing the whole up to date. It also contains two new figures.

It is to be hoped, therefore, that in its English form the book will be worthy of its distinguished author.

THE TRANSLATOR.

PHYSIOLOGICAL DEPARTMENT,
SCHOOL OF PHYSIC,
TRINITY COLLEGE, DUBLIN.
September 1, 1902.

PREFACE TO THE RUSSIAN EDITION

It was not at all my intention, in these lectures, to treat of everything which has been written concerning the work of the digestive glands. I only wished to make known the results of an experimental investigation which, I am convinced, correctly indicates the present position of the subject, and to communicate the same to my hearers, partly by word of mouth and partly by direct demonstration. The subject of these lectures represents the work of my laboratory for nearly ten years; and since every experiment which deals with the functions of the gastric glands, and of the pancreas, has been many times repeated, elaborated, varied, and extended; the material has, for us at least, lost its fragmentary character and grown into a complete whole.

When I employ the word "we" in the following text, I wish to indicate the whole laboratory. In the description of the several experiments I always mention the author. But the object of the experiment, its meaning and its position in the whole series, is spoken of from the point of view of the laboratory, without giving the individual opinions and views of the author. It is of essential advantage to the reader to see how a uniform guiding principle has developed, and taken shape in the form of tenable and harmoniously linked experiments. In its main idea the book embodies the latest views of our laboratory; it embraces all the facts, even the most recent, which have been constantly tested, frequently corrected, and now appear to be securely established. In its production all my fellow workers have individually taken part; but it is a joint work, the result of the principle, which animates the whole laboratory. It owes its existence to the acuity of each individual, but in its totality to the guiding conception which has inspired us all.

When I look back upon what the laboratory has accomplished in our field of research, I know well how much the work of every individual is to be valued. I should, therefore, like to take this opportunity of sending heartiest greetings, in the name of the laboratory, to all our dear cö-workers, who are widely scattered over our native land, with the hope that they have preserved as friendly recollections of us as we have of them.

These lectures were first delivered before an audience of medical men in the Institute for Experimental Medicine, and later, in a shorter form, in the Military Medical Academy. All the experiments which were demonstrated before both these audiences have been included in the work.

THE AUTHOR.

ST. PETERSBURG, *April* 1897.

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THE WORK OF THE DIGESTIVE GLANDS.

LECTURE I.

A GENERAL SURVEY OF THE SUBJECT: METHODS.

General Survey: Introductory—The digestive apparatus may be compared to a chemical laboratory—Unsolved problems in the physiology of digestion—Methods, their ideal requirements—Temporary and permanent pancreatic fistulæ—Difficulties connected with making the latter—Gastric fistulæ: the same combined with œsophagotomy—Methods of forming a stomach *cul-de-sac*—The author's operative experience—Importance of surgical methods in physiology—The surgical department of a physiological laboratory.

Gentlemen,—The physiology of the digestive glands has engaged the attention of my whole laboratory—*i.e.*, of myself and my fellow workers—for many years, and I believe we have obtained results, both theoretical and practical, which deserve serious consideration. The work of secretion in the alimentary canal, so far as it concerns the most important organs of digestion, viz., the stomach and the pancreas, has not by any means proved to be that which is represented in text-books, and which in consequence dwells in the mind of the physician. A desire, therefore, arose to replace the older teaching by bringing into life a fuller and more correct representation. With this object I gave, in 1894, an oration* before the Festival Meeting of the Society of Russian Physicians in St. Petersburg, which was dedicated to the memory of the celebrated Russian clinician, S. P. Botkin. In the short space of one hour, however, I could give a general survey only of the work of many years, and was denied the possibility of sustaining my words with documentary references. In my present lectures I hope to make good these deficiencies and to be able to convince my hearers by relating actual experiments. The substance of the lectures is taken from work which for

* *Transactions of the Soc. Russ. Physicians in St. Petersburg.* 1894–95 (Russian).

the most part has already appeared in print. But many unpublished facts which the laboratory is now in possession of will also be referred to.

In view of the chief duty which the digestive canal has to perform in the living organism, it may be compared to a chemical factory, where the raw materials—the foodstuffs—are submitted to an essentially chemical process. They are thus brought into a condition in which they are capable of being absorbed into the body fluids and made use of for the maintenance of the processes of life. This factory consists of a series of compartments, where the food, according to its properties, is either retained for a time or at once sent on to the next. The factory and, indeed, each single compartment is provided with suitable reagents. These are either prepared in neighbouring little workshops, buried in the walls of the structure itself, or else in distant and separate organs, which are connected, as in other large chemical factories, with the main laboratory, by a system of transmitting tubes. These latter are the so-called secreting glands with their excretory ducts. Each of the workshops furnishes a special fluid, its own particular reagent, endowed with definite chemical properties which only act on certain portions of the food, this latter being ordinarily formed of a complex mixture of different ingredients. These properties are chiefly determined by the presence of special substances in the reagents, the so-called ferments. The separate fluids, the digestive juices, as they are usually termed, attack at one time only a single ingredient of the food, at another several. They thus combine the properties of many individual reagents, each of which acts in its own special way. But even a juice which has only one ferment is a very complex fluid, since, in addition to the ferment, it holds other substances also in solution—to wit, alkalies, acids, albumin, &c.

Physiology has learned all this by obtaining either the fluids in question or the pure ferments from the organism, and studying, in the test-tube, their effects upon the constituents of the food as well as their reciprocal behaviour towards each other. Indeed, it is mainly upon knowledge thus acquired that the teaching of the science with regard to the elaboration of the food or, as we say, of digestion, is based.

But our conception of the digestive process, which is essentially deductive, suffers from many and not unimportant defects. A considerable gap without doubt exists between such a form of knowledge on the one hand and the physiological reality, or even the empirical teaching of dietetics, on the other. Many questions still remain undecided, many have not even been raised. For example, why are the fluids poured out on the raw material in one particular order and not in any other? Why are the properties of certain reagents often repeated in combination with other properties? Are all the constituents of a particular fluid simultaneously poured out on the food, and does this happen with every kind of food that gains entry to the digestive canal? Are the reagents subject to variations, and if so when, how and why do such alterations appear? Do these variations only concern the composition of the fluid as a whole, or may the individual constituents alter in different cases and in different directions according to the requirements of the raw material? How do the reagents vary with augmented or diminished activity of the whole factory? Is there not a species of contest between the different constituents of the food, in that one may require a special reagent the activity of which would interfere with that of others on the remaining ingredients? No one can deny that these questions touch upon the vital facts of the case.

The mechanism of digestion cannot be presented in the abstract manner which is current in the physiological teaching of the present time. The differences and complexity of the reagents indicate that the work of the digestive canal in every single case is elaborately contrived, beautifully performed, and most carefully adapted to the task in hand. If we reflect, we must *à priori* admit that for each meal—*i.e.*, for each set of materials to be dealt with—a suitable combination of reagents with special properties is produced. It is not, therefore, to be wondered at that the subject of dietetics, apart from some general and empirical principles, represents one of the most intricate sections of therapeutics. Nor is it enough for the physiologist to have a knowledge of the separate elements concerned in the process of digestion, that is to say, the working of the individual agencies. He must, in order to fully grasp his subject, include also within the sphere of his observation the actual progress of digestion as a whole. This was recognised by many previous investigators who attempted, and doubtless would have accomplished, the solution of the problem had it been of an easier description.

A comprehensive knowledge of the processes of digestion may be acquired in one of two ways—either by determining in what state of elaboration the raw material is to be found at each separate part of the digestive canal—this was the method of Brücke, as well as of Ludwig and his pupils—or, on the other hand, by ascertaining the exact quantity of the digestive fluids which is secreted for each individual constituent of the food, as well as for the meal as a whole, how this digestive fluid is provided, and when it is poured into the alimentary canal. This method has been adopted by many investigators who have studied the progress of the secretion of the various digestive juices.

It is often said, and not without truth, that science advances by stages determined by the results obtained from particular methods.

With each advance in technique we reach a higher level from which a wider field of vision is open to us, and in which we see events previously out of range.

Our first problem consisted, therefore, in the working out of a method. We had to observe how the reagents were discharged upon the food brought into our digestive factory. To accomplish this in an ideal manner required the fulfilment of many and difficult conditions. Thus it was necessary to be able to obtain the reagents *at all times*, otherwise important facts might escape us. They must be collected in *absolutely pure condition*, if we were to determine how their compositions varied. We must be able to *estimate their quantities accurately*; and, lastly, it was necessary that the *digestive canal should function normally*, and that the *animal under experiment should be in perfect health.*

It is but natural that the solution of these difficult problems should only be gradually achieved by physiology, that not a little trouble should be spent in vain, and that many investigators should see their efforts fruitless, notwithstanding that several of the most prominent representatives of our science have devoted their attention to this field.

We begin our consideration with the pancreas, as the simpler case. It might appear that here our problem was very light. We have apparently only to seek out the duct through which the secretion of the gland is delivered into the intestine, to fasten a cannula into it, and thereby afford a free outflow of the fluid towards the exterior, collecting it in a graduated cylinder. All this, in reality, is very easily done, but our problem is far from being solved; for digestion may be very active, yet, as a rule, there is no flow of pancreatic juice from the tube after the operation; or if there is one the quantity is very small and obviously sub-normal. In such a case it would be out of the question to observe the rate of secretion, still more to determine the alterations in the juice dependent upon the nature of the food. On following the matter up, it became evident that the gland is a very sensitive organ, and suffers such a severe disturbance of its activity from the unavoidable conditions of the operation (narcotisation, opening of the abdominal cavity), that in the majority of instances not even a trace of normal function remained. This method is known in the literature under the name of "temporary" pancreatic fistula; its want of success naturally led to attempts being made on other lines.

It was hoped that an improvement might be attained by collecting the juice some time after the completion of the operation, that is, when its disturbing influence had fully passed away. The fluid was therefore allowed to escape freely from the excretory ducts for a considerable time.

This was accomplished either by tying a glass tube into the duct and leading it through the abdominal wall (*Claude Bernard*), or by fastening in a T-shaped piece of twisted lead wire in a similar manner (*Ludwig's School*). These were named "permanent" fistulæ. Both modifications proved effective, but only for a short period, generally for three to five days, in exceptional instances for as long as nine days. After this time the glass tube fell out and the fistula closed up; even the lead wire was unable to prevent this occurrence. In reality, therefore, these must also be regarded as temporary fistulæ only. But this was not their only defect. When the inhibitory influence of the operation had passed off after one or two days, another abnormal condition, in many instances set in, viz., an incessant irritation of the gland producing a secretion independent of whether the dog was fed or not. The question then arose, which was the better; the "temporary" or the "permanent" fistula? Evidently neither was faultless. In the "temporary" form the conditions were rendered abnormal by the effects of the operation; in the so-called "permanent" form by inflammatory results in the pancreas, which often set in (especially in the older laboratories) within one or two days.

Only one thing remained, namely, to discover a means of access to the gland lumen which would keep the duct open for any length of time; that is to say, till the above-mentioned disturbances had completely disappeared. Such a means was first described by me in the year 1879, and afterwards independently in the year 1880 by Heidenhain.*

My method was as follows. It differs slightly from Heidenhain's. From the wall of the duodenum, an oval piece, containing the orifice of the pancreatic duct, is cut out, the bowel, the lumen of which is not appreciably narrowed, stitched up, and the isolated piece of intestine sewn (with the mucous membrane outwards) into the slit in the abdominal wall. The whole heals quickly; the operation, which requires no special skill, is only of short duration (about half an hour), and is well borne by the animals. After two weeks they are ready for observation. In the healed-up wound a roundish elevation, 7 to 10 mm. in diameter, is to be seen. This is formed of mucous membrane, and in the more successful cases shows the cleft-like orifice of the duct exactly in its middle. If the animal be now supported in a suitable frame, the juice may be either directly collected as it drops from the mucous papilla, or if there be a tendency to escape along the abdominal wall, by means of a funnel with its wide end upwards fixed in the requisite position. Neither of the two disadvantages which beset the investigators who employed "temporary" or "permanent" fistulæ any longer exists.

* Hermann's *Handbuch der Physiologie*. Bd. v.

The gland undoubtedly remains in a normal condition, but the difficulties of the experimenter have by no means reached an end. In a very short time the abdominal wall becomes macerated by the escaping juice, and in places even fairly large bleeding patches appear. These continuously irritate the animal and prevent the collection of pure juice by means of the funnel. What was to be done? Many things helped—*e.g.*, frequent washing of the macerated skin with water and smearing with emollient ointments. The healing is, however, still better promoted if the dog be retained for several hours every day in its frame, with the funnel tied in position. But the best means of all is to allow the animal constantly to lie, except during the hours of the experiment, upon some porous material, such as a bed of sawdust or sand or old mortar, &c. Many animals soon discover the best position in which to lie down, so that the escaping juice is at once absorbed by the porous material. In this way the abrasion and maceration of the skin can most readily be avoided. It is interesting to relate that the hint which led to the adoption of this last method was given by one of the animals operated upon.

I may perhaps take the liberty of giving a fuller account of this interesting case. In one of the dogs the eroding effects of the juice became evident after ten to fifteen days. The treatment employed yielded no good results. At night the dog was tied up in the laboratory, but one morning, to our great annoyance, we found a heap of mortar beside it, torn from the wall. The animal was then chained elsewhere in the room. Next morning the same thing presented itself to our view, and once more a portion of the wall was damaged. At the same time we noticed that the dog's abdomen was dry and that the appearances of cutaneous irritation were considerably reduced. It was only now that we grasped the true meaning of the circumstances. We prepared the animal a bed of sand, after which the wall ceased to be damaged, and the flow of juice no longer gave trouble. We (Dr. Kuwschinski and I) acknowledged with gratitude that the common sense of the animal had helped us as well as itself. It would be a pity if this fact were lost concerning the psychology of the animal world. We thus overcame another difficulty, but our final goal was not yet attained.

Three to four weeks after the operation, the animals, previously well to all appearance, became suddenly ill. Food was almost at once refused and a rapidly increasing debility supervened. This condition was accompanied, as a rule, by convulsive symptoms, at times even by violent general cramps, followed, after two or three days, by death. Obviously here we had a peculiar form of ailment. Starvation was out of the question, for the animals often died with almost normal body-weight. The idea of any form of post-operative illness, such as an insidious peritonitis, had also to be given up, since neither the condition of the animals before death nor the appearances *post mortem* afforded ground for such belief. Finally, the possibility of any auto-intoxication from incomplete and abnormal products of digestion due to the loss of so much pancreatic juice, such as Dr. Agrikoljanski in his Dissertation has suggested, was also excluded. In the first place, with many dogs before death, absolutely no symptoms of digestive disturbances were observed; neither vomiting, nor diarrhœa, nor constipation. Secondly, we have convinced ourselves by means of special experiments, in which the pancreatic duct was ligatured and divided, that this operation is absolutely harmless. There remained only one supposition, viz., that the animals, in the escape of the pancreatic juice, lost something essential to the normal processes of life. Starting with this idea, we adopted two measures to guard against the ill effects. We had previously known that the nature of the food exerted a powerful influence on the composition and quantity of the pancreatic juice. We (Dr. Wassiliew) therefore omitted flesh altogether from the dietary of these dogs, and fed them exclusively on bread and milk. Bearing also in mind the fact that a large quantity of alkali is lost in the pancreatic juice from the body, we regularly added a certain quantity of sodium bicarbonate to the dietary (*Dr. Jablonski*).

By paying attention to these two rules it is tolerably easy to maintain an animal for many months, or even years, in a fit condition for experiment without the necessity of adopting any other special precautions. The difficulties encountered in the management of different animals naturally vary, but in every four or five dogs one will generally be found which tolerates the operation without any nursing. In what way the sodium bicarbonate helps is not yet clear. Possibly its administration makes good an injurious deficit of alkali in the blood, or possibly it acts, as Dr. Becker pointed out, by diminishing the secretion of the juice. In the latter case the nature of the substance whose loss is so harmful to the organism would still remain obscure. You see, then, of what great importance this question is, for have we not here a new pathological condition, capable of being called forth by experimental procedure? Dr. Jablonski has undertaken in the laboratory the investigation of this matter, but as yet it has not been completed.

To return to the subject; the juice is collected by means of a glass or, better, a metallic funnel, so fastened to the abdomen with an elastic band or thin elastic tube brought round the body that its wide end receives the orifice of the pancreatic duct. Hooks are fastened to the neck of the funnel, from which a graduated cylinder hangs, the animal being fastened in its frame. These arrangements are very convenient for the observer, but less comfortable for the animal, for the dog quickly tires and becomes restless. Nevertheless, the animal soon learns to sleep excellently, even under these circumstances, especially if one makes its position more comfortable by supporting the head. When first used in the laboratory, however, it is better to collect the juice from the dogs in the lying posture. In such cases it is necessary to employ a suitable vessel pressed more or less firmly to the body-wall beneath the opening of the duct.

I have intentionally described all these accidents which may arise in connection with the formation of a permanent pancreatic fistula. I wished to show how difficult an apparently easy problem may become when dealing with material of such a peculiar nature.

Our solution of the problem is evidently by no means an ideal one. It would be in the highest degree desirable to possess a method which would permit us to collect the juice when desired during the experiment and yet allow it to return to the intestine during the intervals. In this way not only would much pancreatic juice be saved to the organism, but the possibility of other serious disturbances of the digestive glands from the effects of the fistula would also be excluded. One may justly assume that the continued loss of so important a secretion as the pancreatic juice is compensated, on the one hand, by an augmented or otherwise altered activity of the remaining digestive glands, or, on the other, that this loss is rendered less injurious by a depreciation in the value of that which falls useless to the floor. We must not, however, overrate the importance of these somewhat far-fetched suppositions. Further investigations showed us how clear, consistent, and instructive are the numerous results which we obtained by this method.

A more recent method which has been published by the Italian investigator Foderà * approximates to a perfectly faultless one. He succeeded in causing a T-shaped metallic cannula to heal into the duct, so that the juice, as one must accept it, could be either collected on the outside, or by closing the outer end of the tube, be diverted into the alimentary canal. This experiment possesses, however, for the time being, an important defect; we have no guarantee that, notwithstanding the outflow from the tube, there may not be a considerable quantity still entering the intestine.

The evolution of a method for obtaining *gastric juice* and observing its secretion was no less difficult and protracted. We may pass over the old and admittedly inadequate experiments, and consider more carefully the starting-point of the method now in use—the making of a

* Moleschott's *Untersuchungen zur Naturlehre der Menschen und der Tiere*, Bd. xvi. 1896.

gastric fistula. In the year 1842, the idea occurred to our countryman, Professor Bassow,* and in the year 1843, independently to the French physician, Blondlot,† to reproduce artificially in animals a similar condition to that observed by an American physician whose patient suffered from the effects of a gunshot wound. After his recovery, a permanent opening remained in the abdominal wall which led directly into the stomach. They therefore made an opening through the dog's abdominal wall into the stomach, and fastened into it a metal tube, closed exteriorly by a cork stopper. The tube healed firmly into the opening, and could remain for many years in position without causing the least harm to the animal.

This method raised great hopes at first, since it afforded, when desired, easy and free access to the cavity of the stomach. But, as time went on, the expectations gave place to disappointment, and for the purpose of studying the action of the ferment of the gastric juice nearly all investigators were obliged to employ an extract made from the mucous membrane, since only very little and very impure gastric juice could be collected from the fistula. It was likewise very difficult to obtain any idea of the rate of flow during digestion, or of the properties of the secretion under different conditions. Voices were, therefore, loud in denunciation of the gastric fistula; it had justified none of the hopes, and had proved quite valueless.

This condemnation was naturally exaggerated and was mainly due to the vexatiously slow progress made in our knowledge of the phenomena of secretion in the alimentary canal and especially in the stomach. Why had not many important observations been made earlier with the help of the gastric fistula? It required only to be perfected by a slight modification, to enable fundamental questions to be solved by its aid.

In the year 1889, we (myself and Madam Schumow-Simanowski) performed the operation of œsophagotomy on a dog already possessing a gastric fistula; that is to say, we divided the gullet in the neck, and caused both its divided ends to heal separately into an angle of the skin incision. We thereby accomplished the complete anatomical separation of the cavities of the mouth and stomach. Dogs so operated upon recover perfectly with careful nursing, and live many years in the best of health. In feeding, their food must naturally be brought directly into the stomach.

With such animals one can make the following interesting experiment. If the dog be given flesh to eat the food drops out again from the upper segment of the divided œsophagus. From the perfectly

* *Bulletin de la Soc. des Natur. de Moscou.* T. xvi.

† *Traité Analytique de la Digestion.* 1843.

empty stomach, previously washed out with water, an active secretion of gastric juice, however, soon commences which continues as long as the animal eats, and even for a short time longer. One can easily obtain in this way hundreds of cubic centimetres of gastric juice. I leave the matter open till the next lecture why the gastric juice flows under such conditions, and what importance for the whole question of digestion is to be attributed to the phenomenon, merely remarking for the present that this method has definitely settled the problem of obtaining pure gastric juice. You can collect on any day or every day from a dog thus operated upon a couple of hundred cubic centimetres of juice, without any apparent injury to its health; that is to say, you can procure gastric juice from a dog almost as one obtains milk from a cow.

For pepsin experiments we need no longer prepare an infusion of mucous membrane, since enormous quantities of the purest pepsin can now be obtained with much greater ease and rapidity from the living animal. The dog is converted into an inexhaustible manufactory of the finest product. This fact, as it appears to me, must also claim the attention of the pharmaceutist, since it is often considered desirable by the physician, indeed in many cases essential, to prescribe pepsin and hydrochloric acid to patients. Exact comparative experiments made by Dr. Konowalow, with solutions of commercial pepsin, and with natural gastric juice as obtained from our dogs, showed that the former was incomparably inferior. The possible objection that the gastric juice is procured from a dog can hardly count as a serious obstacle to its employment and distribution as a pharmaceutical preparation. Many experiments in the laboratory upon ourselves bear testimony to its easy toleration and to the absence of any ill effects. The taste of the juice is by no means unpleasant; it is, indeed, in no way different from that of a solution of hydrochloric acid of corresponding strength. To do away with the prejudice one might even procure gastric juice from animals whose flesh is eaten by mankind, and I cannot but express my regret that this substance, which, at all events deserves a trial, has not been more used in Russia, although I have frequently drawn the attention of my medical colleagues to it. The wish to try my fortune once more in this matter is the cause of this deviation from the description of our procedures. Last year pure gastric juice, collected by Dr. Fremont from the stomach of the dog by means of a fistula made on the principle of Thiry's intestinal one, has been recommended in foreign lands as a therapeutic agent in various affections of the digestive canal. Is it to be the same in our case, that a product long known to us would have met with greater success had it appeared under a foreign flag?

I now come back to our methods. The problem of how to obtain pure gastric juice has been already settled, but it does not afford us the means of observing the secretion of the juice and of studying its properties during digestion. Obviously to accomplish this there must be the continuance of normal gastric digestion side by side with a quantitative collection of perfectly pure juice. That which was quite simple in the case of the pancreas (where the gland duct is separate from the alimentary cavity with its food contents) becomes a task of the greatest difficulty in the case of the stomach, since its glands are microscopic and are embedded in the walls which surround the food receptacle.

A happy idea for overcoming difficulties of this kind was hit upon by Thiry. In order to procure succus entericus—a secretion likewise formed by microscopic glands embedded in the intestinal wall—and to study it in the act of formation, he isolated a cylindrical piece of gut, formed this into a *cul-de-sac*, and sewed its open end into the abdominal wound. The idea was taken advantage of by Klemensiewicz* in 1875 for the purpose of obtaining the secretion of the pyloric end of the stomach in pure condition. But, unfortunately, his dog lived only three days after the operation. Heidenhain,† however, soon afterwards succeeded in keeping one alive. He‡ also isolated a portion of the cardiac end of the stomach, out of which he formed a pouch which poured its secretion externally.

In this way the above requirements were fulfilled. When the food in the ordinary way reached the stomach, which was still in position, a perfectly clear juice began to flow from the pouch, and could easily be measured quantitatively. But to draw conclusions with complete certainty concerning the normal work of the organ during digestion it was necessary to retain the nervous connections of the isolated piece intact. In Heidenhain's operation this was obviously not the case, since in making the transverse incision by which he resected the piece of stomach the branches of the vagus which course lengthwise along the wall of the cavity were cut through. To overcome this disadvantage a further improvement of the method was therefore necessary.

With this view we (myself and Dr. Chigin) have modified Heidenhain's operation in the following way. The first incision, which begins in the fundus of the stomach, two centimetres from its junction with the pyloric end, is carried in the longitudinal direction for ten to twelve centimetres, and divides both the anterior and posterior walls. A triangular flap is thus formed, the apex of which lies in the long axis of the stomach. A second incision is made exactly at the base of this flap,

* *Sitzungsberichte der Wiener Akademie.* 1875.

† Heidenhain: Pflüger's *Archiv.* Bd. xviii. ‡ *Ib.* Bd. xix.

but only through the mucous membrane, the muscular and peritoneal coats remaining intact. The margins of the mucous membrane all round these incisions are separated for a little way from the submucous tissue; on the side of the stomach for a width of one to one and a half centimetres; on the side of the flap for two to two and a half centimetres. The raised edges of mucous membrane belonging to the large stomach are applied to each other for half their width and sewn together. Out of the piece which belongs to the flap a cupola is formed. Both the stomach and the margins of the flap are then closed by sutures along the edges of the first incision. A septum is thus made between their respective cavities, consisting of two layers of mucous membrane;

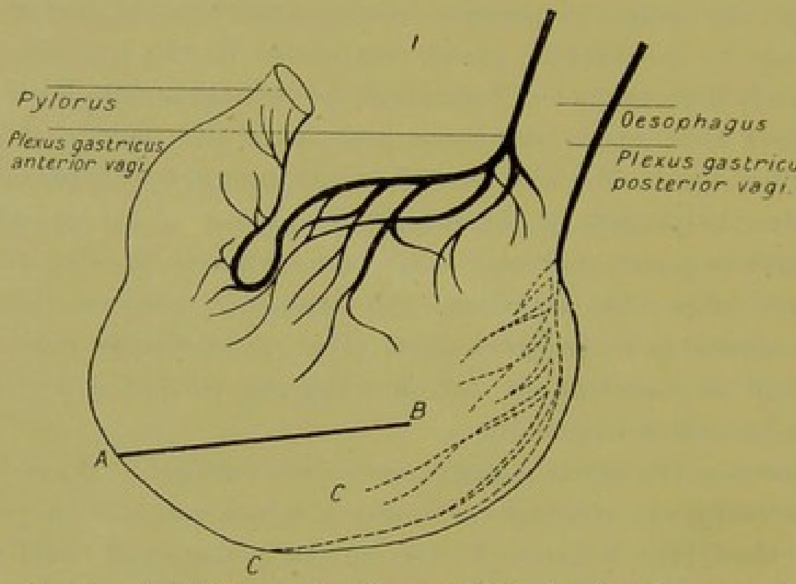


FIG. 1.—*A.-B.* Line of incision. *C.* Flap for forming stomach pouch of Pawlow.

one, that of the cupola, being intact, the other stitched along the middle.

It was only by forming the mucous membrane of the flap into a cupola that we were able to retain a dog with a permanent and closed pouch for any length of time. No sooner were the two layers of mucous membrane sewn in the middle line than a communication formed after a shorter or longer time between the stomach and the *cul-de-sac*. The animal was then useless for our purpose. It is still better to make cupolas out of the mucous membrane on both sides. To describe the matter in a few words, we separated an elongated piece from the stomach, formed it into a cylinder, the orifice of which we sewed into the opening in the abdominal wall, and allowed the other end to remain connected with the stomach. The cavity of the pouch is separated from that of the stomach by a septum formed only of mucous membrane. To make the description clearer, I give here illustrations of the operation borrowed from the work of Dr. Chigin (Figs. 1 and 2).

Naturally our addition to the operation of Heidenhain makes it more difficult, but as will be apparent farther on, we are compensated as a reward of this increased difficulty by an intact condition of the nervous relations of the stomach, which was our aim. It is clear that the fibres of the vagus nerve reach the separated portion of the stomach, since they course between the serous and muscular layers of the flap.

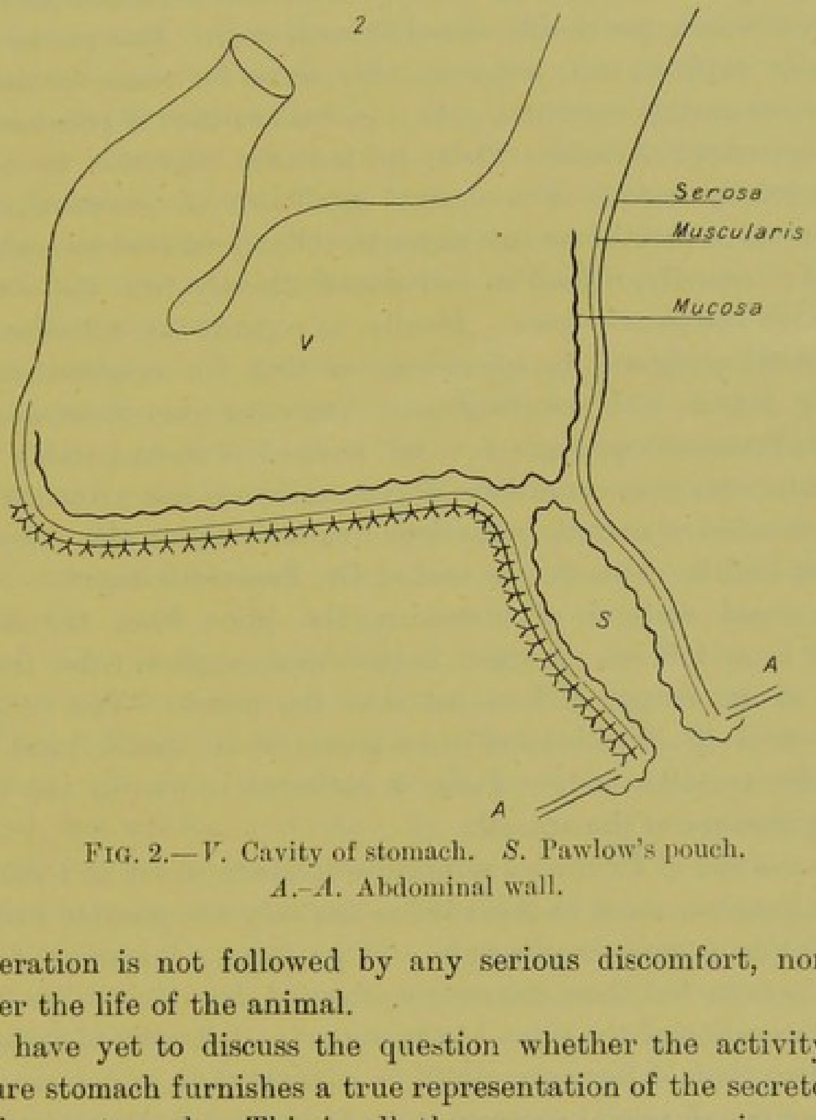


FIG. 2.—*V*. Cavity of stomach. *S*. Pawlow's pouch. *A*.-*A*. Abdominal wall.

The operation is not followed by any serious discomfort, nor does it endanger the life of the animal.

We have yet to discuss the question whether the activity of our miniature stomach furnishes a true representation of the secretory work of the large stomach. This is all the more necessary since the food comes into contact with the walls of the latter during digestion, while the former remains empty. A full answer to this question I shall reserve for a later lecture, when we are in possession of more material. At present I shall merely state in a few words that, in addition to rigorous inferences drawn from a series of unquestionable facts, there are numerous direct experiments in which the small and large stomachs were compared both as regards conditions of work and properties of their secretions, and which leave no room for doubt that we may with perfect safety employ the small stomach as a means of studying the function of the normal organ. In our next lecture even the miniature stomach will show itself to be an instructive object worthy of earnest attention.

As has already been related, Dr. Fremont has recently succeeded (since the publication of our method) in isolating the whole stomach of the dog after the principle of Thiry; that is to say, the lower end of the œsophagus was united to the duodenum and a cannula made to heal into the stomach, previously closed at both ends. This procedure, as I shall later explain, can, however, only serve for some special experiments upon gastric secretion. As a general method it possesses two or three important defects. First, in ordinary digestion in such dogs we can hardly reckon upon normal conditions of secretion, since the gastric mucous membrane can never be reflexly excited by contact with the food; secondly, if food be introduced directly into the stomach, it mixes with the gastric juice. Finally, as regards the collection of juice for practical purposes, it appears to us that our combination of the ordinary fistula with œsophagotomy possesses important advantages over Dr. Fremont's procedure. Our method is incomparably simpler, and, under suitable conditions of operation, is not attended by any useless sacrifice of animals; the dogs live for years in the enjoyment of excellent health. Can this be said of Dr. Fremont's dogs?

The usual method of obtaining the juice from the miniature stomach is as follows. A small indiarubber or glass tube, freely perforated at its deeper end, is led into the pouch. The tube either remains in of itself or is fixed in by means of an elastic band brought round the animal's body. Juice is collected either in the lying or standing posture of the animal.

This method of forming a miniature stomach, so far as I can for the moment imagine, must be regarded as the only one possible which is at the same time correct in principle. It possesses a few small disadvantages, it is true, but these are only matters of detail, such, for instance, as the maceration of the edges of the wound and the loss of some gastric juice. But these defects can easily be counteracted, and, moreover, are in themselves of trivial importance. They can, I hope, in time be altogether avoided. Indeed, in the interests of a thorough investigation of the whole secretory work of the alimentary canal, a universal simplification of the technique is to be desired, with a weeding-out of minor defects, so that it may be possible to make several fistulæ on the same animal without endangering its life or health.

It is obvious, from the sketch of digestion now given, how important simultaneous and rigidly concordant investigations of the several glands, both with regard to periods of activity and quantitative relationships of work should be. This can only be achieved, however, when the activity of all or many glands is simultaneously observed on one and the same animal.

In bringing the description of methods in this lecture to a close, I consider it essential to point out the importance to physiology of surgical technique. It appears to me that the methods of surgery, as contrasted with those of vivisection, must obtain unquestioned recognition in the series of procedures which we adopted: I mean in the performance—the conception and carrying out—of more or less complicated operations having for their object either the disconnection of certain organs, the ready observation of deeply seated processes in the organism, the severance of existing relationships between organs, or *vice versâ*, the establishment of new ones, &c. With these must go hand in hand the means of healing the injury inseparable from the operation, and of restoring the animal to its normal condition so far as the nature of the procedure permits.

Such a discussion of operative methods appears to me necessary, chiefly because it becomes more evident every day that, in the ordinary method of the so-called "acute" experiment, carried out at one sitting, and complicated by free bleeding, many sources of error lie concealed. The crude damage done to the integrity of the organism sets up a number of inhibitory influences which react upon the functions of its different parts. The body as a whole, in which an enormous number of different organs are linked together in the most delicate fashion for the performance of a common and purposive work, cannot in the nature of things remain indifferent to forces calculated to destroy it. It must, in its own interests, restrain some functions while others are allowed free course, and thus, by appropriately economising its energies, rescue that which is possible to save.

This circumstance was formerly, and still is, a great hindrance to the efforts of analytical physiology, while, in the developments of synthetic physiology, where it is of value to determine the real course of this or that phenomenon on the uninjured and normal organism, it continues to be an unavoidable obstacle. Operative discovery, as a means of physiological research, has by no means been played out. On the contrary, it is only just coming into full activity, as is testified by the achievements of the present day. For example, we need only mention the extirpation of the pancreas by Minkowski; the transference of the portal blood into the vena cava by Eck; and, finally, the amazing operations of Goltz, in which he removed bit by bit the various parts of the central nervous system. Have not many physiological questions been thereby settled, and do not innumerable others arise from the results already obtained? It may be objected that I am warmly contending for what is already recognised. Yes, but such operations are altogether rare, and only carried out by the few. If, for instance, the number of physical instruments which are yearly invented and introduced for the investigation of physiological phenomena, as well as the number of chemical methods and their variations, be compared with the number of new physiological operations which permit of the survival of the animal, the paucity of the latter stands out in marked contrast to the richness of the former. Again, it is remarkable that many of these operations are introduced by surgeons and not by physiologists. The physiologists do not regard such problems as essential, or perhaps are not in possession of the means necessary for their solution. The clearest testimony in proof of the fact that surgical methods have not assumed their legitimate position in physiology is evidenced by the fact that in the buildings for a physiological laboratory of the present day, while provision is made for chemical, physical, microscopic, and vivisecting departments, none is made for an efficient, well-equipped surgical set of rooms. The general rooms of a laboratory cannot be used for carrying out frequent and complicated operations with safety to the life of the animal afterwards, without the sacrifice of much time and labour; moreover, the surgical precepts of the age must not be neglected. There can be little doubt that even single operations in the general rooms of the laboratory, performed with the aid of anti- or a-septic precautions do not succeed, or perhaps are not attempted, because it is almost impossible to maintain a sufficient degree of animal cleanliness during and immediately after their performance from want of a large surgical department expressly fitted out for the purpose. Take, for example, the well-known history of the Eck's Fistula, which consists in the establishment of a communication between the portal vein and the inferior vena cava. In the old laboratories its inventor, notwithstanding his energy and acumen, could not succeed in keeping the animals alive for any length of time after the operation. The same misfortune attended Dr. Stolnikow, who repeated the operation with the assistance of Dr. Eck, sparing neither trouble nor animals. It was only in the operative section of the physiological department of the St. Petersburg Institute for Experimental Medicine, then just founded, and consequently in the surgical sense clean, that any considerable proportion of successful cases was attained. This happy period lasted, however, only for a year. The physiological institute was at that time small, and therefore, in spite of the employment of every precaution, became so rapidly impure that the Eck's operation, though carried out by the same, but still more experienced hands, degenerated into a fruitless waste of time. This continued for a year, notwithstanding all the endeavours

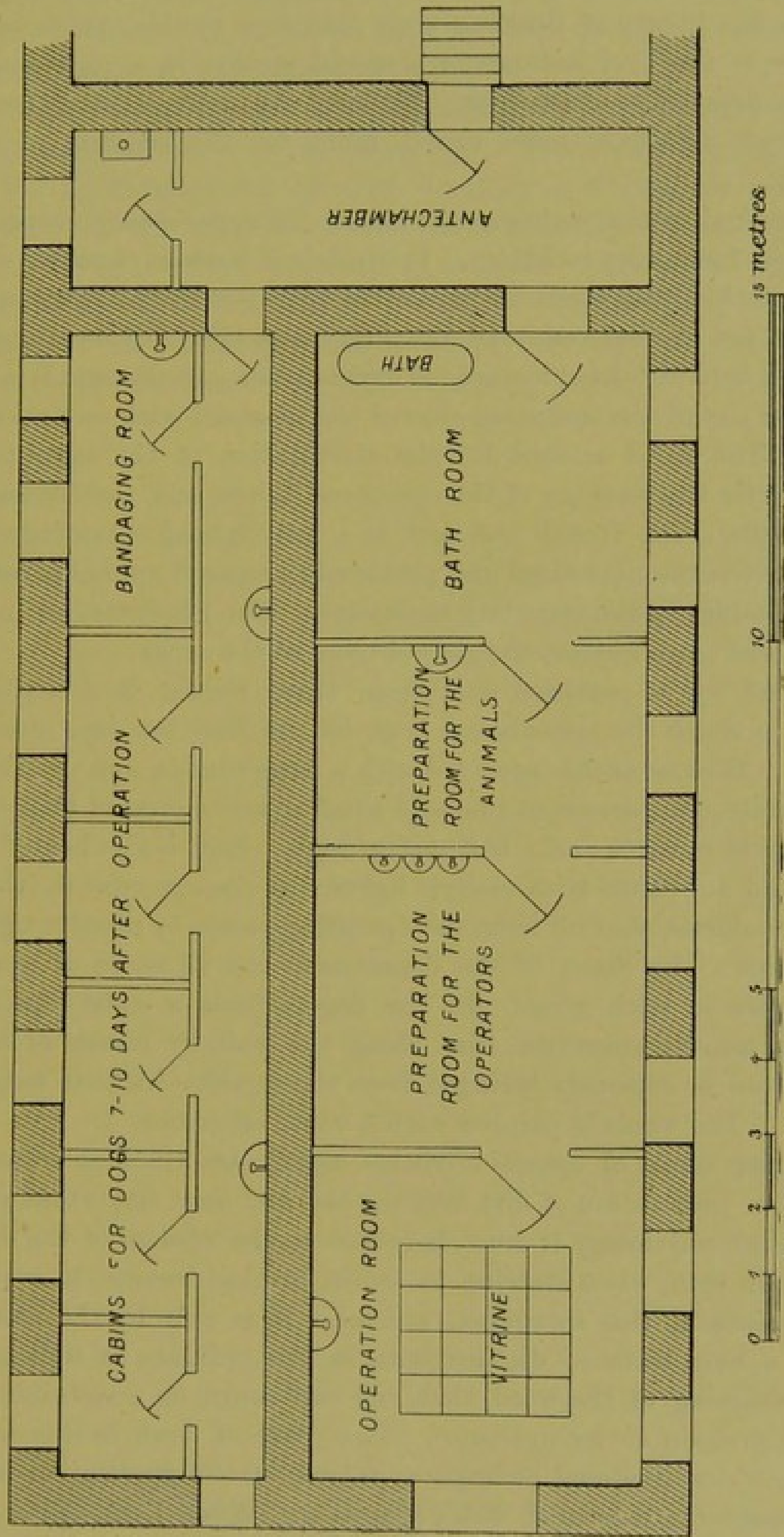


FIG. 2*a*.—Plan of the Surgical Department of the Physiological Laboratory in the St. Petersburg Institute for Experimental Medicine.

of the operators, till a new physiological department, in which greater space was allotted to the operative section, was added to the building.

I take the liberty of drawing your attention to this, which, so far as I know, is the first instance of a special section in a physiological laboratory devoted to operations. Perhaps the example may give my physiological colleagues some useful hints for the erection of new institutes.

The surgical section embraces the half of the upper storey—a quarter of the whole laboratory buildings. It consists of a series of rooms along one side, in which the preparations for the operation as well as the operation itself are carried out. In the first room (Fig. 2*a*) the animal is washed in a bath and dried in a special drying place. In the next it is narcotised, the site of the operation shaved and cleansed with an antiseptic solution. The third is used for the sterilization of the instruments and cloths, for the washing of the operators' hands, and the donning of their overalls. The fourth and last is a well-lighted operating-room. Into this room the narcotised and previously prepared animal is carried (without a table) by the operators themselves. The laboratory attendant is not allowed to go beyond the second room of the series.

Separated by a partition-wall from these rooms, is a series of cabinets, in which the animals are kept for the first ten days after the operation. Each cabinet is provided with a large window and ventilating arrangements, occupies about four and a half square metres of floor space, and is more than three and a half metres high. Each is also heated with hot air and furnished with electric lights. A passage runs in front of these dog cubicles, shut off from the operating-rooms by massive tightly-fitting doors. The floors of the department are all made of cement, with gutters in each room. In the dog cabinets a water-pipe, with numerous minute apertures, runs along the wall, by means of which the floor can be copiously syringed from the corridor without entering the room. The whole is painted with a white oil colour.

The long series of operation-rooms constitutes the best protection against the penetration of dirt into the last and most important room; for, although physiology is much indebted to the wisdom of the dog, it would be in vain, when striving to attain surgical results, to count on the assistance of this intelligent animal. It is only by the arrangement of a long series of dirt-catchers, in the ordinary as well as the surgical meaning of the word, that one can count on maintaining the operative division at its optimum. Two years of work in this department have not rendered it impure, judged by the application of our surgical test—the success of Eck's operation. When I call to mind the results of operations carried out during the last twenty years in different buildings, and always upon equally healthy material, with constant repetition of the same operations, I am convinced of the magnificent success which attends cleanliness, possibly in even a more striking way than the surgeon. It has preserved numerous animals alive and spared our operating staff both time and trouble.

I hope you will pardon this long digression concerning the importance of surgical methods in physiology. I am convinced that it is only by the development of our ingenuity and skill in performing operations on the alimentary canal that the exquisite chemical work effected by it will be revealed to us, the outlines of which can already be traced by the aid of the present methods. I beg of you to reflect on these closing words of my present lecture; you will then, I am persuaded, be convinced of their truth.

LECTURE II.

THE WORK OF THE GLANDS DURING DIGESTION.

The beginning of gland secretion is connected with the entry of food into the alimentary canal—The quantity of juice is proportional to the amount of food—The curve of secretion; its importance and exact regularity—Qualitative changes in the juice during secretion; examples—Methods of investigating the properties of the juices—The gastric juice possesses a constant acidity—Meaning of the qualitative variations of the juices—Differences in the rate of secretion and in the digestive capabilities of gastric juice, with diets of flesh, bread and milk—Meaning of these differences—The course of secretion and properties of pancreatic juice, with the same diets—The work of the digestive glands under the prolonged influence of different dietaries.

Gentlemen,—Having considered the means by which the work of the digestive glands may be more or less perfectly observed, we may now turn to the work itself. By the aid of the older methods (the ordinary gastric fistula and the earlier forms of pancreatic fistula), the first and most elementary facts concerning the activity of the digestive glands were established, not however without trouble and difficulty. Thus, it was recognised by all authors that the glands only first began to secrete when the food entered the alimentary canal, and, thanks to the methods now at our command, hardly any physiologists doubt that the activity of the glands is strictly dependent upon the taking of food. Every one of our experiments on dogs gives, in this respect, an unequivocal and positive result. The isolated miniature stomach which, in fasting animals, is perfectly empty, begins to furnish juice within a few minutes after the animal has taken food. Similarly with dogs having pancreatic fistulæ: the quantity of juice, which is only two to three cubic centimetres per hour, is increased to many times that amount after the entry of food. This is a fact which has long been suspected, but has only now been fully established. It is, moreover, consistent with the requirements of the case. The juice is only poured into the alimentary canal when the raw material, the elaboration of which is demanded, makes its appearance therein. This is an apparently simple fact, but it is obvious that it involves a multitude of subtle problems connected with the activity of the glands.

The older methods were quite unable to give an answer to such a question even as the following: How does the quantity of juice alter with varying amounts of the same diet? In other words, is the quantity of juice directly proportional to the amount of food taken, or do these two factors hold a different relationship to each other? As a matter of fact, it was scarcely possible to solve this question, so far as the stomach was concerned, by means of the simple fistula alone. The juice could neither be separated from the food nor its quantity correctly determined. At present we are in command of perfectly accurate data upon this point. The problem is easily solved on the dog with the isolated stomach. We simply give it different quantities of the same food and collect the corresponding quantities of pure juice. It appears, from these investigations, that there exists an almost exact proportional relationship between the quantity of juice secreted and the amount of food taken. Thus, for raw meat, Dr. Chigin gives the following mean values: For 100 grms. flesh, 26·0 c.c. of juice were secreted; for 200 grms., 40·0 c.c.; for 400 grms., 106·0 c.c.

For a mixed diet, consisting of meat, bread and milk, the following figures were obtained:

With a diet of { 50 grms. meat, 50 „ bread, 300 c.c. milk } 42·0 c.c. of juice escape.
With double the above quantities, 83·2 c.c.

Hence, we are justified in concluding from these figures that the gastric glands work with great precision, inasmuch as for varying quantities of diet administered, they pour out an exactly proportional amount of juice, determined in the first instance by the quality of the food. I regard this result as extremely instructive; it points, without doubt, to the great accuracy and precision of the work of the digestive canal.

And now we proceed to other questions: How does the work of secretion proceed? Is the requisite quantity of juice poured out once and for all on the ingested food; or, does the secretion continue so long as the food remains in that particular segment of the alimentary canal, and does it vary regularly with the decreasing quantity and altering properties of the mass?

These questions long ago gave origin to a multitude of investigations from which it appears that the secretion of juice is continuous throughout the whole period of digestion but with a varying rate of progress. The data in question do not, however, give the impression of much conformity. The cause is to be sought for partly in the defects of the methods, partly in the investigators themselves, who did not always endeavour to give the requisite degree of exactness to their researches. Thus, food was often administered in unknown quantities, of indefinite composition, and under varying conditions of appetite or the reverse.

In our researches, to compare accurately the work of excretion under different conditions, we have bestowed from the first, a minute degree of exactitude upon the experimental arrangements. As a matter of fact, the course of the secretion when the same conditions are applied has now become an absolutely constant one. This, so to speak, almost physical exactness of complex physiological processes imparts a feeling of satisfaction to the experimenter which rewards him for his many hours of perseverance in watching the glands under a condition of activity. As guarantee for what I have said, I give here two experiments on the gastric glands, taken from the work of Dr. Chigin, and likewise two on the pancreas taken from that of Dr. Walther:

Work of the Gastric Glands after a meal of 100 grms. flesh. (Two experiments, 3rd and 5th July 1894.)			Work of the Pancreas after a meal of 600 c.c. milk. (Two experiments, 14th Feb. and 5th March 1896.)		
Hour after feeding.	Quantity of juice in c.c.		Hour after feeding.	Quantity of juice in c.c.	
1st . .	11·2	12·6	1st . .	8·75	8·25
2nd . .	8·2	8·0	2nd . .	7·5	6·0
3rd . .	4·0	2·2	3rd . .	22·5	23·0
4th . .	1·9	1·1	4th . .	9·0	6·25
5th . .	0·1	a drop	5th . .	2·0	1·5
Total	25·4	23·9	Total	49·75	45·0

The foregoing results are also represented in the following curves, the time in hours being given on the abscissa, the quantity of juice on the ordinate line. The curves read from left to right. (Figs. 3and 4.)

The results, naturally, are not always so concordant as those given; nevertheless, when such a correspondence is found in two experiments out of five, it must, in all justice, be accepted as striking testimony to the exact regularity with which the glands work. We have every reason to believe that the existing deviations are to be ascribed to differences in the conditions of experiment as yet undiscovered; that is to say, that even the variations which occur from time to time in secretory work are determined by fixed conditions.

The work of the glands, viz., the secretion of juice, follows therefore a definite periodic law. The fluid is not poured out at the same rate from the beginning to the end of digestion, nor even in regularly diminishing quantities, after having attained an initial maximum. The curve is by no means a straight line gradually approximating the abscissa. It is a special curve which slowly or rapidly ascends, or preserves for a time a uniform height, or gently or suddenly falls, as the case may be. Examples of these will be given later. Since these curves repeat themselves under the same conditions with stereotyped exactitude, we must admit that this or that rate of secretion is not determined by mere blind chance, but in all cases follows a necessary

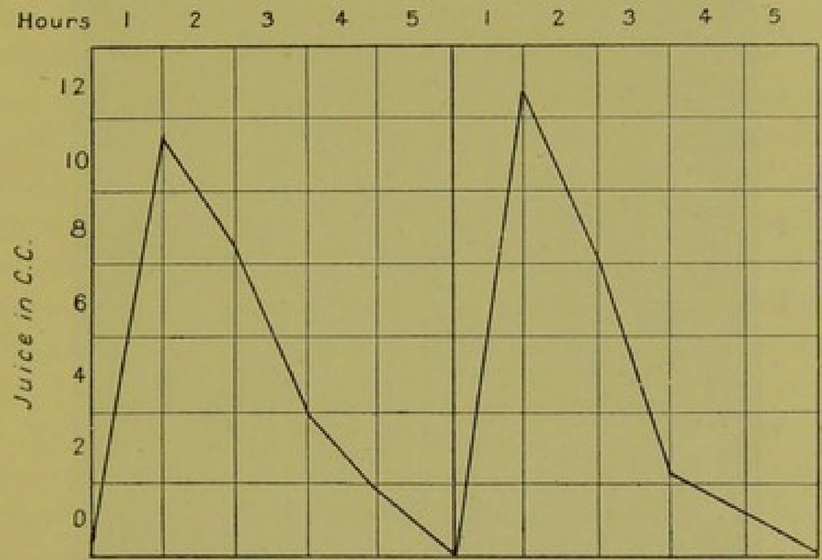


FIG. 3.—Curve of secretion of gastric juice, after a meal of flesh. (Two experiments.)

law, requisite for the due elaboration of the food and therefore beneficial to the organism. The curves, however, are not easy of interpretation in all their separate features; indeed, for the present, this is almost impossible. The line of descent with its fluctuations can more or less satisfactorily be explained on the principle of corresponding variations in the quantity of ingesta at any particular part of the digestive canal. But the meaning of the complex line of ascent remains in many cases obscure and inexplicable. How, for example, can the late appearance of the maximum be explained, which we see during the third hour after a meal, in the curve of pancreatic juice? A scientific exposition of the curves, that is, one which fully and accurately corresponds with the actual facts of the case, can only be furnished by physiology when, as mentioned in our first lecture, the changes both quantitative and qualitative, which the food and its admixed secretion undergo, are followed, step by step, throughout the whole alimentary canal.

We now pass on to a further question. If the glands, as we have seen, are in a position to vary their work so remarkably, with regard to the quantity of juice which they produce, are they not also able to extend similar variations to the properties of the secretion? Judging from a theoretical standpoint, one would expect that in different phases

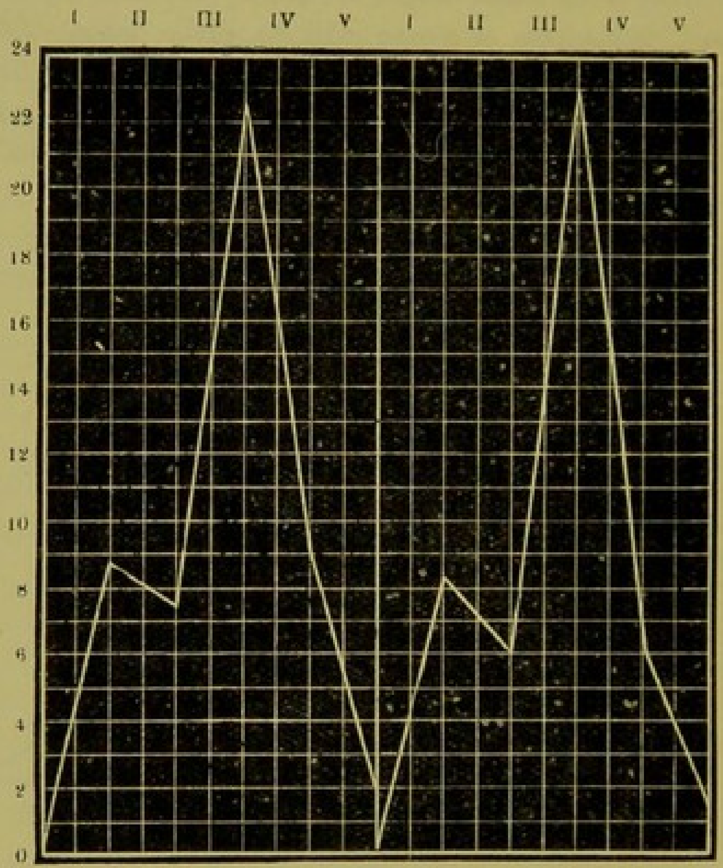


FIG. 4.—Curve of secretion of pancreatic juice. Food, 600 cc. milk. (Two experiments.)

of the digestion of the same food, a juice of varying properties would be necessary. The total mass of food can have so altered, both in chemical and physical respects, under the influence of the first portions of juice, that it may need for its further digestion a juice of different composition. Thus, more or less water, or a varying degree of acidity or alkalinity, or a different content of ferment in the fluid, may be required. All these separate conditions of juice activity are naturally not without importance. But so long as we dealt only with digestive experiments performed *in vitro,* we could render no account of these matters. It is true that science has long since answered our question in the affirmative, viz., that the properties of the juice do alter during the period of secretion. But the observation, it appears to me, has not been appreciated to its full extent, otherwise it would have become an inexhaustible source of persevering inquiry as to why and how these variations come to pass. Later I shall adduce instances from our storehouse of observations dealing with these highly interesting qualitative variations of the juice during the separate periods of digestion. Naturally, it will be found that the greatest interest is attached to variations in the ferment content, although, strictly speaking, the remaining properties of the digestive juices demand an equally careful investigation to arrive at a satisfactory explanation.

The available material, especially as regards gastric juice, could not be considered sufficient. Experiments with the ordinary gastric fistula permit of only very hypothetical deductions, since they deal, not with pure juice, but with a mixture of juice and food. Nor can Heidenhain's observations on the isolated fundus be taken as an index of normal digestive work, since the activity of the isolated stomach, after division of its secretory nerves, obviously differs greatly from the normal. The investigations of Heidenhain on the pancreatic secretion in dogs operated upon by his method, must however be recognised as scientifically exact, though, unfortunately, the food was not of definite composition. Nor were all the details published; they merely appeared in Hermann's Encyclopædic Handbook in condensed form.

But before I take up the question of our own results, I must draw your attention for a short period to the methods we employed in our study of the digestive juices. The proteolytic power of the fluid was determined by the process of Mett—a procedure worked out in this laboratory and since then constantly retained in use. It consists in this; fluid egg-white is sucked up into a fine glass tube of 1 to 2 mm. lumen, and coagulated therein at a definite temperature (95° C.). The tube is then cut into small pieces, which are placed in one or two cubic centimetres of the fluid to be investigated. The whole is kept in the thermostat at 37° C. to 38° C., and requires no further watching. Solution of the proteid occurs at the ends of the small glass tubes. After the termination of a certain period, the length of the pieces of tube, and that of the undigested remains of the proteid columns, are measured off with the aid of a millimetre scale and a microscope of low magnifying power. The difference gives the length of the digested proteid cylinders in millimetres and fractions of a millimetre. This method leaves nothing to be desired so far as convenience of application, and clearness with exactness of results is concerned. Test experiments specially carried out (Dr. Ssamojloff) have convinced us that the digestion of the proteid columns, at least within the first ten hours (employing the fluids which we have to deal with) is directly proportional to the length of the period. This was the case even when the fluid possessed its highest digesting power. These experiments did away with the very natural mistrust that the solution of the proteid may proceed at varying rates at different depths of the tubes, dependent upon more or less stagnation of the digestive products within the lumen. It may therefore be accepted that the length in mms. of egg-white dissolved by the several juices in a certain time, gives us an exact relative measure of the digestive power of the fluid. In the researches of Borrisow, carried out upon this question in the laboratory of Professor Tarchanoff, the relationship which lies at the basis of the connection between the length of the digested column of egg-white and the pepsin contents of the fluid under investigation, came out with perfect clearness. The following is the rule which expresses it, viz., *the quantity of pepsin in the compared fluids is proportional to the square of the rapidity of digestion*—*i.e.*, to the square of the column (expressed in millimetres) which the juices are capable of digesting in the same period of time. An example in figures will make this clear. If one of the fluids digests a column of 2 mm. of proteid, and the other a column of 3 mm., the relative quantity of pepsin in each is not expressed by the figures 2 and 3 respectively, but by the squares of these numbers—*i.e.*, by 4 and 9. The difference is instructive. According to linear measurement, we should have in the second fluid one and a half times more ferment, but according to our rule of squares, the second fluid is two and a quarter times stronger than the first. This rule has, of course, been deduced from comparisons made with numerous artificial solutions of pepsin exactly prepared. Moreover, the result which Dr. Borrisow arrived at independently, had already been discovered before him, by Schütz, from polarimetric estimation of the amounts of peptone formed during the digestion of egg-white. This correspondence in the data furnished by different methods affords strong assurance of the correctness of the rule. I must here express my regret that the method of Mett, which was published so long ago as the year 1889, has not been as widely employed as it in reality deserves. How easily could it be made a universal means of comparing proteid digesting ferments, so that investigations upon these ferments would be comparable with each other? No one will deny that this is desirable in a high degree, for then all observations on the juices of different animals and men would be represented upon a uniform scale, which would lead to important deductions concerning variations of ferment in the individual, the species, and the genera. We have still to add that the diameter of the tube, even within wide limits, is without importance, and that the white of the hen's egg is of sufficiently constant composition to be employed as a test object for the purpose. The law of Schütz and Borrisow applies also in its full extent to the action of trypsin.

The methods of comparing the working of other ferments are less perfect, and in our experiments have been, and still are, frequently modified. The activity of the amylolytic ferment of the pancreas was for a long time determined in the laboratory by titrimetric estimation, after the method of Fehling, of the sugar, which is formed from a given quantity of starch paste exposed under certain conditions to the activity of the ferment. The number of milligrammes of sugar produced, served as a measure of the amylolytic activity. This method furnished good and reliable results, but necessitated a great expenditure of time, and was, therefore, not wholly satisfactory in a research where numerous estimations were required. Hence a more rapid one was sought for, and recently an attempt was made by the laboratory (Drs. Glinski and Walther) to estimate the activity of the proteolytic and amylolytic ferments of the pancreas by analogous methods. Thin glass tubes were filled with coloured starch paste and then exposed in the thermostat to the action of the ferment for a certain period, usually for half an hour. The paste was dissolved from the ends inwards, the limit of ferment-action, thanks to the colouration, being clearly visible. As in peptic digestion, the length of the digested column was measured and expressed in millimetres. From numerous experiments with artificial solutions of ferment (pancreatic juice diluted twice, thrice, &c.) the relationship between the quantity of ferment and the length of the dissolved column of starch has been established. The law of Schütz and Borrisow is valid here also to its full extent—*i.e.*, the content of ferment in the fluids, varies with the square of the length of the column of digested starch measured in millimetres. The activity of the amylolytic ferment will therefore be expressed in both ways in the experiments given below, viz., in terms of the milligrammes of sugar formed, and also in that of the number of millimetres of starch-column dissolved.

Unfortunately all attempts to base an evaluation of the fat-splitting ferment upon the same system have, up to the present, remained fruitless, and we had finally to set to and determine by titration with baryta solution, the acidity of the permanent emulsion formed by fat and pancreatic juice, after it had stood for a certain time (with periodic shaking) at a given temperature. The number of cubic centimetres of baryta solution which were necessary for the neutralisation of the fat acids, served as measure of the activity of the fat-splitting ferment. But naturally our failure will not prevent us from endeavouring to obtain a method uniform with those applied to the other ferments. As matters now stand, the method we are compelled to use demands the continuous attention of the experimenter, and is therefore very troublesome where numerous estimations have to be made. But this is unavoidable when the properties of the juice have to be followed from hour to hour, or even at still shorter intervals. To this it must be added that the results of the method are not always equally reliable. The law of Schütz and Borrisow was, however, confirmed here also. Naturally our experiments deal in general only with *comparisons* of ferment *activity*, and our deductions concerning "quantities" and "total amounts" of ferment must therefore be accepted conditionally. In

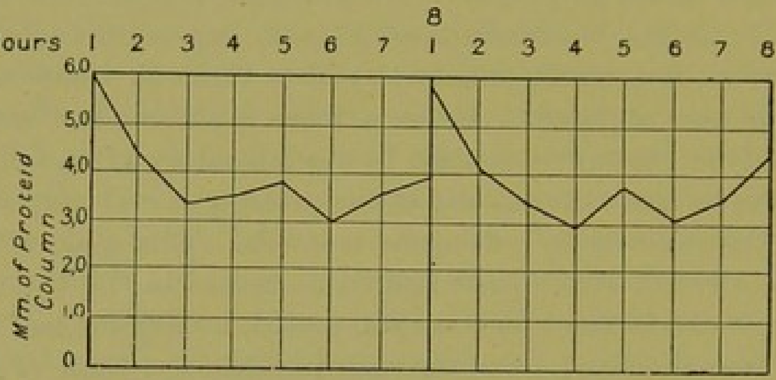


FIG. 5.—Digestive power of hourly portions of gastric juice after administration of 400 grms. of flesh. (Experiments of 15th and 16th May 1895.)

many instances however, perhaps with gastric juice in all, we may correctly speak of a quantitative determination of the ferment, since in the case of this juice the digestive power always runs parallel with its content of organic material.

A few words concerning how we estimated the alkalinity of pancreatic juice. The solid residue of a measured quantity of juice was incinerated over a weak fire, and the salts, dissolved in water, and titrated. The result was reckoned in terms of Na_2CO_3 and expressed in percentages of the original quantity of juice.

The experiments, from the description of which I broke off in order to give these necessary explanations of methods, will now be given in two pairs: the one pair dealing with the gastric glands, the other with the pancreas. They furnish evidence showing that the *properties* of the digestive juices vary during the progress of secretion according to the same laws which we have learned to hold good for their variations in hourly *quantity*.

HOURLY VARIATIONS IN DIGESTIVE POWER OF GASTRIC JUICE AFTER A MEAL OF 400 GRMS. OF RAW FLESH.

Experiments of 15th and 16th May 1895 (taken from the work of Dr. Lobassoff).

Hour.	Millimetres of egg-white column digested.	
1st	6·0	5·8
2nd	4·3	4·1
3rd	3·4	3·4
4th	3·5	3·0
5th	3·8	3·8
6th	3·0	3·1
7th	3·6	3·5
8th	3·9	4·5

The same results are given in the form of curves. (Fig. 5.)

THE DIGESTIVE POWER OF PANCREATIC JUICE HOUR BY HOUR AFTER A MEAL OF 600 C.C. OF MILK.

Experiments of 27th and 29th December 1896 (from the work of Dr. Walther).

Hour.	Fat-splitting ferment.		Amylolytic ferment.		Tryptic ferment.	
	27 Dec.	29 Dec.	27 Dec.	29 Dec.	27 Dec.	29 Dec.
1st	14·0	14·0	5·1	5·0	5·8	5·5
2nd	20·0	13·0	5·0	4·7	5·9	5·5
3rd	7·0	5·2	2·4	2·4	4·3	4·1
4th	6·0	7·0	3·3	3·4	4·5	4·4

The same is represented in curve form. (Fig. 6.)

We are now in a position to appreciate once more the astonishing exactitude of the work: that which is demanded of the glands they furnish each time to a hair's-breadth, no more and no less. And we can also convince ourselves of a fact which is of great importance as a characteristic of gland activity. These organs are capable of producing a secretion of varying composition, with a greater or less quantity of ferment, or with a different proportion of the individual ferments, when, as in the case of the pancreatic juice, several such are present. Moreover, other properties of the juice, not alone its content of ferments, are likewise varied. If we examine the figures which deal with this point, and compare them with the hourly quantities secreted, we shall see that the alterations in the concentration of the juice are not determined solely by the rapidity of secretion. We encounter the most diverse relations between the content of water and the richness of the juice in ferments; a strong digestive power may recur both with a copious as well as with a scanty secretion. In one and the same juice, the different ferments may suffer variations running courses independently of each other, a fact which undoubtedly shows that glands such as the pancreas, which possess a complex chemical activity, are able to furnish, during given periods of their secretory work, now one product and now another. That which has been said of the ferments may also be applied to the quantities of salts present in the juices.

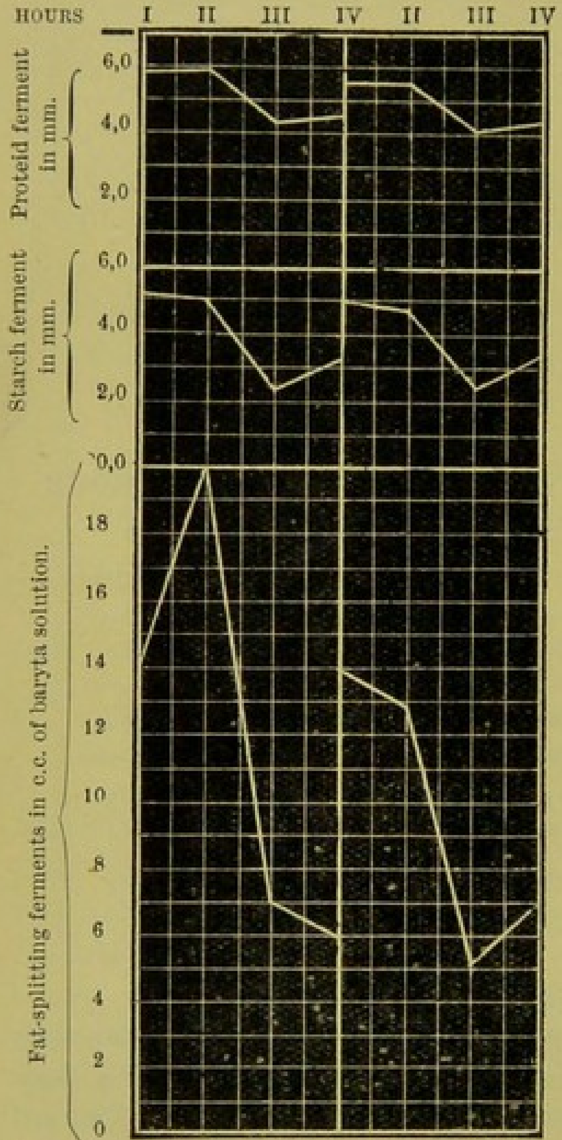


FIG. 6.—Ferment content in hourly portions of pancreatic juice after a meal of 600 c.c. milk.

All the more interesting, therefore, appears the fact, as one must accept it, that the gastric juice possesses a constant acidity. It is true that clinical investigations of the secretory activity of the human stomach are almost daily concerned with variations of acidity, and even in our observations, where we deal with absolutely pure juice, such fluctuations are also to be seen. But a careful investigation of all the data leads to the almost indubitable conclusion that the juice, as it is poured out by the glands, always possesses the same degree of acidity. We do not, however, receive the juice directly from the glands, even in our method. After it is secreted by these it has to flow down over the alkaline mucous membrane and inevitably becomes partially neutralised, that is to say, has its acidity reduced. To this circumstance must be attributed the apparent fluctuations of acidity, as is clearly shown by numerous observations. It is a rule almost without exception that the acidity of the juice is closely dependent upon the rate of secretion; the more rapid the latter, the more acid the juice, and *vice versâ*. This relationship is easily to be understood in the light of our explanation. The greater the quantity of juice the more rapidly will it flow over the stomach-wall, and therefore the less will it become neutralised. The acidity observed under these conditions will thus more closely approximate to that which is real and authentic. In order to test this explanation, experiments of various kinds were instituted by Dr. Ketscher. Since the wall of the stomach is usually covered with a considerable layer of mucus, it is quite natural that the first portions of juice secreted, for example under the influence of sham feeding, will manifest the lowest acidity. The more freely and rapidly the juice flows, the greater will be its acidity. During the decline of the secretion we find an absence of the low acidity pertaining to a corresponding rate of outflow at the beginning of the experiment. Obviously this is because the stream of juice has been neutralised by the mucus, and if the stomach has been washed, so to speak, in this manner several times in succession, not unfrequently all connection between rate of secretion and degree of acidity can be removed. That is to say, the juice is equally and strongly acid whether it be rapidly or slowly poured out. On the other hand, Dr. Ketscher has collected the juice in the following way during the course of the same sham-feeding experiment for periods of five minutes duration each. During one five minutes the fistula remained open, during another it was kept closed, and the juice allowed to escape at one rush. It resulted, in nearly all cases, that the portions of juice obtained in the second way—*i.e.*, after a delay of five minutes in the stomach, possessed a lower acidity than the others. And if fluctuations of acidity can occur in this way with pure gastric juice, all the more easily will they arise in a stomach to which food mixed with saliva can gain access. Moreover, a short time ago we made observations in the laboratory upon a dog suffering from strongly marked hyperacidity of pathological origin. But in no single sample of the juice did the acidity prove to exceed the normal. (*Pawlow.*) If all this be correct, the varying necessity for acid during the course of digestion is supplied by variations in the quantity of juice and not by changes in its acidity. It is, however, possible that the neutralisation of the gastric juice must be looked upon as a purposive and desirable event with a definite aim. In the normal stomach a perfectly pure juice may have its acidity reduced to the extent of twenty-five per cent. by neutralisation with mucus. Who knows, perhaps nature has found it serviceable in the interests of the organism, or the elaboration of the food, to vary the acidity precisely in this way! That it does fluctuate remains a fact, however it may happen to come about.

We may now take up the threads of our discourse once more. You have seen striking instances of the fact that the juice furnished by the pancreas and by the digestive glands during the course of the same act of digestion does not remain uniform, but is varied in many respects. It is in the highest degree both interesting and important to determine in what way these variations are related to the progress of the act of digestion, and whether they are of service to it. A complete solution of this problem must be left to the future. Some of the details, however, disclose an obvious purpose. Take, for example, the first secreted portions of gastric juice: they are distinguished from the others by a stronger digestive power. It is evident that at the beginning of digestion, when the quantity of food is large and its external structure still coarse, this is well timed. The strongest juice is thus poured out when it is most needed.

In the case of the pancreatic juice it is much more difficult to show that the alterations in its composition are purposive. Here the matter concerns a later stage in the work of our factory, where a food material already modified and assorted by the stomach has to be further worked up. To this end chemical conditions must be provided in the intestine which help on the action of the pancreatic juice. This means that the conditions under which gastric digestion has been accomplished must be radically changed, since they are injurious to the action of the pancreas. We know that trypsin is digested by pepsin, and that a high degree of acidity injuriously influences its activity. I merely raise these questions now. Their elucidation will be taken in hand after we have discussed the mechanism of excitation of the glands.

The facts already communicated indicate that the glands are able to adapt themselves to the separate and successively occurring phases of the elaboration of the food. In connection therewith we may rightly suppose that this adaptability will only appear to its full extent when we compare the variations in the progress of secretion under different dietaries with each other. Since the food is made up of several constituents, and since different juices are poured out into the alimentary canal, the supposition appears natural that each fluid, with accentuation of certain of its properties, is furnished chiefly for a particular kind of food.

Is this in reality the case? It is obvious that an answer to this question was impossible by the aid of the older methods. Now, however, the fact that we are able to consider it is, of itself, a brilliant testimony to the essential service rendered by our newer methods. At present we can convince ourselves by actual experiment of what *à priori* only appeared probable, viz., that every individual kind of food calls forth a particular activity of the digestive glands, with special properties of the digestive juices.

We may commence with the stomach. Researches carried out by

Dr. Chigin on dogs with isolated miniature stomachs have shown that both a mixed diet, as well as the separate administration of milk, bread or meat, &c., produce each time characteristic modifications of activity of the gastric glands. The speciality of the work applies not alone to the properties of the juice, but to the rate and duration of its secretion, and also to its quantity. We will deal with these points in order.

The greatest digestive power belongs to the juice poured out on bread, which for shortness we may name "bread-juice."* Its mean proteolytic power, according to Dr. Chigin, is represented by 6·64 mm. A diet of flesh calls forth a juice of 3·99 mm. digestive power, and one of milk of 3·26 mm. If we now turn to a comparison of these juices with one another we find, according to the law of Schütz and Borrisow, that "bread juice" is represented by 44 ($6·64^2$), "flesh juice" by 16 ($3·99^2$), and "milk juice" by 11 ($3·26^2$).

In other words, "bread juice" contains four times as much ferment as "milk-juice," and, is in this respect, four times as concentrated.

The matter may be illustrated by the following protocols taken from experiments of Dr. Chigin:

At eight o'clock in the morning the dog was given 200 grms. of bread to eat.

Time.	Hourly quantity of juice in c.c.	Digestive power in mm.
8–9 A.M.	3·2	8·0
10 "	4·5	7·0
11 "	1·8	7·0
Dog then given 200 grms. raw meat.		
12 noon	8·0	5·37
1 P.M.	8·8	3·50
2 "	8·6	3·75
Dog now received 200 c.c. milk.		
3 P.M.	9·2	3·75
4 "	8·4	3·30
An additional 400 c.c. of milk now given.		
5 P.M.	7·4	2·25
6 "	4·2	2·2

The influence of the different foods upon the digestive power of the juice is striking. In order to exclude the possibility that the order of administration could have influenced the result I append another experiment.

* In harmony therewith we shall also speak of "meat-juice" and "milk-juice" instead of the longer, but more correct, terms of "juice secreted after the administration of meat and milk" respectively.

The dog received 200 c.c. of milk.

Time.	Quantity of juice in c.c.		Digestive power in mm.
8.30–9.30 A.M.	7·0	...	1·5
10.30 "	6·0	...	2·0

145 grms. of bread were now given.

11.30 A.M.	2·0	...	3·37
12.30 P.M.	3·6	...	5·0

200 c.c. of milk again given.

1.30 P.M.	5·4	...	3·37
2.30 "	3·4	...	2·0

Not alone the digestive power, but likewise the total acidity,* varied according to the nature of the diet. The latter is, however, greatest with flesh (0·56 per cent.) and lowest with bread (0·46 per cent.). In a similar way the quantity of juice poured out and the duration of its secretion are dependent upon the kind of food. And this relationship is equally clear whether, when estimating the food, one takes into consideration its total quantity, or its amount of dried substance, or, lastly, its content of nitrogen (since the gastric juice acts only on its proteid constituents).

If the quantity of juice produced during a given digestion period be divided by the number of hours in the period, the mean hourly quantity of juice is obtained. Even this number, which represents the mean hourly intensity of gland work, is different for the different sorts of food. Comparing equivalent weights, flesh requires the most, and milk the least gastric juice; but taking equivalents of nitrogen, bread needs the most and flesh the least. The hourly intensity of gland work is almost equal in the case of milk and flesh diets, but far less, with bread. The last, however, exceeds all the others in the time required for its digestion, and the duration of the secretion is correspondingly protracted.

Nor is this speciality of gland work, which depends on the variety of the food, limited to the distinctions given. It likewise prominently reveals itself in the hourly rate of secretion and in the qualitative variations of the juice. This time I furnish only one example for each kind of food, and beg you to believe that it repeats itself with the same admirable precision which we have already seen.

* The acid was estimated titrimetrically, and is expressed in percentages of HCl.

QUANTITIES AND PROPERTIES OF GASTRIC JUICE WITH DIFFERENT DIETS: 200 GRMS. FLESH, 200 GRMS. BREAD, 600 C.C. MILK.

(According to mean values obtained by Dr. Chigin.)

Hour.	Quantities of juice in c.c.			Digestive power in mm.		
	Flesh.	Bread.	Milk.	Flesh.	Bread.	Milk.
1st . .	11·2	10·6	4·0	4·94	6·10	4·21
2nd . .	11·3	5·4	8·6	3·03	7·97	2·35
3rd . .	7·6	4·0	9·2	3·01	7·51	2·35
4th . .	5·1	3·4	7·7	2·87	6·19	2·65
5th . .	2·8	3·3	4·0	3·20	5·29	4·63
6th . .	2·2	2·2	0·5	3·58	5·72	6·12
7th . .	1·2	2·6	—	2·25	5·48	—
8th . .	0·6	2·6	—	3·87	5·50	—
9th . .	—	0·9	—	—	5·75	—
10th . .	—	0·4	—	—	—	—

The same is represented in the following curves. (Figs. 7 and 8.)

These facts are interesting in a high degree and also of the greatest importance. Each separate kind of food corresponds to a definite hourly rate of secretion, and calls forth a characteristic alteration of the properties of the juice. Thus, with flesh diet the maximum rate of secretion occurs during the first or second hour, and in both the quantity of juice furnished is approximately the same. With bread diet we have always a sharply indicated maximum in the first hour, and with milk a similar one during the second, or the third, hour.

On the other hand, the most active juice occurs with flesh in the first hour, with bread in the second hour and the third, and with milk in the last hour of secretion. The point of maximum outflow, as well as the whole curve of the secretion, is always characteristic for each diet.

It appears to me that the facts here given lend strong support to our previous conclusion, that the variations in secretion which occur during the progress of a digestion period must have some essential meaning. When, for example, a characteristic curve of secretion is peculiar to every single kind of food, surely this must have a definite aim and possess a special significance.

We have now learned many of the fluctuations to which, under different conditions, the work of secretion is subjected. Their conformity to laws is a guarantee that they are important. It might at this point be interesting, or even necessary, to endeavour to comprehend the meaning of every such variation. This would bring the different facts into uniformity which up till now, by reason of their want of connection, have burdened the attention and memory of my hearers to an undesirable extent. But in cursorily introducing them I did not by any means intend that you were to retain all their complicated details in your minds; this would naturally need frequent repetition and a thorough study of the circumstances. I wished merely to bring home to you the

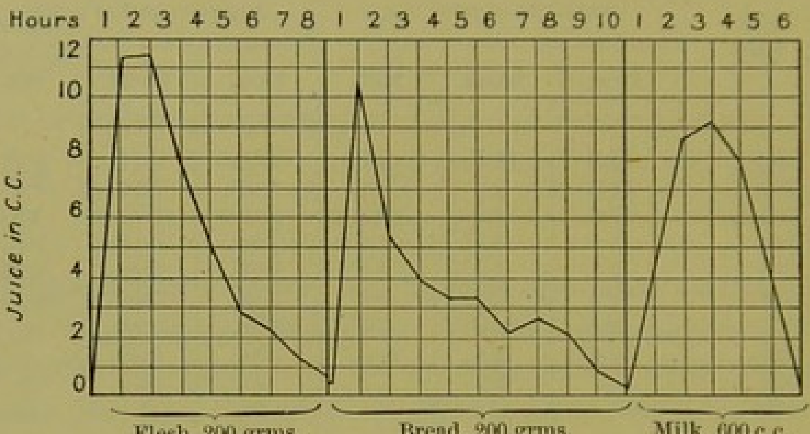


FIG. 7.—Curves representing the rate of secretion of gastric juice with diets of flesh, bread, and milk.

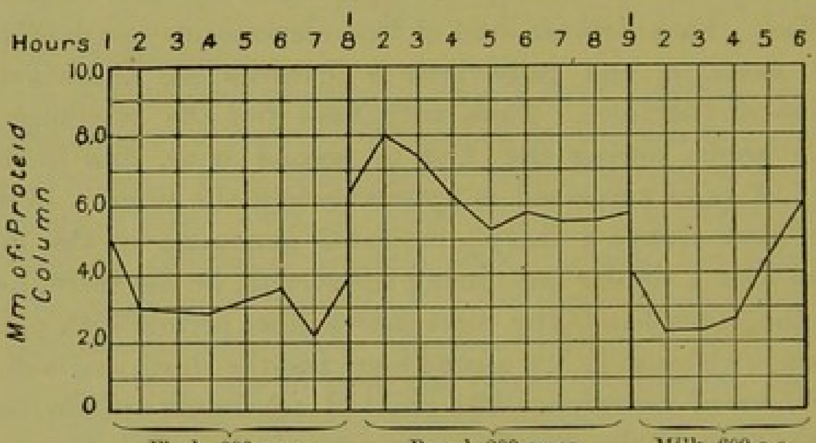


FIG. 8.—Curves representing the digestive power of gastric juice, hour by hour, with diets of flesh, bread, and milk.

conviction that the work of the digestive glands is, if I may say so, elastic to a high degree, while it is at the same time characteristic, precise and purposive. It is to be regretted that till now the *rationale* of the latter feature has remained a field of investigation but little touched upon. The belief that gland work conforms to laws largely depends at the present time on general inferences, and only in part upon facts not altogether clear in themselves and not wholly free from objection. Take, for example, the quantities of ferment which the stomach pours out on corresponding nitrogen equivalents of the various kinds of food:

on bread, 1600 ferment units; on flesh, 430; and on milk, 340. These figures I have obtained as follows: 100 grms. of flesh contain approximately the same amount of nitrogen as 600 c.c. of milk and 250 grms. of white bread. As shown by Dr. Chigin on

100 grms. flesh, 27 c.c. of juice of 4·0 mm. digestive strength,

and on

600 c.c. milk, 34 c.c. juice of 3·1 mm. digestive strength

are secreted. For 250 grms. bread we find no corresponding data, since he experimented with different quantities. They may, however, be easily constructed from the data at hand, on the basis of a proportion between amount of food ingested and the quantity of juice secreted. It results that for

250 grms. white bread, 42 c.c. of juice of 6·16 mm. strength

are secreted.

The squares of the digestive strengths (in millimetres) yield 38 for bread, 16 for flesh, and 10 for milk. These figures afford us the possibility of comparing the ferment concentrations in similar volumes of juice. Since, however, different quantities of juice are called forth by the different varieties of food, we must take this also into consideration in calculating the quantities of ferment. Multiplying, therefore, the squares of the numbers representing digestive strengths by the number of c.c. poured out on the corresponding food, we obtain the above-mentioned numbers, 1600, 430, and 340. These indicate that, on proteid in the form of bread, five times more pepsin is poured out than on the same quantity of proteid in the form of milk, and that flesh nitrogen requires 25 per cent. more pepsin than that of milk. These different kinds of proteid receive, therefore, quantities of ferment corresponding to the differences in their digestibility which we already know from physiological chemical experiments.

When comparing the work of the gastric glands with different foodstuffs, we must recognise that it is purposive in another sense also. The vegetable proteid of bread requires for its digestion much ferment. This demand is supplied less by an increase in the volume of the juice than by an extraordinary concentration of the fluid poured out. One may conclude from this that it is only the ferment of the gastric juice which is here in great requisition, whereas considerable quantities of hydrochloric acid would remain unused, possibly, indeed, would be injurious. We see, from other properties of the juice in this case, that as a matter of fact during the digestion of bread by the stomach an excess of hydrochloric acid is avoided. The total quantity of juice secreted on bread is only a little larger than that secreted on milk. It is distributed, however, over a much longer time, so that the mean hourly quantity of juice with bread diet is one and a half times less than after taking milk or flesh. Consequently, in the digestion of bread, but little hydrochloric acid is present in the stomach during the whole period of secretion. This harmonises well with the physiological-chemical observation that the digestion of starch, which is contained in large quantities in bread, is impeded by an excess of acid. From clinical observations we know further that, in cases of hyperacidity, a large part of the starch of bread escapes unused from the gastro-intestinal canal, while flesh is excellently digested.

Towards aiding the digestion of starch, or at all events with relation thereto, another phenomenon also plays a part which has already been several times mentioned but not yet explained. I mean the long pause of at least five minutes' duration which always intervenes between the taking of food and the beginning of secretion. This interval always occurs, whether the observation be made on the complete stomach with the aid of sham feeding, or on the miniature stomach of a dog normally fed.

This latent period, as it may be termed, is never less than four and a half to five minutes, but may often be as long as ten minutes. What is its significance? We have no reason for interpreting its occurrence on the basis of extrinsic conditions, to wit, such time as might be supposed to be necessary for the glands to fill up to their mouths, or till the juice moistens the inner wall of the stomach and runs in streamlets towards the fistular orifice. This cannot be the explanation, since the latent period occurs when the glands are already filled with juice, and the secretion spreads out over the gastric wall. Further, it would be singular to suppose that the gastric glands *per se*, are incapable of responding to a stimulus before the lapse of five minutes after its application. Nothing, therefore, remains but to recognise in the occurrence of the latent period a definite aim. Perhaps these five to ten minutes are reckoned upon to allow the action of the amylolytic ferment of the saliva to proceed. But this explanation cannot, of course, be regarded as very convincing, so long as the question has not been systematically brought under the scrutiny of scientific investigation.

All the more gladly do I now proceed to the work of the pancreatic gland, since here the adaptation of the secretion to the nature of the requirements is beyond all doubt. In the following table the experiments of Dr. Walther are collected together, which illustrate the work of the pancreatic gland upon different diets:

Diet.	Quantity of juice.	Proteolytic ferment.		Amylolytic ferment.		Fat-splitting ferment.	
		Strength of the juice.	Total quantity of ferment units.	Strength of juice.	Total quantity.	Strength.	Total quantity.
Milk, 600 c.c. .	48 c.c.	22·6	1085	9	432	90·3	4334
Bread, 250 grms.	151 ,,	13·1	1978	10·6	1601	5·3	800
Flesh, 100 grms.	144 ,,	10·6	1502	4·5	648	25·0	3600

By strength of juice in the above we mean the square of the number of millimetres in the column of dissolved proteid or starch, or the square of the number of cubic centimetres of standard alkaline solution employed. By total quantity of ferment units, we mean the product of the strength of the juice multiplied by the quantity of the same in cubic centimetres. The amounts of food chosen for comparison, represent as before, equivalents of nitrogen.

We see here again that each sort of food determines the secretion of a definite quantity of pancreatic juice, while the results, as regards the ferments, are truly striking. In this respect, also, each kind of food has its own particular kind of juice. The greatest amount of proteid ferment is found in "milk juice," less in "bread" and "flesh juice"; the most amylolytic ferment occurs in "bread juice," less in "milk" and in "flesh juice." On the other hand, "bread juice" is extraordinarily poor in fat-splitting ferment; "milk-juice," on the contrary, very rich, "flesh juice" taking an intermediate position. It is clear, without anything further, that, as regards the two latter ferments, the properties of the juice correspond with the requirements of the food. The starch-holding diet receives a juice rich in amylolytic ferment, the fat-containing, a juice with much fat-splitting ferment. This is manifest from the strength of the juice, but still more so from the absolute quantities of ferment. (See table.)

The behaviour of the proteid ferment may, however, at the outset puzzle you. In the work of the gastric glands we saw exactly the contrary; there we found the weakest, here, however, the strongest solution of ferment poured out on milk. When, however, we take the quantity of juice into consideration, we find here also that the administration of like quantities of proteid in the form of bread, flesh and milk calls forth a secretion, as regards the first, of 1978, as regards the second of 1502, and as regards the third of 1085 ferment units; that is to say, vegetable-proteid likewise demands from the pancreas the most, and milk-proteid the least ferment. The difference between the stomach and pancreas is limited to this, that the former pours out its ferment in very concentrated form upon bread, the latter in very dilute condition. It appears to me that this fact strengthens our previous supposition, that in the digestion of bread a large accumulation of hydrochloric acid has to be avoided.

In any case, the relationship just discussed between the gastric and pancreatic secretions bears interesting testimony to the complexity

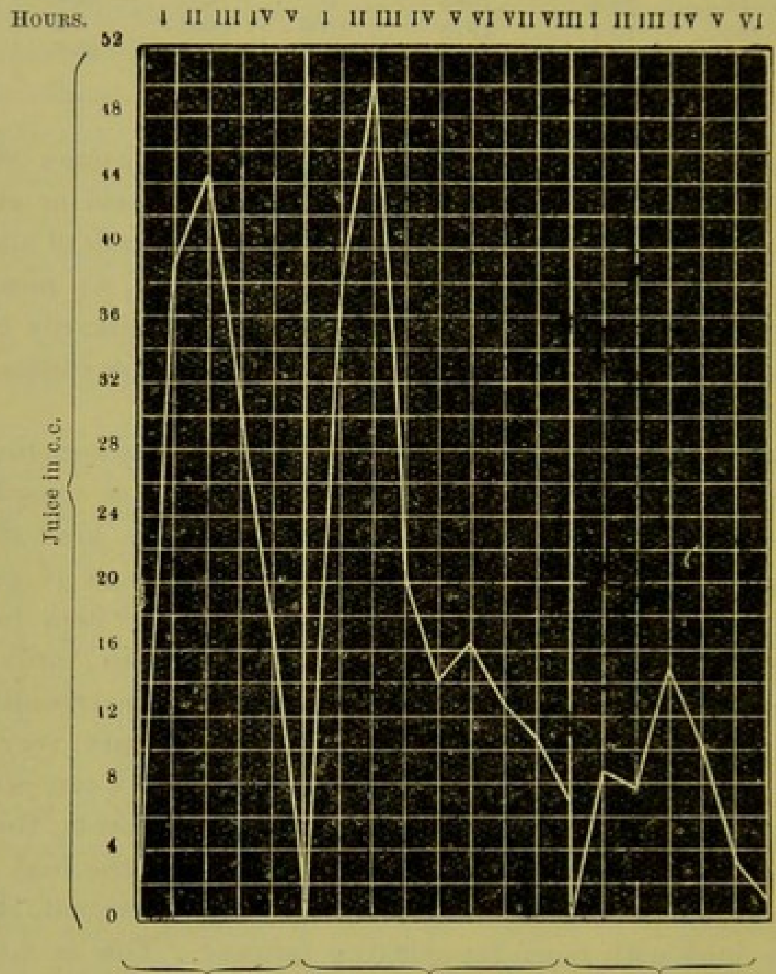


FIG. 9.—Curves of secretion of pancreatic juice with different diets.

and beauty of the digestive mechanism. Obviously a rich field of work lies here, full of important and, as yet, unsolved problems.

The work of the pancreas, like that of the gastric glands, is specialised both as regards the quantity and property of its juice, and the rate of progress which the secretion takes for the different classes of food. This is represented in the accompanying figures and curves (Figs. 9 and 10) taken from the work of Dr. Walther.

The secretion of pancreatic juice in hourly quantities

With 600 c.c. milk . .	8·5, 7·6, 14·6, 11·2, 3·2, 1·0 c.c.
With 250 grms. bread . .	36·5, 50·2, 20·9, 14·1, 16·4, 12·7, 10·7, 6·9 c.c.
With 100 grms. flesh . .	38·75, 44·6, 30·4, 16·9, 0·8 c.c.

VARIATIONS OF FERMENT-CONTENT IN HOURLY PORTIONS OF PANCREATIC JUICE, ON DIETS OF 100 GRMS. FLESH, 250 GRMS. BREAD, AND 600 C.C. MILK RESPECTIVELY.

(See Fig. 10, p. 42.)

Hour.	Proteid ferment.	Starch ferment.	Fat ferment.
		FLESH.	
1st	3·5	2·62	5·2
2nd	2·88	2·5	5·7
3rd	2·5	2·0	4·1
4th	3·88	2·69	4·8
		BREAD.	
1st	3.0	2·75	2·2
2nd	2·88	2·38	2·1
3rd	3·5	2·62	1·6
4th	3·88	3·12	1·7
5th	4·12	3·88	2·1
6th	4·25	4·25	2·5
7th	4·62	4·75	3·1
8th	6·0	5·12	—
		MILK.	
1st	5·75	5·0	14·3
2nd	5·88	5·0	19·7
3rd	4·25	2·38	7·0
4th	4·5	2·31	5·9

In view of the foregoing facts and of the tendency of all organised tissues (under the influence of forced work or its opposite) to enter into conditions of a more or less stable nature, one might imagine that similar effects follow also in the case of the glands. An investigation of the pancreas with this aim proved fruitful.

When, in feeding animals, the kind of food is altered, and the new diet maintained for a length of time, it is found that the ferment-content of the juice becomes from day to day more and more adapted to the requirements of the food. If, for example, a dog has been fed for weeks on nothing but milk and bread, and is then brought on to an exclusively flesh diet, which contains more proteid but scarcely any carbohydrate, a continuous increase of the proteid ferment in the juice is to be observed. The capability of digesting proteid waxes from day to day, while, on the contrary, the amylolytic power of the juice is found to be continuously on the wane. Here is an experiment taken from the work of Dr. Wassiljew. A fistula dog was given daily for a month and a half, two bottles (1200 c.c.) of milk and one Russian pound

(410 grms.) of white bread. The hourly quantities of juice for the first six hours after the meal had the following digestive powers:

For the proteid ferment in mm. 0·0, 0·25, 0·25, 0·25, 0·25 ;
For the starch ferment in mgms. of sugar, 8·13, 10, 16·18, 15.

Afterwards the dog was fed daily on a pound and a half of flesh. Even

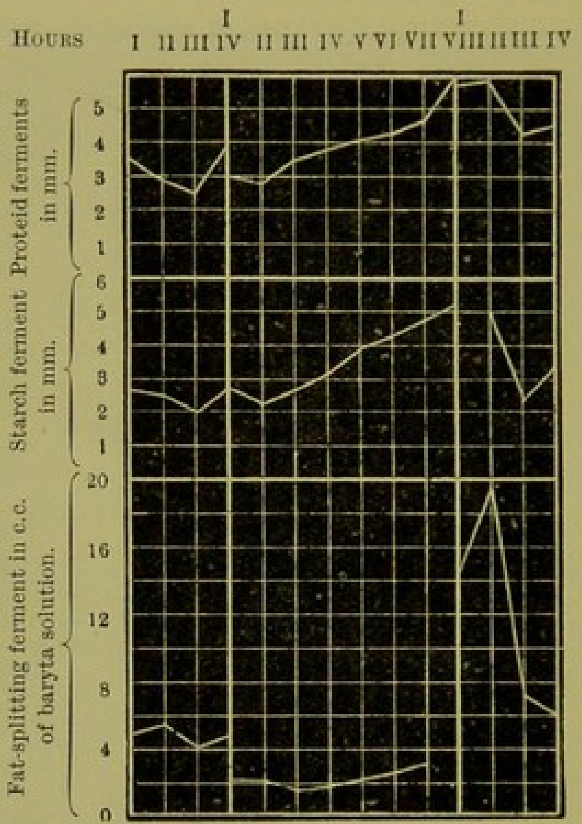


FIG. 10.—The ferments of pancreatic juice on diets of flesh, bread, and milk respectively. If read horizontally, the curves represent the same ferment on different diets; if in a vertical direction, the different ferments on the same diet.

after the lapse of three days, one could see that the proteid ferment tended to increase, while the starch ferment declined. On the twenty-third day of the flesh diet, during which time the juice continuously altered in the direction mentioned, we obtained the following results, likewise for the first six hours after feeding:

For the proteid ferment, 1·5, 1·0, 1·5, 3·5, 3·5, 3·0 ;
For the starch ferment, 4, 3, 3, 7, 4, 6.

To this must be added, that in this second case the starch ferment was allowed to act for twice as long as in the first case.

Although the result of the foregoing experiment is apparently indubitable, it is possible the objection may be raised that the quantity of ferments produced in both cases is the same, but that it had merely been distributed over different hours of the digestion period. We resolved, therefore, in order to give the character of absolute certainty to our results, to compare the fermentative properties of the juice secreted every hour over the whole twenty-four hours. This prolonged experiment was carried out by Dr. Jablonski.

A dog which had long been fed on flesh, and whose pancreatic juice worked very actively on proteid, was placed on a milk and bread diet. The proteid-digesting power of the juice sank continuously, so far as one could conclude from the experiments of the first six hours after the feeding. On the thirtieth day of this diet the whole juice secreted in twenty-four hours was collected. Its power of digesting proteid, according to Mett was exactly 4 mm. Ten days later the experiment was repeated, when the digestive power of the twenty-four hours' juice had declined to 2·25. A third trial was made after the lapse of a further twelve days, which gave a digesting power of 1·25 mm. In the fourth and last experiment carried out twenty-four days later, the digestive power for proteid was absolutely *nil.*

The starch ferment at the beginning steadily increased; later, however, it showed irregular fluctuations, with a slight tendency to fall. The latter circumstance must, however, be further investigated.

The result of the experiment, so far as concerns the proteid-digesting ferment, leaves nothing to be desired. It is naturally of importance, however, to investigate the behaviour of the other ferments with equal exactness.

When, under the influence of a given diet, this or that condition of the pancreas had been established in our experiment animals in characteristic form, we were able, by altering the feeding, to reverse it several times in one and the same animal. This shuts out all suspicion that we were dealing with a spontaneous and inevitable alteration of the glands, such as might have arisen from the effects of the operation or other pathological condition.

Since the food so powerfully affects the nature of the work of the glands, is it not possible that a permanent type of pancreatic activity could be produced under the influence of long-standing natural conditions of life, or from the effects of a long-continued form of diet maintained perhaps throughout the whole period of life, such, for example, as obtains in the case of pedigree dogs? It appears to me that our experimental material gives some indications in this direction. Although our laboratory dogs live and are fed under the same conditions, nevertheless the pancreatic juice of the different animals often differs very essentially in the amount of ferment. In harmony with the same thing, a change of diet in the case of one dog may very soon manifest itself in altered properties of the juice, while, in that of another, the remoulding of the pancreas takes place in the slowest manner. In such cases as the latter, an abrupt transition from one *régime* to a different one can often produce serious illness.

Dealing now with the gastric glands, the question of lasting alterations in ferment production must be left unanswered. We have up to the present obtained gastric juice in the laboratory from a very large number of dogs (twenty to thirty) by means of the sham feeding, but, notwithstanding, have never seen any striking or constant differences in the digestive power of the juice obtained from the dogs. Towards solving this problem Dr. Samojloff (in experiments not yet published) has made observations on three gastro- and œsophagotomised dogs. The dogs were tested beforehand by oft-repeated sham feeding experiments and then placed on different diets. After a considerable time they were again tested with the sham feeding, but the gastric juice showed no essential divergence from that previously obtained. How are we to interpret these results? Are our methods of estimating the ferment content of the gastric juice defective, or do the gastric and pancreatic glands differ in this important respect? It is, of course, possible that the pancreas plays the *rôle* of a supplementary, so to speak, reserve gland, whose duty is now augmented, now diminished, in accordance with the burden of work placed upon the digestive canal, while the gastric glands, as the first important digestive agency, must always work at maximum pitch. A fact not easy of interpretation, however, has recently been observed in our laboratory by Dr. Lobassoff, which possibly indicates that lasting alterations of the gastric glands may appear under the influence of prolonged dietetic conditions. We have in our possession a dog with a portion of the fundus of the stomach isolated according to the method of Heidenhain—that is to say, involving division of the vagi. I ought to add that, when such dogs live for a length of time after the operation, the secretion of gastric juice becomes gradually less and less (observation of this laboratory). The dog in question presented the following condition: When it had been fed freely every day on flesh for a considerable period of time, a certain test meal always yielded a much greater secretion than when the animal had been fed upon other foods, such as oatmeal porridge, &c. Since, however, in a dog thus operated upon, the gastric glands live and work under altered conditions, too great stress cannot be laid upon this instance.

All the facts given accord sufficiently with our previous conclusion, which may be once more repeated—namely, that the work of the digestive glands so far investigated is unusually complex and elastic, but at the same time astonishingly exact and purposive. It is true we have only encountered the latter property with unquestioned distinctness, up to the present, in a small number of cases.

LECTURE III.

THE CENTRIFUGAL (EFFERENT) NERVES OF THE GASTRIC GLANDS AND OF THE PANCREAS.

Earlier* experiments upon the influence of section and excitation of the vagi nerves on the gastric glands—The gastric glands can be excited by remote influences—The sham-feeding experiment—Repetition of the same after division of the vagi—The latter convey secretory fibres to the gastric glands—This is proved by excitation of the vagus nerve in two different forms of experiment—The vagus is the secretory nerve of the pancreas (experiment)—It also conveys inhibitory influences to the foregoing glands—These depend upon the activity of inhibitory nerves of secretion.

GENTLEMEN,—On the last occasion we were occupied with wearisome figures and curves, which, however, have taught us an extremely interesting lesson. It was made evident that the gastric and pancreatic glands have what we may call a form of instinct. They pour out their juice in a manner which exactly corresponds, both qualitatively and quantitatively, to the amount and kind of food partaken of. Moreover, they secrete precisely that quality of fluid which is most advantageous for the digestion of the meal. We naturally ask ourselves at once, by what means is this made possible? On what does this apparent instinct of the glands depend and in what does it consist? A probable answer to this question is easily given, and naturally an explanation of the adaptability of the glands is above all to be sought for in their innervation. It is only when such supposition proves itself to be untenable that we must seek for another. We will therefore concern ourselves in the present lecture with a study of the influence which the nervous system exerts upon the activity of the gastric glands and the pancreas.

It is appropriate that I should mention by way of introduction, that the widely renowned physiologist of Leipzig, the late Professor Carl Ludwig,* was able to prove by a classic experiment, no less than forty-five years ago that the salivary glands possess a special nerve which immediately

* *Zeitschrift für rat. Medizin*, N.F., i. 1851.

calls into play the chemical activity of the gland cells, and thereby brings on the secretion of saliva. This nerve receives the name of a "secretory" or "katabolic" nerve. Heidenhain,* the late physiologist of Breslau, carrying the matter farther, produced undoubted proof that the secretion of saliva in the glands, resolves itself into two processes; to wit, the production of the watery and inorganic constituents of the secretion, and the preparation of a specific organic body, the ferment. Corresponding to these two subdivisions of the process, Heidenhain, and with him the majority of physiologists, recognise two kinds of special nerve-fibres which govern the activity of the salivary glands. The one influences the secretion of water and of the inorganic salts which it holds in solution, the other leads to an accumulation of the organic body, the specific agency of the secretion. For the former, Heidenhain retained the old name of "secretory" nerve, the latter he termed "trophic." It has also been termed an "anabolic" nerve.

The question as to whether the gastric glands have likewise a special secretory innervation is now a very old one and has had an interesting career. In this matter physiology stood for a long time in sharp conflict with practical medicine. Physicians bringing forward their observations in proof, had long answered the question in the affirmative, and looked upon the existence of secretory nerves to the stomach as undoubted. They had even come to recognise different morbid conditions of the innervation apparatus. Physiologists, on the other hand, had fruitlessly endeavoured for decades to arrive at definite results upon this question. This is a striking, but by no means isolated, instance where the physician gives a more correct verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never make their appearance in the normal course of life. It is a series of physiological experiments which nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at his command. Clinical observation will consequently always remain a rich mine of physiological facts. It is therefore only perfectly natural that the physiologist should endeavour to maintain a close connection between his science and that of medicine.

Notwithstanding the wide range and perplexing nature of the literature of the innervation of the gastric glands, we are fortunately

* R. Heidenhain, *Studien des physiol. Instituts zu Breslau*, iv. 1868 and Pflüger's *Archiv*. Bd. xvii. 1878.

now in a position to pick out, with clearness and precision, the fundamental truths of the earlier researches, to grasp the cause of their want of success, and from their historical teaching to draw precepts for the performance of an ideal experiment which shall definitely answer our question.

We have three commonly employed methods by means of which the existence of nervous control over any organ may be determined. First, we can cut through, or in other way paralyse, certain nerves which are in anatomical connection with the part in question, and then submit the organ to accurate observation in order to determine whether its activity has been suspended or increased, or in any other way made to deviate from the normal, either quantitatively or qualitatively. Naturally our conclusions regarding the relations between the nerve and the organ will be all the more accurate, and come nearer the truth, the more completely and perfectly we compare the two conditions. A second and striking proof of the existence of a nervous influence over an organ is afforded by the results of excitation of its associated nerve. When the stimulation calls forth each time the same alterations of function, and when these at once disappear on cessation of the stimulus, we may rightly and justly look upon this nerve as governing the organ. Even here, however, one must not disregard the possibility of two contingencies. It may occur that the function of the organ suffers no alteration because the nerve or the organ is placed under abnormal conditions, and in view of the defects which still, unfortunately, cling to many of our physiological methods, this is very possible. For this reason, experiments with a negative result enjoy only a very qualified reputation, and by many authors are never published. On the other hand, the alterations of function which appear in an organ on stimulation of this or that nerve may have been brought about indirectly through the intervention of one, or several other organs. Only a careful and complete physiological (and where necessary anatomical) isolation of the organ can guard us from this source of error.

There is still a third mode of proof which, perhaps, should have been more correctly given in the first instance. It furnishes evidence of a nervous influence even where the first direct method remains fruitless. This consists in the most general evidence of relationship between the organ in question and the nervous system. It is nothing more special than making accurate observations in the clinique and in everyday life. The well-known fact of salivation at the sight of appetising food has in this way always been accepted as a sound proof of nervous influence over the salivary glands.

Into this path research also wandered when the innervation of the gastric glands was brought under investigation.

Several workers had observed disturbances of the secretory activity of the stomach which concerned the quantity or properties of the gastric juice, as often as the vagi, the chief anatomical nerves of the organ, were divided in the neck. But only very few were convinced that the vagus stood in intimate relationship to the secretory activity of the stomach. As is well known, division of the vagi on both sides of the neck is an operation which is accompanied by the severest consequences to the animal, and is usually followed by death after a few—oftenest after two to three—days. If this operation in the course of such a short time brings the whole functions of the organism to a standstill, it is not to be wondered at, that, amongst other things, the action of the gastric glands is also disturbed. It was consequently hazardous to conclude from such an experiment that the vagus bore a direct relationship to the gastric glands. (This is a good illustration of the second rule given above, relative to the experiment of nerve-division.) Such a cautious attitude towards the experiment seemed all the more justified because Schiff * was able without difficulty to preserve his dogs in good health and nutrition after division of both vagi beneath the diaphragm. The animals increased in weight, and the younger dogs grew and thrived as if nothing had happened.

These experiments of Schiff have had decided weight with many investigators against the recognition of any secretory innervation whatever, and unfortunately the view is still extant. But one can raise two important objections to the experiments. First, the survival of the animals cannot be taken as a proof that no deviation in the activity of the gastric glands from the normal had occurred. We become more and more convinced every day that the animal body is governed on the principle of mutual help and defence by the several organs. In this case it should have been borne in mind that the sympathetic nerve also sends fibres to the stomach. Schiff, moreover, had made no precise and detailed comparison of the secretory activity of the stomach before and after vagotomy. (This is a good example of the importance of the first of our rules for nerve-division experiments.)

Secondly, the subdiaphragmatic division of the nerves takes no cognisance whatever of the possibility that the secretory fibres of the vagus may enter the wall of the digestive tube above the diaphragm and course down to the stomach along its deeper layers.

The results of excitation of the vagus nerve proved to be also uncertain, perhaps even more doubtful. Hardly any of the authors, no matter where or how they stimulated the nerve, could claim a result which recalled a secretory effect. The few and not very

* Schiff, *Leçons sur la physiologie de la digestion*, 1867.

convincing records of positive results received no attention in the loud chorus of confident denial, and this all the more because the experimental arrangements were similar in all these contradictory investigations.

Quite alone, amongst the records, stands the experiment of two French authors,* who stimulated the vagus of a decapitated criminal, and still saw drops of gastric juice forming on the inner surface of the stomach, forty-five minutes after the execution. I must here remark, however, that this was possibly only an expression of gastric juice out of the glands, such as one may well conceive might occur from the contractions of the stomach-wall set up by the nerve excitation. Later we shall adduce facts which make the appearance of a true secretory activity but little likely under the experimental conditions of these authors.

It is interesting to observe how differently the question of secretory innervation of the stomach has been treated by German and French physiologists. While the German physiologists, demanding precise and constant results, have maintained till recent times a rigidly dogmatic attitude against secretory innervation of the organ, one can always find related by the French authors this or that apparently convincing experiment, or at least may happen upon forms of expression which assume the existence of such an innervation to be probable.

Attempts with the sympathetic turned out to be equally negative; consequently, the first two forms of experiment which I have named—the division and the excitation of nerves—have not yielded results when applied to the gastric glands, or at least not such as have convinced the majority of physiologists. The third method of procedure was, however, strikingly productive.

In the year 1852 Bidder and Schmidt † had observed that, under certain circumstances, one needs only to excite a dog by the sight of food in order to call forth a secretion of gastric juice. Although some authors could not verify this statement, the majority have been able to convince themselves of its truth. In recent times the French physiologist Richet ‡ has had the opportunity of making observations on a patient on whom the operation of gastrotomy had been performed for an incurable stricture of the œsophagus. Soon after the patient took anything sweet or acid into the mouth, Richet was able to perceive a secretion of pure gastric juice. Bidder and Schmidt's experiments and Richet's observations prove that the nervous system exerts an influence on the secretion of gastric juice, be this direct or indirect. This fact must, therefore, form the point of departure for new researches

* Regnard et Loye, "Expériences sur un Supplicié," *Progrès Med.*, 1885.

† F. Bidder u. C. Schmidt, *Die Verdauungssäfte*, &c., 1852.

‡ *Journal de l'Anatomie et de la Physiologie*, 1878.

on the subject. It proves incontrovertibly that the gastric glands are influenced through nerves by "distant effect," since the phenomenon comes to pass without any immediate contact between the food and the gastric mucous membrane. It only remained to make the experiment constant and simple; in other words, to facilitate its reproduction and seek out its proper interpretation.

As a matter of fact, I am now able to demonstrate experiments to you which yield absolutely constant and unequivocal results. We have here before us a dog operated upon in the manner I have described in the first lecture. It possesses an ordinary gastric fistula with metallic cannula, and has had its œsophagus divided as well, so that the mouth is cut off from all communication with the cavity of the stomach. Its stomach has been washed out before the beginning of the lecture, and, as you see now, not a single drop of fluid escapes from the fistula. I give the dog food. The animal eats greedily, but the whole of the food swallowed, comes out again at the œsophageal opening in the neck. After feeding in this way (which for shortness we will henceforth name "sham feeding")* for five minutes, perfectly pure gastric juice makes its appearance at the fistula, the stream steadily becomes greater and greater, and now, five minutes after the commencement of secretion, we have already 20 c.c. of juice. We may continue to feed the dog as long as we wish, the secretion will flow at the same rate for one, two, or more hours. We have even had dogs so greedy that they did not tire of eating in this fashion for five or six hours, secreting during the time a total quantity of up to 700 c.c. of the purest gastric juice. The meaning of this experiment is clear. It is obvious that the effect of the feeding is transmitted by nervous channels to the gastric glands.

Concerning what constitutes the actual stimulus in this case I will deal later. At present we will carry our experiment a step farther by dividing the vagi nerves. If now, before the division, we take away the animal's food, the secretion does not cease immediately, but is continued for a long time—three to four hours—gradually dying out. Without waiting, however, for its complete cessation we may proceed to further experiments. In the case of this dog, at the time of making the gastric fistula, the right vagus nerve was divided below its recurrent laryngeal and cardiac branches. In this way, only the pulmonary and abdominal branches on the side in question were thrown out of function, the laryngeal and cardiac fibres remained intact. About three hours before the present lecture, I prepared the left vagus free in the neck, passing a loop of thread round the nerve, but not

* The corresponding Russian expression would be better represented by the term "make-believe feeding." It expresses the idea, from the dog's point of view, that it has really been fed.

dividing it. I now pull gently on the thread to draw the nerve outwards, and sever it with a sharp snip of the scissors. At present the pulmonary and abdominal vagi on both sides are paralysed, while on the right side the laryngeal and cardiac fibres are intact. The result is, as you see, that the dog, after division of the left cervical vagus, shows no indication whatever of a pathological or otherwise uncomfortable condition. There are even no symptoms of cardiac or laryngeal distress, the usual causes of danger to the animal after complete division of the cervical vagi on the two sides. We again offer the dog food to eat, which it eats with increasing greed for five, ten, fifteen minutes, but, in sharp contrast to the previous sham feeding, we do not see a single drop of juice flowing from the stomach. We may feed the dog as long as we wish, and repeat our experiment in the next few days as often as we desire, but never again shall we see a secretion of gastric juice in this animal as the result of sham feeding. The experiment demonstrated to you may be repeated at will, and always with the same result.*

These investigations were first carried out by me in conjunction with Madam Schumow-Simanowski, and the same result was observed by Dr. Jürgens with dogs having both vagi severed below the diaphragm. Finally, a like effect was obtained by Professor Ssanozki in a dog with the fundus of the stomach resected after the manner of Heidenhain, an operation which involves, as is well known, the division of the vagus fibres in forming the flaps.

Basing my conclusions on these results, I take the liberty of asserting that the proof of the matter in question has been raised beyond the possibility of all doubt or chance. You see then, gentlemen, that it is only necessary to accomplish the division of the vagi nerves under suitable conditions in order to achieve indubitable and invariable results, and this, as I have said, always happens when these conditions are fulfilled.

Since the fibres of the cervical vagus which go to the larynx and heart are not completely divided (the abdominal fibres are, however, totally severed), there can be no question of any general feeling of severe discomfort producing a harmful influence on the secretion of gastric juice. There is, indeed, no feeling of general ill-health whatever, the dog eats immediately after the operation quite as lustily as before. (This is an essential advantage of our procedure over the former method, of carrying

* The dog which served for the above experiment remained alive for several months. Later the right vagus was also divided *in the neck*, nevertheless the animal continued in perfect health and enjoyed its life to the full. Oft-repeated experiments with sham feeding never gave a secretion. The same condition was manifested by another dog which likewise survived a double division of the cervical vagi for many months.

out a double vagotomy.) Lastly—and this is the most essential characteristic of our experiments—we employ in the sham feeding an immediate, uniform, and perfectly adequate criterion. This is an important improvement as compared with the experiments of Schiff.

The negative effect of sham feeding after the vagotomy does not prove, however, that the gastric glands are deprived of all secreting power. It only shows that certain exciting impulses, which reach the gastric glands by way of the vagi, have been removed. It is possible that other forms of stimuli exist, which act on the gastric glands through other nerves, or even in some wholly different way, entirely without nerves. In the act of eating, however, the gastric glands receive their normal impulses to activity by means of nerve fibres which run in the vagi.

But what kind of fibres are these? Are they special secretory fibres or do they only influence the glands indirectly—for example, through the medium of the vessels? According to the view now prevalent with regard to secretory phenomena in glands generally, the second supposition is but little probable, and it becomes still less so could we adduce direct proof in favour of the truth of the first. The stimulating effect of the sham feeding experiment can easily be graduated. We can, for instance, give a dog a highly appetising food, or, on the other hand, offer it a meal but little relishing. It is well known that a dog eats flesh with much greater greed than bread. If we give it bread we obtain much less juice, and of a much more watery kind; that is to say, less rich in ferment. Likewise, when we give pieces of flesh at long intervals, we obtain not only less juice than if the dog had been fed rapidly, but the juice possesses a much lower digestive power. It follows from this that the stronger we stimulate, the more and the richer the juice we receive. This fact is, however, the best proof of the specific activity of the nerve fibres supplying the glands. If only vasomotor (dilating) fibres for the glands were contained in the vagi nerves, an augmented flow of juice from strong excitation would mean a *lessening* of the concentration. The more rapidly the fluid passes through the glands, other things being equal, the less specific constituents could it carry away in solution from them.

In proof of the above I give here a few figures taken from the work of Dr. Ketscher:

DIGESTIVE POWER OF THE JUICE.

Pieces of flesh given at intervals.	Pieces of flesh given continuously.
6¼ mm.	8½ mm.
4½ „	7 „
4¾ „	8 „
5½ „	7¼ „

In all instances when the pieces of meat were administered at intervals, the quantities of juice were much smaller than when the animal was continuously fed.

From the above data it follows, first, that specific secretory fibres, and not merely vaso-motor, run in the vagus to the gastric glands; and, secondly, that one must divide these fibres, as Heidenhain did for the salivary glands, into true secretory and trophic. This is shown by the fact that the separation of the water and the preparation of the solid constituents obviously take place independently of each other. We have already seen a number of instances in the second lecture where similar hourly quantities of juice were secreted with wholly different amounts of ferment, dependent on the working conditions of the glands.

But while the nerve-section experiment speaks eloquently in favour of the existence of secretory nerves to the stomach, it is nevertheless desirable, for many reasons, to take into consideration the excitation method also. It is only by artificial excitation that we can study accurately and in all its features the mode of working of a given nerve and the process which it controls. In certain cases great difficulties come in the way of the experiment. This accounts for the failure of the many authors who have previously worked at the question. In carrying out the investigation we have had once more to resort to a special arrangement of our own. We started with the assumption that it is very doubtful if the ordinary so-called "acute" experiment, performed at one sitting on a fresh unprepared animal, can be accepted as a true interpretation of normal conditions in the organism. In such experiments many physiological phenomena are misrepresented or, indeed, wholly masked. In our case this doubt was all the more justified because unquestioned proof of the inhibitory effects of sensory and reflex stimuli in general, upon the activity of the most important digestive glands had already been recorded in the literature. It was shown by Bernstein,* in Ludwig's laboratory, and later by myself, in conjunction with Professor Afanassjew,* that sensory stimuli frequently and unquestionably inhibit the work of the pancreatic gland for long periods of time. Dr. Netschajew † has found also that an excitation of the sciatic nerve for two or three minutes is able to bring gastric digestion for several hours to a standstill. From this arose the attempt to excite the nerves passing to the stomach in such a way that no sensory or other reflex impulses could precede or accompany the experimental stimulation.

* Pflüger's *Archiv.* Bd. xvi.

† *Über hemmende Einflüsse auf die Absonderung des Magensaftes.* Inaug-Diss. St. Petersburg, 1882.

This we (Madam Schumow-Simanowski and I) achieved with dogs prepared in a manner similar to that which has been now demonstrated to you. Gastrotomy and œsophagotomy had previously been carried out, the right vagus was cut through below the origin of the inferior laryngeal and heart fibres, the left divided in the region of the neck. A longer or shorter piece of the peripheral end of the latter had been prepared free, placed on a ligature, and for the time being preserved under the skin. After three to four days the stitches were carefully removed from the skin and the wound painlessly opened, when the nerve lay free before us. In this way we avoided appreciable discomfort to the animal before exciting the nerve. By such precautions we invariably succeeded in obtaining a secretion of juice from the empty stomach when the nerve was subsequently excited by slow induction shocks at intervals of one to two seconds (so-called "rhythmic excitation").

And now that we had the matter under perfect control we attempted to achieve the same thing in the "acute" experiment, that is to say, on a dog prepared at the time, but naturally with the observance of certain precautions. Dr. Uschakoff, in his first experiments, after a speedy but careful tracheotomy, divided the spinal cord below the medulla oblongata with the greatest possible rapidity (a few seconds) in order to prevent all reflex effects on the gastric glands from his further operative procedures. The vagi nerves were now sought out and divided; an ordinary fistula cannula was brought into the stomach, the food passage ligatured in the region of the neck and also at the pylorus. The animal was then suspended in a standing position in a frame. In his later experiments Dr. Uschakoff employed a short chloroform narcosis (10–15 minutes duration), during which all the above operations were carried out in great haste. Experiments specially performed with this object on dogs previously gastro- and œsophagotomised had shown that a chloroform narcosis of such short duration was not followed by any serious interference with the glands or their nerves. Fifteen to twenty minutes after the narcosis the dogs were again lively, ate with greed the food set before them, and, after the usual interval of five minutes, gastric juice of strong digestive power began to flow from the stomach in perfectly normal quantity.

In dogs prepared as described at one sitting, we proceeded to excite the nerves, and were able to see, as we expected, an undoubted and vigorous effect from the stimulation. This occurred, however, only in half of all the cases. In our later experiments, carried out under narcosis, we obtained a positive result much oftener. In none of the successful cases was the effect of the stimulus seen immediately, it only appeared after the lapse of a preliminary period, during which the excitation remained ineffective. This period lasted from fifteen minutes to an hour or more. If, after the nerve began to work, the stimulus were removed, the secretory effect disappeared only gradually, to return however, and this time with rapidity, if the stimulus were reapplied a few minutes later. The administration of a drug such as atropin, which restrains secretion, destroys the irritability of the nerves.

The existence of so lengthened a period during which stimulation of the nerves gives no result may be explained, in the first instance, on the ground that the shock of the operation depressed the excitability of the gastric glands. It can, however, be explained in another and more likely way. We have already remarked that sham feeding, very soon after the anæsthetic, gives a perfectly normal secretion of juice, and yet the period of latency is quite as long in this form of experiment with narcosis as without it. It is hardly conceivable that the operation, notwithstanding the narcosis and the division of the spinal cord, exercised any important reflex inhibitory influence on the gastric glands. We are forced to conclude, therefore, that in artificially stimulating the vagus, both exciting as well as restraining impulses are transmitted to the glands. This view would find its simplest expression in a hypothesis which assumes the presence of inhibitory nerves acting in antagonism to the secretory, in a manner similar to what we already know exists in the innervation of the heart, the vessels and other organs. This hypothesis will be more fully discussed in connection with the pancreas, where we shall find ourselves in possession of a series of appropriate facts and, indeed, of direct proofs recently established.

From both forms of experiment, therefore, the chronic as well as the acute, we are fully justified in concluding that the vagus nerve contains secretory fibres for the gastric glands. It is necessary to repeat, however, that one must not infer that the integrity of the vagus is the only requisite condition for the secretory work of the stomach. Many previous investigators, and we ourselves as well, have been convinced that the stomach is capable of preparing its specific secretion in the absence of vagus influence. Naturally the work of secretion under these conditions deviates not inconsiderably from the normal, both as regards the commencement of the flow as well as the product formed. Whether this secretion, which occurs after the vagi are severed, is to be ascribed to the action of the sympathetic nerves or to some other agency cannot for the present be decided. Furthermore, Professor Ssanozki has been able to verify the inhibitory effects of atropin, in a perfectly convincing manner, on a dog with Heidenhain's resected stomach, and therefore with the vagus fibres divided. Atropin, however, paralyses secretory nerve mechanisms in a very special manner, and we must hope that further investigations into the work of the sympathetic nervous system—now that we know the relationship between the vagus nerve and the gastric glands—will finally elucidate the problem.

We cannot leave this subject without expressing regret that physiologists have grown accustomed to look upon the gastric glands as being independent of nervous influences, and, in consequence, continue to disregard the results just given, although they have been published for more than seven years, not only in the Russian but also in the foreign literature of our subject. Some of the authors speak of the continuance of gastric secretion after severance of the vagi, but pay no regard to the peculiar alterations of the secretion, which is the special point in question. In the case of many other organs we are able to divide their nerves without stopping their particular forms of activity, but we do not conclude therefrom that these organs have no innervation. Other authors adhere rigidly to the traditional formulæ of the acute experiment, taking no precautions against reflex inhibition. Only a few (Axenfeld, Contejean, Schmeyer) have obtained more or less positive results with dogs and other animals, such as birds and frogs. We confidently believe that every single repetition of our experiment, if only the conditions we have given be observed, will yield the selfsame results in the hands of every investigator, and will no longer leave any room for doubt in the existence of a secretory innervation to the glands of the stomach.

The same difficulties which we had to encounter with regard to the innervation of the gastric glands were also met with in the case of the pancreas. To illustrate these difficulties, I need only give here the following expressive remarks taken from the classic work of Heidenhain upon the pancreas: "Indeed, every observer who has occupied himself for any length of time with investigating the functions of the pancreas will leave this field with a feeling of dissatisfaction in consequence of the extremely large number of fruitless experiments he is obliged to deduct from the total number of his investigations; for not even the greatest care, nor the ripest experience in the making of pancreatic fistulæ, will be able to overcome the incomprehensible sensitiveness of the organ, which only too often annuls its function for a length of time after completion of the operation, a function which it does not resume even under the influence of the most favourable secretory conditions. A degree of uncertainty, therefore, always clings to the results of such observations, which is not set aside even by a numerous repetition of the single experiments. I must openly declare that I have never undertaken a series of experiments which was so lavish in the sacrifice of dogs and so poor in corresponding results." *

* Pflüger's *Archiv.*, Bd. x. 1875, p. 599.

At the present moment, however, the investigation of the nervous relationships of these glands has greatly advanced. We have already stated that Bernstein, in Ludwig's laboratory, and afterwards myself, with Professor Afanassjew, have shown that sensory stimuli exert an inhibitory influence on the pancreatic gland. Then Heidenhain, with his pupil Landau,* from excitation of the medulla oblongata, obtained, in a few experiments out of many fruitless ones, an undoubted effect upon the gland. On the whole, however, the question of innervation of the pancreas remained very obscure. Why could Heidenhain obtain an effect only in exceptional cases? By what channels were the impulses conducted from the central nervous system to the gland? To what influences were the inhibitory effects of sensory stimuli to be attributed? There was as yet no answer to all these questions.

Beginning with the year 1887, it was the good fortune of myself and my co-workers to be able to solve them all, more or less satisfactorily.

It resulted that the vagus is to be looked upon as the secretory nerve of the pancreas. For this discovery we have to thank the adoption of a special experimental procedure, and the method by which we were first convinced of its activity will be immediately demonstrated to you. The dog before you is provided with a permanent pancreatic fistula, made in the manner I have described in the first lecture. The animal has fully recovered from the operation and everything is healed. Four days ago the cervical vagus was divided on one side; the peripheral end of the nerve was laid bare, furnished with a ligature, and preserved under the skin. I now carefully remove the cutaneous sutures, and cautiously draw forward the ligature with the nerve, without causing the dog appreciable discomfort. I beg you to note that from the metallic funnel, the wide end of which embraces the site on the abdominal wall where the orifice of the pancreatic duct is situated, not a drop of juice flows. Now I begin to excite the nerve with an induction current. As you see, the dog remains perfectly still in its frame without exhibiting the least degree of pain. Two minutes elapse without any result from the stimulus—this I ask you especially to bear in mind—and now, in the third minute, the first drop of juice makes its appearance, and is followed by others in quicker and quicker succession. After three minutes I interrupt the excitation, but the juice continues to flow spontaneously, and only stops at the end of four to five minutes from the cessation of the stimulus. I again apply the current, and obtain the same effect, and this is invariably the result, upon every dog. To this must be added that the vagus nerve naturally was stimulated before,

* *Zur Physiologie d. Bauchspeichelabsonderung.* Breslau, 1873, Dissert.

with the same object, and yet what we are now able publicly to demonstrate was never seen. The reason of our success lies in the nature of our preparations for the experiment. These specialities are two: The animal is subjected to no painful sensations, and not even narcotised, as is the usual custom elsewhere. On the other hand, thanks to the time which has elapsed (four days) since the vagus was divided, all circulatory disturbances are excluded which would otherwise follow the excitation of this nerve. On the fourth day after its section, the cardio-inhibitory fibres, for example, have lost so much of their irritability that the strongest excitation of the nerve is scarcely able to produce even an insignificant and momentary slowing of the heart-beats. In order to comprehend this circumstance it is necessary to remember that the excitability of different nerve fibres disappears after section, with different degrees of rapidity. Thus, in this case the cardio-inhibitory fibres lose their irritability earlier than the secretory fibres for the pancreas. In our experiment, therefore, the *glands* have neither suffered by the operation nor by the circumstances accompanying the excitation.

But one can also obtain a positive result with the acute experiment, if it be only carried out on a suitable plan. Our procedure is as follows: Tracheotomy is performed as quickly and painlessly as possible; then the cervical cord is severed from the medulla, occupying only a couple of seconds, after which artificial respiration is set up. And now we may quietly proceed further. The chest is opened in order to seek out the vagi below the heart, and then, after opening the abdominal cavity, a cannula is tied into the pancreatic duct. Under such conditions we are able in every experiment, to observe the secretory effect of the vagus on the pancreatic gland, although we may have to excite the nerve perhaps several times at the beginning of the experiment without result. The meaning of the foregoing procedure is at once clear. By division of the spinal cord the harmful inhibitory effects of the exceedingly lengthy operations are prevented, while, by exciting the vagus in the thorax, its influence on the heart's beats is avoided.

Further investigations carried out in this manner have brought to our notice two conditions under which the secretion of the pancreas may be inhibited by nervous influences. In our own experiments, as well as in those of earlier authors, the pancreas has shown itself to be extraordinarily sensitive to circulatory disturbances. It is only necessary to excite its vaso-constrictors for a short period (two to three minutes), or to compress the aorta for the same length of time, in order to prevent it for a long time from reacting to a previously effective stimulation of the vagus. From these experiments it can easily be understood why, in the ordinary method of operating, accompanied by the strongest sensory stimulation, and consequently by vascular constriction, even the gland of an animal taken at the height of digestion, often does not yield a single drop of juice.

Great importance must also be attached to another circumstance which likewise attracted our attention during the investigation. In the experiment just now demonstrated, as also in the "acute" experiment, excitation of the vagus did not call forth the secretion of juice instantaneously. A certain period of time always elapsed (from fifteen seconds to one minute) between the application of the stimulus and the appearance of the secretory effect. In very many instances the juice began to flow only after the stimulus had already ceased. Finally, one can often observe the following phenomenon (*Mett*). Suppose the right vagus be excited for a considerable length of time, and thereby a steady flow of juice set up, it is now only necessary, without interrupting the stimulus, to excite the other vagus in like manner, when, after a definite—often considerable—length of time, the secretion is brought to a standstill. All these phenomena have led to the idea that not alone exciting influences, but also inhibitory, pass through the vagus to the pancreas.

With respect to the latter, one is at liberty to make several suppositions: they may come into play through the vaso-constrictor nerves of the organ, or through constrictor effects upon the excretory ducts, or, lastly, through genuine inhibitory nerves antagonistic to the secretory. But when it has been proved beyond doubt for several organs that the nerves which regulate them may be classed into two opposing groups, why may not the same be rightly maintained for the glands? It is quite possible that an antagonism of this nature applies to the general principle of innervation. In the physiological literature of the last few years one may find references here and there to inhibitory innervation of the glands. It appears to me, however, that the question of their existence must be finally decided by a study of the nerves to the stomach and pancreas, because here the inhibitory phenomena are mostly prominently marked.

Before considering this question more fully, I will now bring forward some experiments dealing with the influence of the sympathetic nervous system upon the secretion of pancreatic juice. They will furnish us at the same time with material for the discussion of the above subject. The following are the results of the work of Professor Kudrewezki:

If, in the acute experiment described above, the sympathetic nerve be excited by means of an induced current, a gentle intermittent advance of the secretion is observed, but only during the first few seconds; during the later stages of the excitation, and after its stoppage, the secretion is completely arrested. If, instead of the electric current, mechanical stimulation (for example, a series of taps with Heidenhain's tetanometer) be employed, a different result is to be observed: a little time after the beginning of the excitation a tolerably strong secretion sets in. The same may be obtained by means of electrical stimulation, not, however, with a fresh nerve, but with one which has been divided three or four days before, and which, in consequence, is partially degenerated. The meaning of these events is easy to understand when one calls to mind a few facts from the physiology of the vascular nerves.

We know that vaso-constrictor nerves are much less sensitive to mechanical stimuli than many others, and lose their irritability much earlier after division. We may, therefore, correctly assume (1) that both vaso-constrictor as well as secretory fibres for the pancreatic gland run in the sympathetic nerve; (2) that in ordinary electric excitation the vaso-constrictor effects completely mask the secretory; and (3) that only under special conditions which eliminate the activity of the vaso-constrictor nerves (*e.g.*, mechanical excitation, or the application of the electric current to a previously divided nerve) can the secretory fibres manifest their effects.

In the case of the sympathetic nerve we are now able to recognise clearly the mutual relationship which exists between the vaso-motor and secretory fibres of the pancreas. Our opinion regarding the effect of the vagus upon the glands has suffered, however, no alteration as a result of the employment of the special modes of stimulation mentioned above. Its inhibitory effect upon the secretion remains to the full. This gives us good reason for believing that the influence of the vagus in question, does not depend upon a contraction of the vessels. The question with which we are dealing has recently made an important advance, thanks to the work of Dr. Popielski. He has, in the first instance, worked out a plan of experiment in which the inhibitory effect of the vagus upon the pancreas is shown in a constant and striking manner. During the acute experiment already described a solution of hydrochloric acid is poured into the duodenum. By this means a long-continued and vigorous secretion of pancreatic juice is called forth. If the vagus nerve be now strongly stimulated, a slowing—often to complete standstill—of the secretion is obtained every time without exception. Excitation of the sympathetic, on the other hand, only slows the secretion, and this after the lapse of some time. A compression of the aorta arrests the secretion only after two to three minutes. To this it must be added that, according to the last experiments of François Frank, the vagus nerve dilates rather than constricts the vessels of the pancreas. The possibility of simultaneous action on the part of the motor nerves to the excretory ducts was excluded by administering physostigmin to the animal, a drug which strongly excites the activity of smooth muscle. But absolutely no inhibition, rather an augmentation of the secretion made its appearance. Finally, by a careful preparation of the nerves, some branches were discovered whose excitation caused a secretion without any latent period, almost as promptly as the chorda tympani expels saliva. From the latter fact we must conclude that in the branches mentioned, the secretory fibres of the pancreas have been anatomically separated from the inhibitory, and that the purely secretory nerves, on artificial stimulation, call into play the activity of the organ without any latent period. Finally, Dr. Popielski succeeded also in isolating branches of the vagus which only inhibited and never called forth a secretion. If such inhibitory nerves exist, it is easy to understand their reflex excitation both under normal conditions as well as during the operations. Nor is the possibility excluded that reflex inhibition extends also to the secretory centres for the pancreas.

The observations here given furnish an explanation of all the failures and difficulties which the earlier investigators of the innervation of the pancreas had to fight against. Why, for example, did Heidenhain only obtain a positive result in a few experiments on excitation of the medulla oblongata? To say nothing of the inhibitory effects of the operation; he called forth by excitation of the medulla, a strong contraction of the vessels and an alteration of cardiac activity. Moreover, he excited at the same time the antagonists of the secretory fibres.

You have, of course, already noticed how similar the nervous connections of the stomach and pancreas have turned out to be; the innervation of the one is in every respect a copy of the other. Consequently it is permissible to fill up gaps in our knowledge of one of the schemes of innervation by analogy from the other. We cannot doubt, for example, that secretory fibres for the stomach are present not only in the vagus but also in the sympathetic.

In conclusion, a few words concerning the experiment of the two French authors on the stomach of the beheaded criminal. We have seen how extremely delicate the digestive glands are, and cannot, therefore, easily believe that the authors were able to set up a true secretory effect from excitation of the vagus forty minutes after the organ had been deprived of blood.

I think I may now rest satisfied, after all that has been said and shown to you, that the existence of secretory nerves to the stomach and pancreas will appear to you just as real and unquestioned as those for the salivary glands in the classic and universally known chorda tympani. It need hardly be said that, in addition to these special nerves, vaso-motor nerves—constrictor and dilator—also pertain to the glands.

LECTURE IV.

GENERAL SCHEME OF AN INNERVATION MECHANISM —THE WORK OF THE NERVOUS APPARATUS OF THE SALIVARY GLANDS—APPETITE, THE FIRST AND MOST POTENT EXCITER OF THE GASTRIC SECRETION.

Constituent parts of a complete innervation mechanism—The special duty of the peripheral terminations of afferent nerves—The specific qualities of nerve cells—Analogy between the innervation mechanism of the salivary glands and that of the deeper-lying glands of digestion—The exciting agencies of the nervous mechanism of the salivary glands; their particular properties—Differences between the exciting agencies of the different salivary glands—Discussion of the sham feeding experiment—Mechanical and chemical stimulation of the cavity of the mouth has no effect on the gastric glands—The experiment of Bidder and Schmidt relative to psychic excitation of the gastric secretion—Conditions for success in this experiment—The passionate longing for food—the appetite—alone brings on the secretory effect in the sham feeding experiment.

GENTLEMEN,—As you have learned in the last lecture, and also in part have seen by direct experiment, the nervous system can influence the work of our glands in the most diverse ways. The vagus nerve, already burdened with many duties, has, in addition, proved itself to be an undoubted exciter of the gastric glands and of the pancreas. But we must also assign to the sympathetic nerve a similar *rôle*. This is a matter which cannot be doubted, so far as the pancreas is concerned, and is highly probable as regards the stomach. We also saw good reason for believing that these two nerves contained two different classes of fibres, secretory and trophic, a condition which had already been proved to exist by Heidenhain for the nerves of the salivary glands. As a hypothesis we might even have proceeded a step farther and have divided Heidenhain's trophic nerves into separate classes of secretory fibres. Lastly, we advanced important experimental evidence to show the existence of special inhibitory fibres to the glands, and these fibres also run in the vagus, the list of whose functions seems almost interminable.

We obtained these results by division and artificial excitation of the nerves which run to the glands. But when, how, and by what means these nerves are thrown into activity during the normal course of physiological events remains a question.

In order to avoid repetition, and at the same time impart the utmost clearness to our representation, it may be useful to bring before your minds at once the plan of innervation of a given organ, all the more since this scheme is seldom completely followed out or adequately described in physiological text-books. Consequently, it is not borne in mind with sufficient precision by the majority of medical men.

A complete innervation mechanism consists of the peripheral endings of the centripetal (afferent) nerves, the centripetal nerves themselves, the nerve cells (a group of nerve cells connected with each other is termed a " nerve centre "), the centrifugal (efferent) nerves, and, lastly, their peripheral terminations. Physiology now accepts it as a settled fact, that nerve fibres serve only as *conductors* of nervous impulses, which come in from contiguous links of the nervous chain. Only the peripheral endings of nerves and the nerve cells themselves have the power of transforming the external stimulus* into a nervous impulse. In other words, in the intact organism these alone constitute the normal receiving apparatus of the nervous system. Whether the peripheral ends of centrifugal (efferent) nerves are likewise able to function as normal sites for the application of external stimuli has still to be answered. Consequently, when any external agency excites the peripheral terminations—the receiving stations—of centripetal nerves in this or that organ, the effect of the stimulus will be conveyed through the centripetal nerves, as through a receiving wire, to the central station—the nerve cells. Here it becomes changed into a definite impulse and now comes back along the centrifugal nerves—the outgoing wires.

The utmost importance is to be attached to the fact that only the peripheral endings of centripetal (afferent) nerves, in contrast to nerve fibres themselves, respond to *specific* stimuli ; that is to say, are able to transform definite kinds of external stimuli into nervous impulses. The function of the end organs with which they are connected is therefore of a purposive nature; in other words, these organs are only called into play by certain definite conditions, and

* By the term "external stimulus" I mean here without distinction every outward agency of nature, as well as every agency which has its seat within the organism. The word "external" applies here to everything with the single exception of the nervous system itself.

impart the idea of being aware of their purpose, of being conscious of their duty. We have long known that the peripheral endings of sensory nerves are possessed of a high degree of speciality, and cannot therefore have any doubt regarding the specific nature of the end organs of other centripetal nerves. This is a sore point in present-day physiology. But, notwithstanding our knowledge of the separate parts of the animal body, we shall only be able to form a true conception of the motive agencies of the whole complicated machine, when we have established the specific excitability of the end apparatus of every centripetal nerve, and have discovered all the mechanical, chemical, and other factors which throw this or that end apparatus into an active condition. I always look upon it as a period of scientific inadequacy so long as the effects of the most diverse external agencies upon any normal physiological process, are admitted to be indistinguishable. As the work of the digestive canal is now represented in the majority of text-books, and consequently presented to the mind of the physician, it bears the impress of this period. To impart to the physician a more correct conception of this matter was my chief object in giving these lectures. I hope, indeed, to furnish you with evidence sufficiently convincing, that the alimentary canal is endowed not with mere general excitability; that is to say, does not respond to every conceivable form of agency, but only to special conditions which are different for the different portions of its length. Just as men and animals in the world are only able to maintain their existence and constantly adapt themselves to changing circumstances by aid of the peripheral endings of their sensory nerves, so every organ, indeed every cell of every organ, can only maintain its place in the animal microcosm, and adapt itself to the activity of innumerable associates, as well as to the general life of the whole, by virtue of the fact that the peripheral end-apparatus of its centripetal nerves possesses a specific excitability.

The same applies to the nerve cells: obviously they are endowed with specific sensibility. Irrespective of the excitations which are communicated to them from centripetal nerves, they respond, as originators of nervous impulses, only or at least mainly to definite forms of mechanical, chemical, or other stimuli arising in the organism. This follows not alone from a number of physiological facts but also from various pharmacological data. Thus we learn that various drugs excite or annul the activity of definite portions of the nervous system, at least in the earlier phases of their effects. This specific excitability of nerve cells, just as much as the same property of peripheral end organs, lies at the bottom of the purposive action of these organs.

Hence, our next duty is to endeavour to discover the normal exciting conditions of the centripetal nerves belonging to the glands which we had under consideration in our last lecture, or, more correctly, to find out the conditions which excite the centres, as well as the peripheral endings of the different nerves, which form parts of the nervous apparatus of these glands. We have, therefore, for each phase of the work of secretion, to find out that portion of the nervous mechanism which is for the time being under excitation, and to discover the primary agency by which this condition is elicited. This would include an exact analysis of the stimulating influence which mastication and food exert upon the nervous mechanism of these glands. We shall also be able more fully to comprehend the inner mechanism underlying the facts which formed the subject of the second lecture. This, of course, is an ideal programme which we can only follow out as far as the present state of physiology permits. It may now be instructive, and, for our further conclusions, advantageous, to glance shortly at the nervous control of the salivary glands.

The salivary glands, whose innervation has long ago been investigated, have generally been accepted as types of the deeper-lying digestive glands, and when it became necessary to form a conception of the mode of activity of the latter, medical science resorted to a bold analogy and thought of the nervous apparatus of the salivary glands. But the attempts of investigators to apply rigidly to others the scheme of innervation which holds good for the salivary glands, have done considerable harm to the usefulness of the analogy and have prevented our arriving at a correct idea of the plan of innervation of the abdominal glands. We have already had an example of this nature before us. In the salivary glands we have no clearly marked indications of nervous inhibition, and this circumstance has decidedly retarded the due development of our knowledge of the nervous control of the abdominal glands. Authors naturally expected to see a simple and prompt stimulation-effect from the same conditions of experiment which sufficed for the salivary glands, and the failure of this gave them, as they thought, the right to deny the existence of any extrinsic nervous influence upon the abdominal glands. The error is now obvious; the abdominal glands behave in some ways different from the salivary glands, and for their successful investigation, other conditions of experiment are necessary than those which held good for the former. In the working of the abdominal glands nervous inhibitory processes play a large part, but they are almost wholly absent in the case of the salivary glands. This is an additional warning that one must never push the conclusions drawn from analogy too far, but must constantly bear in mind that the life-functions of all organs are extremely complicated, and that the work of even the most apparently similar organs should be submitted to separate and careful observation. To me it appears that the unjustified analogy drawn between the abdominal and salivary glands has to be credited with another important misapprehension. And precisely for this reason I think it desirable to bring under consideration, if only in brief fashion, the conditions of work of the salivary glands, especially since Dr. Glinski has instituted in the laboratory some easily performed experiments which bear upon the matter.

The experiences of daily life teach us from the outset, that the activity of the salivary glands begins even before the introduction of food into the mouth. With an empty stomach, the sight of food or even the thought of it is sufficient to set the salivary glands at once into activity; indeed, the well-known expression, "to make one's mouth water," is based upon this fact. Hence a psychic event, the eager longing for food, must be accepted as an undoubted excitant of the nervous centre for the salivary glands. On the other hand, the same everyday experience, as well as numerous experiments upon animals, teach us that a number of substances, when brought into contact with the mucous membrane of the mouth, are likewise able to call forth a secretion of saliva. One even acquires the impression that everything brought into the mouth may reflexly influence these glands, the only difference being a gradual shading off in the effect, dependent upon the strength of the stimulation which the substance introduced is able to exert, and it appears to me that it is precisely this impression which has driven the idea into the background, that the peripheral end-apparatus of the centripetal nerves of the digestive canal are specifically excitable. The facts were here correctly observed, but their indications erroneously interpreted.

The great multiplicity of excitants of salivary secretion, has without doubt, some connection with the complicated physiological functions of the saliva. This is the first fluid encountered by everything which enters the alimentary canal. It must, therefore, in a sense play the part of host to every substance taken in—moisten the dry, dissolve the soluble, envelop the hard and bulky with mucus in order to facilitate its passage down the narrow œsophagus; and submit certain forms of food material, such as starch, to a process of chemical elaboration. Nor is its duty by any means ended here. The saliva is secreted in the first compartment of the alimentary canal, which is at the same time the sorting-room of the organism. Much of what enters the mouth may prove in the testing process to be useless, or even noxious, and must either have its deleterious properties neutralised or be completely rejected. The saliva is secreted in the first instance to obviate injurious effects in some way; thus, for example, a strong acid is to a certain degree neutralised, while other corroding substances may be simply diluted, and by mere reduction of concentration have their harmfulness diminished.

In the second place, when the injurious substances have to be wholly removed, the saliva plays the *rôle* of a washing-out fluid; otherwise the material, by clinging to the mucous membrane of the mouth, might in longer or shorter time gain entry into the blood and there develop its noxious influence. This last function of the fluid is hardly taken into account at all in physiology, and yet it is evident that the saliva, as a cleansing fluid, must have a wide importance. If you only think of how often we are impelled to expectorate, that is, to wash out the mouth with saliva after something unpleasant, this will be clear. Such a view finds additional support when we reflect, that a feeling of disgust produces almost as strong a flow of saliva as the sight of a tasty meal. In both cases the secretion performs the office of forerunner: in the first it prepares for the washing out of the mouth, in the second for the requisite elaboration of the food. Think how often, when something disagreeable enters the mouth, with what rapidity the saliva is poured out, even after the unpleasant substance has been for a considerable time removed, and not a trace more is apparent to the sense of taste. Indeed, long afterwards one has only to recall the circumstances to mind in order to bring on anew the secretion of saliva. Apparently the psychic excitation of the nerves of salivary secretion also ushers in the act of vomiting, which, as is well known, can be called forth by mental influence. Further, the function of the saliva just mentioned is probably the true physiological explanation of the feeling of disgust which many persons experience at the sight of the secretion itself.

Hence I hold that substances which obtain entry to the mouth set up a secretion of saliva only because we have here the seat of a definite physiological sense, and not because the peripheral terminations of the buccal nerves are devoid of specific excitability, and capable of being thrown into action by every desired form of stimulus. In other words, the specific excitability of the peripheral endings of the salivary nerves is very comprehensive and widely extended. This is no picture of the imagination, for it can be supported by facts. To say nothing of the testimony of earlier authors, that the salivary glands have each particular exciting agencies to which they specially respond, we can demonstrate the following facts from the material collected in our laboratory.

Dr. Glinski isolated the orifices of the salivary glands in dogs with portions of the adjoining mucous membrane, brought them out of the oral cavity, and caused them to heal into the edges of the skin wounds.

In his first animal the ducts of the submaxillary gland were thus led outwards. By means of a Mendeljeff's clip, the wide end of a conical funnel of waterproof material was attached to the skin surrounding the orifice. To the narrow end a small test-tube, which served to collect the saliva, was attached by a wire. I now offer such an animal a piece of flesh, and, as you see, the tube fills up at once with saliva. I stop tempting the dog, hang on a new test-tube, and give it a few pieces of flesh to eat; once more a strong secretion of saliva results. A new tube is now attached to the funnel, the dog's mouth is opened and a pinch of fine sand thrown in; again there is a flow of saliva. Once more a new test-tube; and now I apply to the buccal mucous membrane, the plume of a feather dipped in acid solution, with the result that I obtain a strong flow of saliva. One may employ a number of substances in this way, when a similar effect is always produced. You see in this, such a comprehensive excitability of the innervation apparatus of the salivary glands that you might readily interpret it as meaning the power of response to all and sundry forms of stimulation. We now proceed, however, to another dog, whose parotid duct has in a similar manner been diverted outwards. The saliva is collected in the same way. We tempt the dog with a piece of flesh, but to our astonishment no saliva flows, and yet the animal is most eager for the savoury meal offered. Now we give it some raw flesh to eat; again the secretion of saliva is as good as absent; only when I come near can I detect one or two drops of saliva running down the sides of the tube. Probably you will say there is something wrong, either with the method or with the glands of the animal. But wait a little. I now give the dog finely powdered dry flesh, and obtain at once an abundant secretion. Should any one happen to think that the variation in the result is dependent, not on a different specific activity of the glands, but on individual differences in the dogs, I respond that Dr. Glinski has had an animal with double parotid and submaxillary fistulæ, and was able to observe on one and the same dog, a like behaviour on the part of the glands to that which we have just seen in two different individuals. An analogous experiment with bread was also carried out by Dr. Glinski. The eating of fresh moist bread produced no secretion worth mentioning, while dry bread, on the other hand, caused the saliva to flow in large quantities. The results of this experiment permit us to draw extremely instructive conclusions. In the first place, the several salivary glands are, as a matter of fact, very sharply differentiated in the conditions necessary for their activity—that is to say, in respect to the agencies which excite their nervous mechanisms. Secondly, the innervation apparatus of the parotid manifests a very sharp selective power in the choice, so to speak, of an adequate stimulus. The mechanical effect of large pieces of flesh is naturally much greater than that of the finely powdered material, and yet it was precisely to the latter that the glands responded. The stimulus is, therefore, not due to the mechanical, but to some other property of the food. This other property is obviously the dryness of the material. Our example illustrates how that which we may term "purposiveness" comes into play in the working of our glands and also how erroneous is the opinion that the mechanical stimulus is all potent. Indeed, previous authors have already pointed out that dry substances cause a specially free secretion of saliva, and yet physiological opinion throughout the length and breadth of the land, as expressed in text-books, has chosen to recognise a *universal* instead of a *specific* excitability. Dr. Wulfson, who is at present carrying on the investigation of salivary secretion in our laboratory, has added a very interesting observation to the results of Dr. Glinski already related. The parotid gland, which is hardly, if at all, excited when one offers fresh meat to the animal, responds with a very active secretion, when dry food (bread or powdered meat) is offered. This phenomenon is all the more surprising since the desire of the animal for eating is much more strongly excited by flesh than by dry bread. I am quite convinced that an exact study of the exciting agencies of the three salivary glands will furnish a number of new data bearing upon the question in hand.

The second reagent which is poured out on the raw material in the digestive canal is the gastric juice. How, in the normal course of events, is the work of the gastric glands, which prepare this juice, called into play? With the first, and manifestly important factor, which has a relation thereto, you are already acquainted, and, indeed, have already seen. I refer to the production of gastric juice in the empty stomach, as a result merely of the swallowing of food in the so-called sham feeding of an œsophagotomised dog. When one takes into consideration the absolute independence of this factor, and the intensity of the effect, which makes itself evident in the secretion of a large quantity of juice of high digestive power, the exciting agency which brings about such secretion must be recognised as one of the most important and effective processes in gastric digestion. But in what does it consist? At first sight it appears—and when I previously drew your attention to the fact I expressed the opinion—that there is here a simple reflex effect from the cavity of the mouth upon the secretory nerves of the stomach, similar to the reflex excitation, *e.g.*, of the parotid gland, by finely powdered flesh thrown into the mouth. Now, however, I assert quite emphatically that this is not the case. We have, it is true, in the activity of the salivary glands an analogous phenomenon to indicate—not, however, that of which we have just spoken. We might apply every conceivable form of stimulus which could possibly come into play in the act of eating, and yet would not obtain the slightest indication of secretory activity in the stomach. In this dog with a gastric fistula, and with also a divided œsophagus, I will try such an experiment, using the most effective chemical stimulus to the buccal mucous membrane, viz., acid solution.

The secretion of saliva begins at once, as you see; the acid is, therefore, effective. From the stomach, however, in spite of continued excitation, no secretion results, although the acid, mixed with the saliva, is swallowed and flows out again from the upper segment of the œsophagus—that is to say, passes along precisely the same path that the food takes in sham feeding.

We could experiment in the same way with a number of other substances: saline, bitters, pepper (strong local excitation), mustard, and so on, and always with the same results; a free secretion of saliva, but perfect quiescence of the gastric glands. We may even, with the same object, employ the soluble constituents of flesh in the form of a decoction, and likewise observe, in most cases at least, no sign of activity on the part of the gastric glands.

With the chemical we may also combine a mechanical stimulus. We can, for example, wipe out the mouth with a sponge soaked in the solution to be experimented with, but always with the same negative result. We may finally give such pieces of sponge, or even smooth stones of considerable size, to the dog to swallow, passing them back behind the anterior pillars of the fauces and allowing them to fall out again, from the upper portion of œsophagus. It may be added that a well-taught dog puts up with all these procedures without the slightest protest. You see that all the manipulations in this case are carried out with bare hands and without instrumental aid. One can easily train a dog to swallow stones which are placed in the anterior part of the buccal cavity. It simply makes a few chewing movements and swallows them down. The dog on which the acid experiment has just been made serves also for the swallowing of the stones. The attendant now places some pebbles in the front part of the mouth, when the animal rolls them round, as if chewing and gnawing them, and then swallows them. The stones fall out, as you see, from the œsophagus, and drop with an audible sound upon the table. This play with the stones has now lasted fifteen or twenty minutes (in the laboratory we have often kept it up for hours), and yet not a drop of gastric juice is to be seen.

In order to prove that the dog is perfectly healthy and normal, we lay aside the stones and proceed to our old experiment of sham feeding. As you see, the first drop of gastric juice makes its appearance precisely at the end of five minutes, and after a further five minutes we have collected more than 15 c.c. of the fluid; consequently there can be no doubt that in this dog both gastric glands and nerves are uninjured and function in normal manner. At one time we even had a dog which voluntarily took the stones out of one's hand and swallowed them; the sagacious creature had seen our object in previous experiments and learned to perform it of its own accord! But in this case also the result was negative.

Clearly, therefore, neither chemical nor mechanical stimulation of the buccal mucous membrane is capable of reflexly exciting the nerves of the stomach. Further, it is obvious that the excitation of these nerves in sham feeding is not the result of a stimulation coincidently produced; that is to say, the excitement of the chewing and swallowing centres does not imply simultaneous action of the secretory centre of the gastric glands. In what, then, does this influence consist which is intrinsic to the sham feeding, but which we have not been able to reproduce in our analytical investigation? There is only one thing to think of, namely, the eager desire for food, and the feeling of satisfaction and contentment derived from its enjoyment.

It has, indeed, been known for forty years, thanks to the experiments of Bidder and Schmidt, that at times, the offering of food to a hungry dog, in other words, the excitement of a keen desire for it, is sufficient to cause a flow of gastric juice from the empty stomach. We shall presently have occasion to observe the force of this physiological factor. Here I bring before you another dog, likewise having a gastric fistula with divided œsophagus. The stomach has been washed out half an hour ago, and since then not a drop of gastric juice has escaped. We begin to get ready a meal of flesh and sausage before the animal as if we meant to feed it. We take the pieces of flesh from one place, chop them up, and lay them in another, passing them in front of the dog's nose, and so on. The animal, as you see, manifests the liveliest interest in our proceedings, stretches and distends itself, endeavours to get out of its cage and come to the food, chatters its teeth together, swallows saliva, and so on. Precisely five minutes after we began to tease the animal in this way the first drops of gastric juice appear in the fistula. The secretion grows ever stronger and stronger, till it flows in a considerable stream. After the lapse of a few minutes we can count the number of cubic centimetres by tens. The meaning of this experiment is so clear as to require no explanation; the passionate longing for food, and this alone, has called forth under our eyes a most intense activity of the gastric glands. If the experiment be frequently repeated, one can easily observe that the keener and more eager the desire on the part of the dog for the food, the more certain and intense is the secretory effect. In extreme cases there is even a quantitative relationship between this effect and that of the sham feeding.

Here is an experiment of Professor Ssanozki, in which the secretory effect of the mere tempting of the animal with the sight of food is compared with that of sham feeding. A few threads of alkaline mucus had just escaped from the stomach, and then the excitation of the dog with flesh was begun. After six minutes the secretion commenced and continued as follows:

Duration of the flow.	Quantity of the juice.
8 minutes	10 c.c.
4 "	10 "
4 "	10 "
10 "	10 "
10 "	10 "
8 "	10 "
8 "	10 "
19 "	10 "
19 "	3 "

Then followed a sham feeding for six minutes.

17 minutes	10 c.c.
9 "	10 "
8 "	10 "

It is clear that in this case the tempting instead of being less effective than the sham feeding, on the contrary excelled it.

Consequently, the observation of Bidder and Schmidt was perfectly correct. It cannot, however, be said that it received general recognition in physiology, or that it was sufficiently appreciated. There are authors who could never convince themselves of its reality, and in many physiological text-books it is not once mentioned. By way of explanation, we shall now consider how this matter must be dealt with by those who wish to observe the effect. It is only under certain conditions that it can be seen. Firstly, the animal must be healthy and vigorous, it must have a perfectly uninjured gastric mucous membrane, and this from the description, in the case of many authors who obtained a negative result, was not the case. Secondly, the success of the experiment, as stated above, is dependent upon the intensity of the desire for eating, and this, again, is dependent upon how freely and how long beforehand the dog had eaten, and also upon what it is tempted with, whether with a dish that excites its desire or leaves its interest unawakened. It is known that dogs have very different tastes, just as men have. Thirdly, one may find among the dogs, positively careless indifferent creatures, incapable of being perturbed in this way by anything which has not actually reached their mouths, and patiently waiting till the food is given them. Hence for success in the experiment, eager, impressionable and excitable animals are necessary. Fourthly, one has to reckon with the sense and cunning of the dog, a factor which is not lightly to be disregarded. Often the animals perceive at once that they are only being teased with the food, become annoyed thereat, and turn away offended at what is being done before them. We must, therefore, so arrange matters as if the animals were not going to be disappointed but fed in reality. If attention be paid to these conditions the experiment of "psychic excitation of the gastric secretion," as we usually term it, will be found to be as reliable as the experiment of sham feeding. When one is occupied for a length of time with the study of the gastric secretion under different conditions, one becomes convinced of what a dangerous source of error this psychic excitability may become in the different experiments. We must constantly fight, so to speak, against this factor, keep it ever in view and guard against it. If the dog has not eaten for a long time, every movement, the going out of the room, the appearance of the attendant who ordinarily feeds the animal —in a word, every little triviality—may give rise to excitation of the gastric glands. The minutest attention is necessary in order to avoid such sources of error, and we should not be far wrong if we said that much which has been ascribed in former investigations to the effect of this or that agency, was in reality a result of unobserved psychic influence. Consequently, in order to verify our own conclusions concerning the effects of this or that condition, we have performed many of our experiments on sleeping animals, having beforehand convinced ourselves by frequent repetition, that sleep exercises no restraining influence on the working of the gastric glands.

When we recall to mind the failure of our attempts to obtain a secretion of gastric juice by any stimulation whatever of the buccal mucous membrane, and at the same time see how constant and intense the action of this psychic impression is, we are forced to the inevitable conclusion, that in our sham feeding experiment the whole secretory effect is due to the psychic stimulus, that is to say, to the keen desire on the part of the animal for food and the satisfaction of enjoying it.

In view of the importance of the act of eating, which even now is apparent, but which will become still more obvious when the succeeding periods of secretion are investigated, we have spared neither time nor trouble to arrive at a correct explanation of the mechanism of this factor. We have, therefore, taken in hand a number of modifications of the sham feeding experiment, and these investigations have confirmed the opinion at which we had arrived. If, for instance, the dog has been prepared by a long fast of two to three days, a very intense secretion of gastric juice will always be obtained by the sham feeding experiment, no matter what may be given it to eat, whether boiled or raw flesh, bread or coagulated egg-white, &c. The dog, however, which has not fasted, that is to say, has been fed fifteen to twenty hours before, will pick and choose amongst the different foods, eating one with great greed, tolerating another, and refusing altogether a third, and, corresponding therewith, the amount and quality of the gastric juice will manifest wide variations. The more eagerly the dog eats, the more juice will be secreted and the greater the digestive power which it possesses. The majority of dogs prefer flesh to bread, and correspondingly less juice will be produced by sham feeding with bread than with flesh. Sometimes, however, we find dogs which will devour bread with greater appetite than flesh. In these cases one obtains more and stronger juice in sham feeding with bread than with flesh. Here is a case in point: a dog is given boiled meat which has been cut into pieces of definite size, and the pieces follow each other at regular intervals of time. The animal eats, but soon, from its behaviour, you see that it develops no particular greed for the meal, and this observation is confirmed by the fact that after fifteen to twenty minutes it ceases taking the flesh. The secretion of juice has meanwhile either not begun at all, or only after a longer interval than five minutes, and remains scanty to the end. Now wait till the secretion has stopped and give the same dog raw flesh, either forthwith or next day, in pieces of the same size and at the same rate as before. The raw meat tastes excellently to the dog, it eats for hours at a time, the secretion of gastric juice begins precisely after five minutes and is very active. With another dog which prefers boiled to raw meat, exactly the reverse occurs. Broth, soup, milk—towards which dogs are usually more indifferent than towards solid food—often produce in sham feeding, either no secretion at all or only very little, although broth, for instance, has essentially the same taste as flesh.

It is therefore clear that in sham feeding the psychic effect may readily become an absolute and independent factor. All the conditions which we enumerated above, and which are necessary for the successful production of the psychic effect, hold good in combined form, for the sham feeding experiment. The dog eats with greed before one's eyes, the food which it receives is pleasant, it not only imagines food but actually eats it, and has therefore no reason to feel offended, for naturally the idea does not occur to any of the dogs that all their trouble is in vain.

Consequently, in the sham feeding experiment, by the act of eating, the excitation of the nerves of the gastric glands depends upon a psychical factor which has here grown into a physiological one, that is to say, is just as much a matter of course, and appears quite as regularly under given conditions as any other physiological result. Regarded from the purely physiological side, the process may be said to be a complicated reflex act. Its complexity arises from this, that the ultimate object is attained by the joint working of many separate organic functions. The material to be digested—the food—is only found outside the organism in the surrounding world. It is acquired not alone by the exercise of muscular force, but also by the intervention of higher functions, such as judgment, will, desire. Hence the simultaneous excitation of the different sense organs, of sight, of hearing, of smell and taste, is the first and strongest impulse towards the activity of the gastric glands. This especially applies to the two latter senses, since they are only excited when the food has already entered the organism or at least has arrived very near it. It is by the establishment of this passionate desire for eating that unerring and untiring nature has linked the seeking and finding of food, with the commencement of the work of digestion. That this factor, which we have now carefully analysed, stands in closest connection with an everyday phenomenon of human life, namely, appetite, may easily be predicated. This agency, which is so important to life and so full of mystery to science, becomes here at length incorporated into flesh and blood, transformed from a subjective sensation into a concrete factor of the physiological laboratory.

We are therefore justified in saying that the appetite is the first and mightiest exciter of the secretory nerves of the stomach, a factor which embodies in itself a something capable of impelling the empty stomach of the dog in the sham feeding experiment, to secrete large quantities of the strongest juice. A good appetite in eating is equivalent from the outset to a vigorous secretion of the strongest juice; where there is no appetite this juice is also absent. To restore appetite to a man, means to secure him a large stock of gastric juice wherewith to begin the digestion of the meal.

LECTURE V.

PERIOD OF OCCURRENCE AND IMPORTANCE OF THE PSYCHIC OR APPETITE JUICE IN THE SECRETORY WORK OF THE STOMACH—THE INEFFICIENCY OF MECHANICAL STIMULATION OF THE NERVOUS APPARATUS OF THE GASTRIC GLANDS.

The psychic secretion is the normal commencement, in the majority of cases, of secretory activity on the part of the gastric glands. If the meal be subdivided and administered at intervals, the psychic juice appears each time—Demonstration of "appetite juice" in a dog with an isolated gastric *cul-de-sac*. The work of the gastric glands if appetite juice be avoided by introducing food through a gastric fistula unperceived by the animal—Digestion of flesh by the stomach with and without sham feeding—Duration of the secretory influence of sham feeding—After the cessation of the psychic effect, how is the secretory work of the stomach maintained?—Experiments to prove the ineffectiveness of mechanical stimulation: excitation of the mucous membrane by means of a glass rod, a feather, a puff of sand, and by rhythmic dilatation of an india-rubber ball—Contact between the food and the stomach-wall may indirectly call the activity of the glands into play by awakening or increasing the desire for food.

Gentlemen,—On the last occasion we made ourselves acquainted with the first normal impulse which, in the natural course of events, calls into activity the innervation apparatus of the gastric glands. This impulse is a mental one, and consists in a passionate longing for food, that which in everyday life, and in the practice of the physician, is called "appetite," and which everybody, both medical and lay, endeavours carefully to promote. We may now venture to say explicitly, APPETITE IS JUICE, a fact which at once displays the pre-eminent importance of the sensation. Medical science endeavours to assist the debilitated stomach by introducing the active constituent of gastric juice—pepsin—from without, or by prescribing other remedies believed to promote its secretion. It is, however, of interest to follow our experimental investigation still farther. What position is to be assigned to the "psychic" or "appetite-juice"* in the course of normal gastric digestion? Is any definite *rôle* to be attributed to it? What course does gastric digestion take when it is absent? Fortunately to all these important questions satisfactory answers are forthcoming by experiment. We have only to regret that these answers come so late.

Let us recall to memory how the secretion of gastric juice proceeded after feeding with flesh or bread in the case of our dog with the isolated miniature stomach. The following are the quantities and digestive capabilities of the first two hourly portions of juice after the administration of 200 grms. of flesh or bread (experiments by Dr. Chigin):

Hour.	Flesh.		Bread.	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1st	12·4 c.c.	5·43 mm.	13·4 c.c.	5·37 mm.
2nd	13·5 ,,	3·63 ,,	7·4 ,,	6·50 ,,

You see at once that the secretion of the first hour is identical in the two cases both as regards quantity and digestive power, and only in the second, is the secretory work differentiated according to the nature of the food. How are we to explain the secretion which takes place at the commencement? Is it not the same which we have already seen in the sham feeding experiments? Is not this first onrush of the stream of secretion the preliminary psychic juice? Unquestionably, gentlemen, this is the case, and we may convince ourselves of the fact in the most diverse ways. Above all, the following is clear: whatever occurs in the so-called sham feeding, cannot wholly be absent in the case of normal feeding, since the former is nothing else than the isolated commencement of normal digestion. This justifiable inference is fully confirmed, if the secretion of the first hours after the administration of flesh and bread be compared with that after simple sham feeding. In the case of feeding with flesh and bread, the identically similar and high digestive power of the first hourly portions is striking, and this power coincides with what we have met in sham feeding. Further, if the quantity of juice from the miniature stomach during the first hour, be compared with that produced by the non-resected part of the organ—to do which we must multiply it by ten, since the resected *cul-de-sac* is approximately one-tenth of the whole organ—it is here again found that the quantity approximately corresponds to the mean values obtained by sham feeding. Finally, the depression in digestive power

* One may be permitted to use this expression for the sake of brevity.

or quantity of juice (with flesh, decrease of digestive power; with bread, decline in the quantity of juice) which sets in soon after the taking of food, indicates that the two conditions are connected with the ingestion of food—*i.e.*, with a transitory factor which soon passes away and gives place to other conditions. Our explanation becomes still more convincing when we take into consideration the effects of other foods. If you give the dog, for example, something else to eat which does not interest it to the same degree as flesh or bread, you will find the initial increase in quantity and strength of juice does not appear. Offer the animal milk, for example, which in sham feeding, especially if it does not last long, calls forth, as a rule, no secretion, or at all events only very little, and the rapid flow of the commencement—the already-mentioned initial rise—absolutely fails to appear. You have already seen the figures which deal with this matter; I think it necessary, however, to bring them forward again in order that you may be better able to compare them with the secretion after flesh and bread.

The dog was given 600 c.c. of milk (experiment by Dr. Chigin).

Hour.	Quantity of juice.		Digestive power.
1st . . .	4·2 c.c.	...	3·57 mm.
2nd . . .	12·4 „	...	2·63 „

We have now begun the analytical examination of the variations of our secretory curve. But owing to the importance of the matter, we did not confine ourselves to conclusions which might be drawn from earlier investigations. We turned to new forms of experiment for further proof.

Thus we divided the ordinary ration of flesh given to our dogs—400 grms.—into four equal parts, which were administered at intervals of an hour and a half. (Experiments by Privat docent Kotljar and Dr. Lobassoff.) Each time after the dog received its 100 grms. of flesh we were able to detect a rise both in the quantity and in the digestive power of the juice. The following table shows the figures in question:

Half-hour periods.	Quantity of juice.	Digestive power.	Remarks.
1st .	3·1 c.c.	5·13 mm.	100 grms. flesh given.
2nd .	5·0 „	4·63 „	
3rd .	4·7 „	4·50 „	
4th .	5·4 „	4·88 „	100 grms. „ „
5th .	5·5 „	3·38 „	
6th .	4·7 „	2 75 „	
7th .	6·0 „	3 75 „	100 grms. „ „
8th .	5·4 „	2·50 „	
9th .	5·9 „	2·50 „	
10th .	5·4 „	3·88 „	100 grms. „ „
11th .	5·3 „	3·0 „	
12th .	4·2 „	2·5 „	

In the curve which follows, only the variations of digestive power are represented.

It is clear that the increase, both of digestive power and of juice volume, is connected with the act of taking in food.

It appeared of interest definitely to determine the volume and properties of the secretion called forth by the act of eating in the dog with the isolated stomach. We endeavoured, therefore, at the beginning, to imitate the conditions of sham feeding as they occurred in the case of the dog with divided œsophagus. In addition to the fistular orifice leading into the isolated miniature stomach, another was opened into the main portion of the organ. If we now fed the dog in the ordinary way with small pieces of flesh, these were received back again at the orifice of the latter fistula, covered with saliva. Precisely as in sham feeding, after five minutes the juice began to flow simultaneously, from both the large and small stomachs. The secretion ran a corresponding course in the two cavities and ceased at the same length of time in both after the administration of food was stopped. Here is an instance taken from such an experiment performed by Dr. Lobassoff.

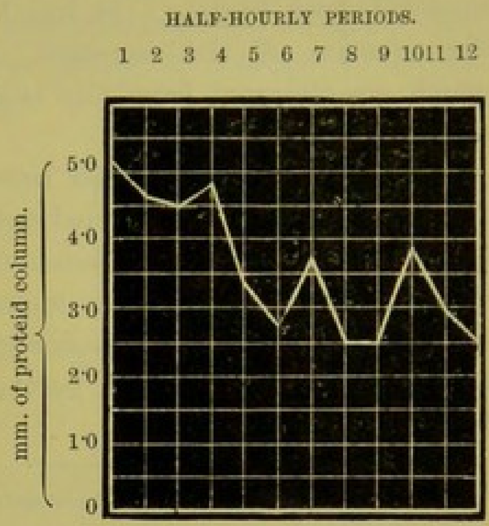


Fig. 11.—Curve of digestive power constructed from the foregoing table.

In five minutes the dog had eaten eighty pieces of flesh (weighing 172 grms.), all of which soon afterwards dropped out at the fistula. The secretion began in both stomachs after the lapse of seven minutes from the commencement of the feeding, and proceeded as follows:

Hours.	Miniature stomach.		Main stomach.	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1	7·7 c.c.	6·25 mm.	83·2 c.c.	5·35 mm.
2	4·5 ,,		58·1 ,,	In consequence of a mixture with bile (10–15 c.c.) the digestive power was greatly reduced.
$2\frac{1}{2}$	0·6 ,,		8·5 ,,	

The secretion from both cavities also came to an end at the same time.

This experiment proves to us, first, that the main and miniature stomachs, work in perfectly parallel manner with each other. The beginning, the end, and the intermediate variations of the secretion correspond in both cases. Secondly, the digestive power of the secretion coincides in both, and is the same which was observed in the so-called sham feeding. It has here remained at the same height till the cessation of the secretion, without falling to the lower value which we observed from the beginning of the second hour onwards, after normal flesh feeding.

This was also confirmed later, when we performed an œsophagotomy on the dog, and carried out sham feeding in typical form. Here follows one of these experiments taken from Dr. Lobassoff's article.

The first drop of juice appeared from both cavities during the sixth minute after commencing the feeding which was kept up for half an hour. The further course of the secretion was as follows :

Hour.	Miniature stomach.		Main stomach.	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1st	7·6 c.c.	5·88 mm.	68·25 c.c.	5·5 mm.
2nd	4·7 "	5·75 "	41·5 "	5·5 "
3rd	1·1 "	5·5 "	14·0 "	5·38 "
	13·5 (total)	5·75 (mean)	123·75 (total)	5·5 (mean)

The secretion came to an end in both stomachs at the same time.

The above is represented in curves in Figs. 12 and 13, the scale on which that for the main stomach is drawn being ten times less than that for the small. As you see, the progress of secretion is identical in both.

The existence of a fistula leading into the large stomach affords us also the possibility of performing an experiment upon our dog which is exactly the converse of the sham feeding experiment, and which constitutes a real *experimentum crucis.* While in sham feeding, we had only, so to speak, the beginning of digestion before us, we are now able in our cross experiment to start at the continuation of this beginning. For this purpose it is only necessary to bring the food into the stomach through the fistula, without attracting the dog's attention. Since in this experiment it is above all necessary not to excite the dog's appetite, it is best to carry out the procedure on the sleeping animal. I may add at once, however, that the same result can be obtained on the waking animal, only the process must be performed unnoticed, and the animal's attention must be diverted from thoughts of food.

The results of this experiment are striking, and do not in any way resemble the secretion after normal feeding. Some kinds of food, for instance bread and coagulated white of the hen's egg, when directly introduced into the stomach, do not yield a single drop of juice during the first hour or more afterwards. This holds good both for the small and large stomachs. When a glass rod is introduced into the food contained in the organ it remains dry. Flesh, if introduced at this

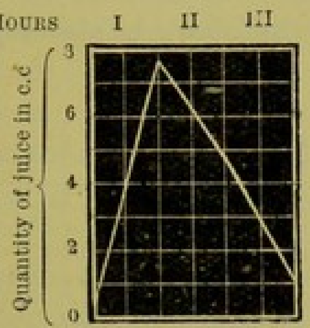


FIG. 12.—Curve of secretion from the miniature stomach.

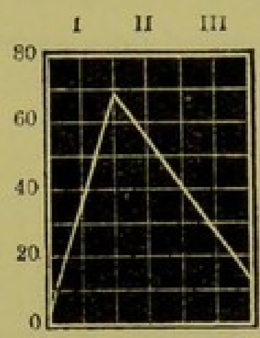


FIG. 13.—The same from the main stomach reduced ten times.

stage, is able to excite a secretion, but the appearance of the juice is considerably retarded. It begins from fifteen to forty-five minutes after the feeding, instead of from six to ten, is under normal circumstances extremely scanty during the first hour (3 c.c. to 5 c.c. instead of 12 c.c. to 15 c.c.), and possesses a very low digestive power.

Here is an experiment by Dr. Lobassoff:

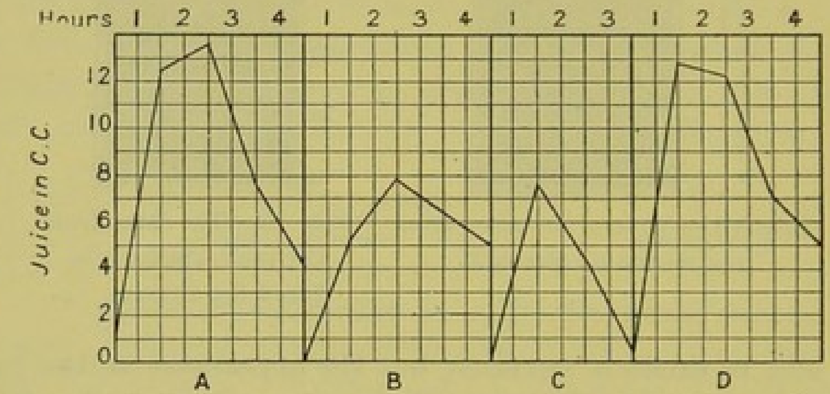
400 grms. of flesh were brought into the stomach.

Hour.	Quantity of juice.	Digestive power.
1st	3·7 c.c.	2·0 mm.
2nd	10·6 „	1·63 „
3rd	9·2 „	1·5 „
4th	7·0 „	1·88 „
5th	5·6 „	2·25 „
6th	6·6 „	2·63 „
7th	7·5 „	1·88 „
8th	5·3 „	2·0 „
9th	3·0 „	5·0 „
10th	0·2 „	— „

The secretion began twenty-five minutes after introducing the food. I now ask you to compare the following tables:

Hour.	Fed with 200 grms. of flesh (Chigin).		Flesh (150 grms.) brought into stomach (Lobassoff).		Sham feeding (Lobassoff).		Total quantity of juice in two experiments.
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.	
1st	12·4 c.c.	5·43 mm.	5·0 c.c.	2·5 mm.	7·7 c.c.	6·4 mm.	12·7 c.c.
2nd	13·5 „	3·63 „	7·8 „	2·75 „	4·5 „	5·3 „	12·3 „
3rd	7·5 „	3·5 „	6·4 „	3·75 „	0·6 „	5·75 „	7·0 „
4th	4·2 „	3·12 „	5·0 „	3·75 „	— „	— „	5·0 „

The progress of juice secretion in the above is also represented in the following curves:



FIGS. 14–17.—A. Ordinary curve of gastric secretion (200 grms. flesh). B. Curve from direct introduction of food (150 grms. flesh). C. Sham feeding with same. D. Summation of B and C.

As you see, the curve which represents the results of the direct introduction of flesh, ascends much more slowly and does not attain anything like the height of that caused by normal feeding with the same food. But if the quantities obtained by direct introduction of the flesh be added to those of sham feeding the resulting curve is almost identical with the normal.

In like manner the digestive power of the secretion in the foregoing experiments can be dealt with, and with the same result. It is a good instance of how a secretion curve can be synthetically constructed from its constituent factors.

Finally, I am able to demonstrate to you the following instructive experiment. In the presence of some of my listeners, whom I had invited to attend an hour before the lecture, I carried out the following procedures on two dogs, both of which had ordinary gastric fistulæ and were, besides, œsophagotomised. Into the stomach of the one, while its attention was distracted by patting and speaking kindly to it in order to avoid arousing any thoughts of feeding, a definite number of pieces of flesh were introduced through the fistula. The morsels were threaded on a string, the free end of which was fastened to the fistular cannula by inserting a cork. The dog was then brought into a separate room and left to itself. A like number of pieces was introduced into the stomach of the other dog in the same way, but during the process, a vigorous sham feeding was kept up, the animal being afterwards left alone. Each dog received 100 grms. of flesh. Since then an hour and a half have elapsed, and now we may draw the pieces of flesh out by means of the thread and weigh them. The loss of weight, and consequently the amount of flesh digested, is very different in the two cases. In that of the dog without sham feeding, the loss of weight amounts to merely 6 grms., while the flesh withdrawn from the stomach of the other dog weighs only 70 grms., that is to say, was reduced by 30 grms. This, therefore, represents the digestive value of the passage of food through the mouth, the value of an eager desire for food; the value of an appetite.

I give also a series of figures obtained by Dr. Lobassoff in analogous experiments. Into the dog's stomach 25 pieces of flesh (100 grms.) were brought. The flesh remained two hours in the cavity. Without sham feeding, 6·5 per cent.; with eight minutes' sham feeding, 31·6 per cent. of the quantity was digested.

Again: the flesh remained an hour and a half in the stomach; without sham feeding 5·6 per cent., with five minutes' sham feeding 15 per cent. was digested.

Once more: the flesh remained five hours in the stomach; without sham feeding 58 per cent., with sham feeding 85 per cent. was digested, the balance of undigested food being 42 per cent. in the one case and 15 per cent. in the other.

I must, however add, that from the nature of this experiment, it is not well adapted for class demonstration, and may often fail. On the one hand, it is not at all easy to conceal the introduction of the flesh from the dog; on the other, the unusual and distracting surroundings of the animal often cause a short period of sham feeding to have less effect than would otherwise pertain. In order to avoid such failures, it is better before an audience, to carry out this experiment only on dogs accustomed to appear in the lecture theatre, and of whose temperament the experimenter is well assured.

I hope you have now been convinced of the great importance which is to be attached to the passage of food through the mouth and œsophagus, or, in other words—and this, according to our former experiences, means the same thing—to the eager desire for food. Without this longing, without the assistance of appetite, many forms of food-stuff which gain entry to the stomach remain wholly devoid of gastric juice. Others, it is true, excite a secretion, but the juice poured out is scanty and weak.

It is only later, when we have still more fully recognised the conditions upon which the secretory work of the gastric glands depends, that we shall be able to grasp the meaning of these facts in a more comprehensive manner. For instance, why does bread brought unnoticed into the stomach of the dog cause no secretion for hours, while flesh tolerably soon (after twenty to forty minutes) provokes this act? This will be explained in the next lecture; now, however, we must consider other questions.

How long does the after-effect, the echo of the first impulse to the secretory nerves of the stomach, continue to last? How long does appetite juice continue to flow after the normal act of eating, which, especially in the case of animals, is not of long duration? We have already determined many times, not only on our dog with the isolated stomach, but also on other animals, how long the after-effect of sham feeding is continued.

Here, for example, is an experiment from the article of Professor Ssanozki which deals with the point. The dog had a gastric fistula and also an opening leading into the œsophagus. After a sham feeding of five minutes the secretion began, and was continued as follows:

Time in minutes.	Quantity.	Digestive power.
10	25·5 c.c.	8·1 mm.
10	20·0 „	8·0 „
10	13·5 „	6·8 „
10	11·0 „	7·5 „
10	8·5 „	8·1 „
10	6·5 „	9·0 „
20	13·5 „	7·4 „
20	11·0 „	7·2 „
20	7·0 „	7·2 „
20	11·5 „	6·8 „
20	11·0 „	6·5 „
30	6·5 „	7·6 „
20	5·5 „	7·2 „

The effect, therefore, even after a short period of sham feeding, stretches over a length of time. Naturally the same holds good for the taking of food in the normal way. One must, however, bear in mind that in sham feeding, with all the force and reality of a hunger sensation not satisfied; the eager desire for food; the effective agency, becomes more and more accentuated, and therefore the secretory influence is prolonged and more powerful. In normal feeding, however, the quelling of the longing, the feeling of satisfaction which, as is well known, sets in long before the termination of the digestive period from the mere filling and distension of the stomach, must diminish the desire for food, and, consequently, bring the secretory effect to an end.

It is, therefore, improbable that the whole secretory process in the stomach, which, in the case of certain kinds and quantities of food, lasts from ten to twelve hours, is dependent on the factors which we have up to the present investigated. This is all the more obvious since a sham feeding of five minutes, even under the most favourable circumstances, does not call forth a secretion for longer than three to four hours. We must, therefore, seek for other exciting agencies of the innervation apparatus of the gastric glands.

Why and wherefore is the secretion instituted by psychic influence maintained? What would first occur to all your minds is naturally the immediate influence which the food exerts upon the walls of the stomach. And this is true, but it does not happen in the simple, direct fashion current in the minds of many physiologists and physicians. When I said that bread or boiled white of egg, introduced directly into the stomach, may not for hours produce a trace of secretion, probably many of my hearers may have asked themselves with natural astonishment, "How, then, is the effect of the forced feeding of phthisical and insane patients, and the artificial feeding of those with gastric fistulæ (performed on account of stricture of the œsophagus) to be explained?" I will introduce my answer by a very unexpected pronouncement relative to the assertion, that mechanical stimulation of the stomach wall by food constitutes a reliable and effective means of calling forth the secretory work of the glands. This assertion, which is so categorically set forth in many text-books of physiology, and which consequently has gained hold of the mind of the physician, is nothing else than a sad misconception degenerated into a stubborn prejudice. My own statement, repeated in many published articles, and at the meetings of various medical societies, that this dictum is only a picture of the imagination, has met, for the most part, either with an unbelieving shake of the head or else with a direct avowal that "it cannot be so." I regret exceedingly that these steadfast unbelievers are not here, so that we might together bring the matter before the tribunal of fact, to the demonstration of which we will now proceed. To this matter I attribute very great importance. It is on this ground, according to my opinion, that the whole battle must be fought out between the generally accepted view, that every agency is capable of exciting the gastric mucous membrane, and the theory that it is only excitable by specific and selected stimuli. If once the defenders of the old opinion are driven from their position, and obliged to admit the inefficiency of mechanical stimulation, there would be nothing further left for them than to build up new theories and search out old facts concerning gland work which have hitherto been rigidly kept in the shade. We may take it that it is mainly because people were so seized with the belief in the direct and simple mechanical explanation, that Bidder and Schmidt's experiment, of the excitation of gastric secretion by mental effect, has been so little taken into consideration, notwithstanding that it appeared so thoroughly reliable and convincing.

I will now repeat the experiment of mechanical stimulation of the gastric mucous membrane before you in the well-known, traditional, and classic manner. Here is a dog with a gastric fistula on which a cervical œsophagotomy has in addition been performed. I open the fistula: as you see, nothing flows out of the stomach; it was washed out clean with water an hour ago. We take the celebrated feather and also a tolerably strong glass rod. Folds of blotting-paper saturated with red and blue tincture of litmus are placed at hand. I now ask my assistant to continuously move the feather and glass rod, alternately, in all possible directions in the stomach, changing from one to the other every five minutes. On removal from the stomach each is carefully dried with red and blue blotting-paper. You have all seen, gentlemen, that this procedure has now been kept up for half an hour. From the fistular orifice not even a single drop has escaped, and, moreover, the drops of moisture, on all the pieces of red blotting-paper I have been able to hand to you, have assumed a distinct blue tinge, caused by the moisture of the alkaline mucous membrane. The blue pieces, however, have merely been made wet without altering their colour. Consequently, with the most thorough mechanical stimulation of the whole cavity of the stomach, we have not been able to find a single spot possessing a noticeable acid reaction. Where, then, are the streams of pure gastric juice of which we read in text-books! What objection can be raised against the conclusiveness of this experiment? In my opinion only one: that we are dealing with a dog out of health, whose gastric glands from some possible cause, are unable to react normally. This single objection can be set aside before your eyes. After failing with the mechanical stimulation, we proceed forthwith to the sham feeding of the same animal. The dog takes the food offered it with keen appetite, and you see that, exactly five minutes after beginning the feeding, the first drops of juice appear from the stomach, followed by others faster and faster. I catch a couple of drops on the blue litmus paper, and you see that they produce bright red specks on the blue sheet. After thirty minutes' sham feeding we have collected 150 c.c. of juice, which, without filtering, looks as clear and transparent as water.

We cannot, therefore, possibly doubt that, when the proper stimulus is used, the gastric glands react to it in a perfectly normal fashion, furnishing a healthy gastric juice. From this it irrefutably follows, that only one explanation is to be found for the negative result in the first half of our experiment, viz., that the mucous membrane of the stomach, so far as secretory activity goes, is perfectly indifferent to mechanical excitation. And yet this mechanical stimulus is demonstrated as an exciting agency in the physiological lecture-theatre. I venture to think that this lecture experiment from now onwards will quit the field, and give place to the one I have just shown you. This apparently simple experiment of mechanical stimulation can, however, only be successfully performed when certain very obvious rules are followed. These, however, physiologists have not observed, probably on account of a preconceived belief in the effectiveness of the mechanical stimulus. These rules are two. First, it is necessary that the stomach should be clean, and that nothing shall gain entry to it from without. Such conditions were not formerly fulfilled. It is true the stomach was emptied by removing the stopper from the fistular cannula, but it was not washed out till an acid reaction was no longer given, and consequently preformed gastric juice was left behind between the folds of the mucous membrane. At the same time, saliva from the cavity of the mouth could gain entry, which quickly became acidified in the incompletely emptied and imperfectly washed-out organ. It is, therefore, not surprising that the glass tube, by setting up contractions of the stomach, was the means of expressing small quantities of acid fluid from the fistula-tube. (The relationship between mechanical stimulation and the motor functions of the stomach is not to be confounded with what we are here speaking of.) That matters are as I state, and that the facts correspond to the explanation, is proved by this, namely, that nobody till now has obtained genuinely pure gastric juice of an acidity amounting to 0·5 or 0·6 per cent. It is only necessary to call to mind that Heidenhain, when determining the acidity of the juice first obtained from the resected stomach, was placed in no little doubt as to whether his results (0·5 to 0·6) were correct, and his assistant at the time (Gscheidlen) was set to verify the correctness of his standard solutions. The acidity of the "purest" juice known at that time was scarcely 0·3 per cent. As a further proof that none of the older observers ever really obtained a secretion from mechanical stimulation pure and simple, we may adduce the fact that none of them made mention of the constant and precise period of five minutes' latency. To overlook this was not possible if a genuine excitation of the glands had been obtained.

Of no less importance is the second condition when we wish to perform the experiment of mechanical stimulation in the correct way. It is very necessary that the gastric glands be not already in activity at the beginning of the experiment, and also that during the experiment no impulse comes into play, which of itself, apart from mechanical excitation, could excite the glands to secretion. Nor have we any proof that observers formerly waited for hours before commencing the experiment, and convinced themselves that the gastric glands had ceased working. On the contrary, we have not the slightest evidence to indicate that the authors had attempted to guard against accidental psychical stimulation of the glands—a matter which we have seen is of considerable difficulty. And some dogs are so easily excited in this way that it is almost impossible to bring their glands to rest, or at least it is necessary to wait for hours. The experimenter must strain his whole attention to preserve such an experiment free from objection. It is only necessary that some food be near the dog, or that the hands of the attendant who has prepared the food should smell of it, or that some other similar circumstance should come into play, and the glass tube, quite undeservedly, will be made answerable for the excitation of the gastric glands. As you have just seen, both of our conditions have been fulfilled on the dog before you, and the result of the experiment stands in irreconcilable contradiction to those of the laboratory and lecture experiment of former times.

The importance of the experiment, which I have already dwelt upon, justifies me in making still further demands upon your attention in order to show you two modifications of it. Nobody has as yet said, with regard to mechanical stimulation, that in order to obtain results, the mechanical agency must simultaneously come into contact with numerous points of the inner surface of the stomach. But in order to meet this possible objection I will now show you two new modifications. Again, a similar dog is used, that is to say, one on which both gastrotomy and œsophagotomy have been performed. The stomach has been washed out clean and is at present in a state of complete rest. Into the fistula I bring a thick glass tube containing a number of small openings (2 to 3 mm. diameter) at its rounded end. The other end of the tube is connected with a glass ball containing tolerably coarse sand. Leading into the ball is a second tube, with which an india-rubber pump can be connected and a blast of sand blown through. By rhythmic compression of the india-rubber ball I inject sand with considerable force into the stomach, and this play is kept up for ten to fifteen minutes; nevertheless, we see no trace of gastric juice. The sand falls out again between the side of the cannula and the glass tube, and it is either dry or scarcely moistened, but in no case is it able to turn blue litmus red. And yet we are here dealing with a strong and widely diffused stimulus. Look for a moment at the performance of the bellows outside the stomach. From every opening of the tube—

numbering considerably more than ten—a strong stream of sand is ejected. If you hold your hand against it, you feel quite distinctly, that the grains of sand strike with considerable force. And now, when our experiment is ended, we may convince ourselves by sham feeding, in easy and unquestionable fashion, that the innervation of the dog's stomach is perfectly normal.

Yet another experiment on a similar dog. Into its empty and resting stomach an india-rubber ball is introduced. This is distended with air by means of a syringe till it is as large as a child's head and maintained in this condition for a time, afterwards being allowed to collapse. The procedure is kept up for ten to fifteen minutes. During this time not a single drop of juice has appeared from the stomach. The surface of the ball taken out of the organ is everywhere alkaline. And here also subsequent sham feeding shows that the dog is in a suitable condition for the experiment. I must add that in making this observation the dog must not be too hungry, that is to say, must have been fed within ten to twelve hours before, otherwise a psychic excitation of the secretion can readily be induced.

If one dispassionately regards this question, and if any of our methods for the study of gastric secretion are reliable, one must be convinced step by step in the laboratory, of the uselessness of mechanical stimulation. In the case of dogs with an ordinary gastric fistula, and failing some special reason, not a drop of gastric juice ever escapes from the stomach other than during the digestive period. How could this be the case if the mechanical stimulus were effective, since the inner rim of the fistula-tube is continuously in contact with the gastric mucous membrane? The same holds good for the dog with resected stomach. During the experiment a glass or india-rubber tube is brought sufficiently far into the *cul-de-sac* to catch the juice, and yet not a drop flows through the tube, nor does its inner surface ever become acid, so long as true secretory conditions are absent. Moreover, the tube has tolerably often to be taken out and set right.

In the ordinary gastric fistula in dogs, when the operation has lasted a long time—over a year—folds of mucous membrane are often formed in the neighbourhood of its inner orifice, which completely close the tube. In these cases a long thick perforated metal tube has to be passed in deeply, and yet the manipulation of itself never calls forth a secretion. Further, it is a daily occurrence to find in the stomach of the dog, thick rolls of hair, and yet their presence in no way hinders the arrest of the secretion, which occurs when digestion has ceased. Such an occurrence would have been specially obvious in our dog with the isolated stomach, since it was bedded with sawdust in order to guard against maceration of the wound by juice trickling out. Very often we found enormous quantities of sawdust in the stomach, as much as half a pound weight; obviously the dog had licked the wound from adherent sawdust, which it then swallowed, together with that sticking to its nose. And yet these particles of sawdust of themselves, which certainly acted as mechanical stimuli, never caused a secretion. It appears to me that this long series of facts ought to suffice to carry the supposition to its grave, that by direct mechanical stimulation, one is able to set the neuro-secretory apparatus of the stomach into activity.

And yet the feather and the glass tube continue the even tenor of their ways to this moment, and function in some text-books, yea, even in articles which specially treat of gastric secretion, as exciters of the gastric glands. There are, it is true, a few physiologists who hold mechanical stimulation, in relation to gastric secretion, not to be very effective, and give it a subordinate position in the series of exciting agencies, but as yet I know of no other physiologist who has wholly denied its influence, and who has not held it possible to obtain at least some juice by it.

To conclude this lecture, we will take into consideration a question connected with the matter we have just discussed. Since the contact of food with the gastric mucous membrane has no direct influence on the secretion, is its entry into the stomach devoid of all connection with the secretory process?

It can hardly be doubted that, under normal conditions, the stomach is the seat of certain definite sensations, that is to say, its surface has a certain degree of tactile sensibility. This sensation is, as a rule, very weak, and the majority of people become accustomed to pay no heed to it in the normal course of digestion. They obtain their sensations of general well-being, and especially of satisfaction from the enjoyment of food, without taking cognisance of the factors contributing to them. The feeling of general hunger, however, is referred solely to the stomach.

On the other hand, all of us have met with men who could describe exactly and with gusto, how they were able to follow a special tit-bit, or a mouthful of a favourite wine, the whole way through the œsophagus down to the stomach, especially when the latter happened to be empty. Naturally the gourmand, who directs his attention continuously to the act of eating, can in the end distinctly perceive sensations and even call them up to consciousness, which in other people are normally masked by other sensations and impressions. We may therefore take it that the satisfaction derived from eating, is caused not only by stimulation of the mouth and throat, but also by impulses awakened by the passage of the food along the deeper portions of the œsophagus and by its entry into the stomach. In other words, food which merely passes through the mouth and throat produces less enjoyment and excites, therefore, a less feeling of appetite, than the food which passes the whole way into the stomach. The appetite, the eager craving after food, is, indeed, a very complex sensation, and often not merely the need of the organism for food material is necessary for its excitement, but also a condition of thorough well-being, together with a normal healthy feeling in all parts of the digestive tract. For this reason it is easy to understand how patients who have diseased sensations in these organs, and who have no feeling of appetite, no desire for food, remember the sensations, whether consciously or unconsciously, even when they are no longer present. Cases are known to neuro-pathologists where people with gastric anæsthesia suffered from this loss of appetite. Such patients are no longer conscious of having stomachs, and dislike the idea of eating because the food, as they express it, appears to fall into a strange empty sack. In this way one can also conceive how the appetite becomes lost in cases of long-continued obstruction of the alimentary tube. The patients forget their stomachs, and in such instances direct introduction of food into the organ, after an operation, may suddenly bring back the appetite.

As a further illustration, I may be permitted to give an instance from my own personal experience. After an illness with which a transient but high fever was associated, although otherwise fully recovered, I had lost all desire for food. There was something curious in this complete indifference towards eating. Perfectly well, I only differed from others in that I could with ease abstain from all food. Fearing that I should collapse, I resolved on the second or third day to endeavour to create an appetite by swallowing a mouthful of wine. I felt it quite distinctly pass along the œsophagus into the stomach, and literally at that moment perceived the onset of a strong appetite. This observation teaches that the tactile sensation of the stomach at the moment of entry of food, is capable of awakening or increasing the appetite. It is known that withholding food from the organism, or in other words, the creation of a necessity for food, does not lead immediately, nor in all cases, to the production of an appetite; to a passionate craving for food. How often does it happen that the ordinary hour for a meal has struck, and yet, owing to some keenly interesting occupation, not the least desire for food is felt? It is known to everybody, indeed it has become a proverb, that real appetite first sets in with eating. If this be true, the initial impulse towards awakening an appetite may originate in the stomach and not in the buccal cavity. When we spoke above of the desire for food being the excitant of the secretory nerves of the stomach, we naturally meant the passionate and conscious longing for food, that which is called "appetite" and not the latent need of the organism for nourishment, the lack of nutrition, which has not yet been transformed into a concrete passionate desire. A good example which enables us to differentiate between these two factors is furnished by our dogs with sham feeding. The necessity for food exists in such cases, even before the experiment; the juice, however, only begins to flow as soon as this need has taken the form of a passionate longing. It is therefore quite possible that in the case of some dogs, and at a certain stage of hunger, the touching of the gastric mucous membrane with any object at hand, its mechanical excitation; its distension by the food mass, may give the impulse which excites the appetite; and when the appetite is awakened the juice flows. This is possibly a third reason why, in the old experiment, the mechanical stimulus came to be considered effective. Viewed from this point it may, to a certain degree, lead to a reconciliation between my assertion concerning the inefficiency of the mechanical stimulus and the generally prevailing belief. I further also admit that mechanical excitation will at times call into play the work of the gastric glands, not however directly by means of a simple physiological reflex, but indirectly, after it has first awakened and enlivened the idea of food in the dog's consciousness, and thereby called forth the passionate desire. I hope that the foregoing will in no way lead to a confusion of ideas in your minds, but will assist you to an exact and concrete analysis of the previous simple explanation of the facts. This representation, which bears more or less of a hypothetical character, could, of course, be submitted to experimental proof. For such, it is only necessary to compare the influence which sham feeding exercises in an œsophagotomised dog with that in one having a simple gastric fistula.

LECTURE VI.

THE CHEMICAL STIMULI OF THE NERVOUS MECHANISM OF THE GASTRIC GLANDS: THE MINIATURE STOMACH A RELIABLE METHOD OF COMPARISON—SEAT OF ACTION OF THE CHEMICAL STIMULI—HISTORICAL.

Water as an excitant of the gastric glands—The effects of watery solutions of the ash of flesh, of sodium chloride, of soda, and of hydrochloric acid on the gastric glands. Solutions of egg-white are ineffective as excitants—Meat broth, meat juice, and solutions of Liebig's Extract are reliable exciting agencies—Neither starch nor fat is able to call forth a gastric secretion—Chemical excitants are also produced in the peptic digestion of proteids—Starch influences the quality of the juice by augmenting its content of pepsin. Fat inhibits the work of the gastric glands, both from a quantitative and from a qualitative point of view—The miniature *cul-de-sac* furnishes a true picture of the work of the large stomach. The chemical excitants of the nervous mechanism of the gastric glands have their seat of action at the surface of the mucous membrane. The investigations of Blondlot and of Heidenhain on the secretory work of the stomach.

GENTLEMEN,—In the last lecture we had settled (1) that psychic excitation, notwithstanding its importance, is not the only source of gastric secretion; (2) that the mechanical properties of the food in themselves are unable to call forth a direct secretion of gastric juice. In order to answer the question as to what circumstances within the cavity of the stomach may act as stimuli to secretion, we must turn to the chemical properties of the food. Our experiments on this point have for the most part been performed on dogs with isolated miniature stomachs. The fluid substances to be tested were at first passed into the stomach by means of a sound. Later, when a second fistula was opened in the main stomach, they were introduced directly through it. Obviously the latter method is incomparably the better, since it contains fewer sources of error and is less troublesome for the observer. The introduction of the sound is unpleasant to the animal, and may influence the secretory process either by causing pain, or in some other way. In passing the sound, vomiting movements may be set up, which, it cannot be denied, may in certain ways affect the work of the glands. Further, in spite of every precaution, during the withdrawal of the sound, a few drops of the liquid injected not infrequently fell on the mucous membrane of the mouth, and these drops may have awakened the idea of food in the dog's mind. All this is, of course, avoided by the fistula leading into the large stomach. The substances may even be introduced when the animal is asleep, without waking it. Moreover, not only fluids, but also more consistent substances, may be employed in this way.

It was natural to commence the investigation with water—the simplest and, from its wide occurrence, the most important constituent of the food. Has water an exciting effect upon the gastric glands? From a long series of experiments we have arrived at the conviction that it has. When, for instance, in the case of our dog with the two stomachs, we introduced 400 to 500 c.c. of water into the larger cavity, we always obtained a secretion of gastric juice (*Dr. Chigin*), though not a large one. The constancy of the result, and especially the regularity of the quantity of juice secreted, clearly indicated that no accidental condition, such as a mental effect, came into play. We have, however, both earlier and later experiments at hand which remove every doubt concerning the stimulating influence of water. Heidenhain had long ago shown that a secretion began from the gastric *cul-de-sac*, isolated by his method, as soon as water was introduced into the main cavity. The same phenomenon was likewise observed at a later period by Professor Ssanozki. In such a case the possibility of a psychic excitation of the secretion is excluded, owing to the division of the vagus nerve fibres. For instance, in dogs whose vagi were cut below the diaphragm, Dr. Jürgens never saw a secretion of gastric juice as the result of sham feeding. As soon, however, as water was poured into the stomach, an undoubted secretion occurred. Finally, I have myself always obtained a secretion from the introduction of water in dogs which I succeeded in keeping healthy for several months after the vagi nerves were divided in the neck. Hence water must be accepted as a chemical excitant of gastric secretion, if only a weak one. Thus, if instead of 500 c.c., only 100 c.c. to 150 c.c. of water be injected into the large stomach of a dog with the isolated pouch, very often—that is to say, in about half the cases—not the least trace of secretion is to be seen. It is only a prolonged and widely spread contact of the water with the gastric mucous membrane, which gives a constant and positive result.

Before passing, I wish further to emphasise the fact that section of the vagi nerves, which suppresses all psychic influence upon the gastric glands, does not in the least prevent the stimulating effect of water upon them; nor could the secretory fibres of the sympathetic, whose existence is almost certain, take the place of the vagi in transmitting the psychic impulses. We have, therefore, before us the interesting fact, that secretory fibres which course in different nerves have in all probability different physiological duties to perform. But why does water act as an exciter? The fluid needs no digestive juice. The chief reason, I believe, lies in this: that in cases where, for example, no psychic juice is present, the impulse to the secretory work of the stomach may be given by means of water. Water is very widely distributed in nature, and the instinct for it—thirst—is even more pressing and persistent than the desire for solid food. If a dry meal be eaten without appetite, thirst will compel one to drink water afterwards, and this fluid suffices to ensure the beginning and continuation of the secretory work of the glands. That the secreted juice at times, when water alone is drunk, remains without finding a use, is of no consequence, and cannot weigh as a serious objection against our explanation. For, in the first place, as we have already seen, the secretion caused by water is not of itself important; and secondly, even the free flow of psychic juice may at times be secreted when there is no use for it—for example, when, with an empty stomach, we have a keen desire for eating, but are unable to do so for some reason or other. But this does not make us doubt the great physiological importance of the psychic juice.

The stimulating influence of water must be kept in view when we are testing the effect of any other substance upon the gastric glands. We must always compare the results produced by a watery solution of the given substance with the effects of a like quantity of water alone.

After water, a number of different inorganic substances, which are constituents of the food or are employed in the practice of medicine, were also tested. Thus, the constituents of meat ash, chloride and bicarbonate of sodium, and hydrochloric acid were repeatedly brought under investigation (*Dr. Chigin*), till we were fully satisfied of the certainty and accuracy of the results. It appeared that not one of these substances, with the exception of bicarbonate of sodium, exercised the least influence on the secretory work of the stomach—that is to say, their watery solutions had precisely the same effect as water itself. To sodium bicarbonate an inhibitory influence must be ascribed. Not one of the soda solutions (varying from 0·05 to 1 per cent. strength), when brought in quantities of 150 c.c. into the large stomach, were able to expel even a single drop of juice from the small cavity. At most a little mucus escaped. Hence the presence of sodium bicarbonate prevents the stimulating properties of the water. These facts are worthy of serious consideration, both on account of their clinical interest as well as on physiological grounds. We will, however, return to them later.

Next, it appeared of special interest to study the effects of the so-called food-stuffs—viz., the carbohydrates, the fats, and the proteid bodies. It was to be expected, from *a priori* reasons, that if the gastric juice were specially adapted to act on the proteids, these substances would also prove to be chemical stimuli of the mucous membrane of the stomach. How astonished were we then to find, that when fluid egg-white was introduced into the stomach of our dog, either pure or diluted with an equal volume of water, we obtained no greater secretion than a similar volume of water had caused. This seemed to us so peculiar, that the experiment with egg-white was repeated till no doubt whatever of its reliability could exist. The result was also corroborated in the laboratory by Professor Rjasanzeff at a later period, when investigating the way in which egg-white, after introduction into the alimentary canal, is able to influence the output of nitrogen in the urine, although it calls forth no digestive work. This is altogether a wholly unexpected fact. It would be difficult to find either a physiologist or a physician who, if asked what happens to egg-albumen when introduced into the stomach by means of the sound, would not reply, "Naturally, it is digested by the secretion of gastric juice, which it sets up."

A positive result from chemical excitation of the gastric mucous membrane was, however, obtained when we injected a peptone product manufactured by the firm of Chapoteau. The experiments with this preparation always gave a marked secretory effect every time they were repeated. Other experiments, however, in which a preparation obtained from Stoll and Schmidt in St. Petersburg was employed, furnished wholly negative results—that is to say, the peptone solutions acted merely as water acts. Dr. Dzierzgowski analysed both preparations for a special purpose in Professor V. Nencki's laboratory, and kindly communicated to us, that the peptone of Chapoteau contained as much as 50 per cent. of pure peptone, while that of Stoll and Schmidt consisted almost entirely of albumose, and only to the smallest extent of peptone.

A comparison of these chemical results with the physiological effects, led myself and Dr. Chigin to infer that peptone must be the chemical stimulant of the neuro-glandular apparatus of the stomach which we sought. This belief, on further investigation, proved, however, to be erroneous; for neither pure peptone nor the products obtained by the action of strong and pure gastric juice on raw fibrin, gave constant effects. On the other hand, meat broth, meat juice, and solutions of meat extract proved to be constant and active exciters of the secretory process in the stomach. From this it seemed natural to conclude that the actual substances which produced the result mentioned must also be contained in the peptone of Chapoteau.

The experiments carried out with the above products, especially with solutions of meat extract, are already to be numbered by tens (*Dr. Lobassoff*). I give one as an example: 150 c.c. of water in which 10 grms. of Liebig's Extract were dissolved, were injected through the fistula into the large stomach of a dog. The first drop of juice appeared thirteen minutes after the introduction of the fluid. In the course of the first hour 5·3 c.c. of juice with a digestive power of 4·25 mm. were secreted; in the second hour 2·6 c.c. with a digestive power of 4·0 mm. In many cases, these experiments were carried out on sleeping animals, for which purpose the funnel and india-rubber tube for pouring in the fluid naturally had to be connected beforehand with the fistula. The exact nature of the chemical excitant remains as yet unexplained. The reality and significance of the fact, is however, in no way thereby diminished. The individual extractives, such as kreatin, kreatinin, &c., were found to be ineffective. Up to the present we only know, from the experiments of Dr. Lobassoff, that when Liebig's Extract is digested with absolute alcohol, the active bodies for the most part remain behind in the residue. We venture to hope that a more complete analysis of the constituents of meat extract will finally bring us on the track of this undiscovered chemical stimulus of gastric secretion.

Thus, in addition to water, we have at present only found one other chemical excitant, viz., in the extractive materials of flesh. Milk and solution of gelatine were, however, also found to be direct chemical stimuli to gastric secretion. What the effective agency in each of these cases is, remains wholly obscure; whether some exciting constituent is actually present in the substance itself, as in the case of meat, or whether the effective agent must first be formed during the course of digestion, after the water has started a secretion, or finally, whether the material comes into existence under the influence of some other alteiation, remains undecided. One must bear in mind, however, that egg-albumen contrasts with the constituents of milk and with gelatine, in possessing a greater degree of stability, and possibly the secretion excited by water is not sufficient to alter it to such an extent as to render it capable of exciting the gastric glands.

The remaining food-stuffs, such as starch and fat, proved in Dr. Chigin's hands not to have any exciting effects. Starch, whether boiled or unboiled, and mixed in different proportions with water, had no greater effect, but rather less, than water alone. The same applies to grape-sugar and cane-sugar. The inactivity of starch as a chemical stimulus was made the basis of the following interesting investigation

(*Dr. Lobassoff*). A solution of Liebig's Extract of Meat, judging from the quantity of juice secreted, is a stimulus of only moderate strength. The reason of this may possibly lie in the fact that the solution quits the stomach, whose surface it should specifically excite, too quickly. If so, it was to be expected that, if the ingredients of the meat extract could be somewhat longer retained in the stomach, a larger quantity of juice would be secreted. As a matter of fact, when we made a mixture of meat extract with starch solution, and divided the cooled jelly into pieces which were afterwards inserted into the stomach, we obtained, as was anticipated, twice as much juice as would be yielded by the same quantity of meat extract in simple watery solution.

Here are the figures from one of the experiments :

Hour.	Quantity of juice.	Digestive power.
1st	2·8 c.c.	5·0 mm.
2nd	2·2 „	5·0 „
3rd	2·8 „	6·25 „
4th	1·8 „	5·88 „
5th	1·2 „	6·25 „
6th	0·6 „	6·5 „ (6th–8th)
7th	0·7 „	
8th	0·2 „	
Total	12·3 „	...

This experiment is also interesting because it materially supports the assumption which we have tacitly made, that all the substances hitherto employed excite the nervous machinery by a reflex stimulus from the mucous membrane, and not that they are absorbed into the blood, and then act directly on the peripheral neuro-glandular apparatus, or even on the glands themselves. It is at once apparent that, if the meat extract acted through the blood, it would be much more effective in solution than when mixed with starch-jelly, and, therefore, in a less absorbable form.

Particular care was also devoted to the investigation of vegetable and animal fats. They were tested not alone on a dog with isolated miniature stomach, but also on animals with gastric and œsophageal fistulæ, and finally on dogs which had survived the operation of section of the vagi in the neck performed several months previously. In all these cases the fat was directly introduced into the stomach without swallowing. The result was invariably negative.

Hence, when separately investigated, the majority of food-stuffs showed an absence of stimulating effect upon the secretion of gastric juice. To the minority which yielded a positive result, water and certain as yet unknown constituents of flesh belong.

From the experiments with simple substances we may now pass on to others, in which we introduced different combinations of ordinary food-stuffs into the stomach, avoiding at the same time the act of eating. We shall then see what the combined influence of the composite food may be, made up as it is, of the already mentioned simple effects, and learn in how far the former may be explained by the latter.

When considerable quantities of finely divided raw flesh are introduced unnoticed into the main stomachs of our dogs the secretion of juice begins (as already stated in the fifth lecture) at the earliest, from fifteen to thirty minutes afterwards. At this point I must not overlook an arrangement which was used for bringing the flesh into the stomach (*Dr. Lobassoff*). When meat is introduced piece by piece into the fistula, the dog guesses what is happening, and this may naturally lead to a psychic excitation of the secretion. Sometimes, it is true, the animal may be asleep, but the procedure always awakens it, and the feeding has then to be finished in the waking condition. To prevent this mishap, we filled a wide glass tube with the meat-pulp from the mincing-machine, introduced it gently into the fistula-tube, and then pushed the flesh into the stomach with a suitable rod. If the dog should wake up, it can no longer guess what has happened, for the whole thing is finished, and it drops off to sleep again immediately. But flesh always sets up a secretion even under these conditions. This was to be expected after what has been said in the beginning of the present lecture, and is easily to be explained. Obviously the secretion is chiefly to be attributed to chemical substances dissolved in the meat juice. Dr. Lobassoff, who undertook the investigation of this question, adopted several modifications of the experiment in order to test the validity of these conclusions. Thus he boiled the flesh thoroughly for several days, and then saw that its introduction into the stomach occasioned either no secretion at all or only a very weak one. It was only necessary, however, to add some Liebig's Extract to the sodden flesh in order to restore to it the activity proper to raw meat.

When analogous experiments were undertaken with bread and boiled egg-albumen, that is to say, by introducing the food-stuffs into the stomach in a manner which wholly excluded psychic influence, a negative result, as has been said, was always obtained. They remained two or three hours (as long as the observation was kept up) without exciting the least trace of secretion. It is justifiable to suppose, either on the one hand that these unexpected results were due to the unfavourable physico-chemical condition of the material (locking-up of the water), or, on the other hand, that direct chemical excitants are really absent. The negative effects of fluid albumen must be borne in mind, however; and, further, Dr. Lobassoff found that watery infusions of bread had no stronger stimulating influence on the gastric glands than equal quantities of water.

Are we then to rest content with these results? Do they furnish a complete explanation of the progress of secretion in normal digestion? Obviously, No! In the case of flesh diet the condition of matters is tolerably clear. The secretion here is partly set up by psychic effect and partly by chemical substances peculiar to flesh. With bread and boiled-egg albumen the case is otherwise. Their relations are by no means clear. Only the initial secretory period, which has its origin in the psychic effect, is explained; the further periods, which count from the end of the first three or four hours, are dependent upon an unknown process, since only a portion of the secreted juice can be accounted for by conditions at present revealed to us. To make the importance of these questions more manifest, I beg you to compare the experiments with starch jelly, in the one case eaten, in the other directly brought into the stomach. As I told you previously, starch paste, when directly introduced, calls forth no secretion worth mentioning, while, if eaten by the animal, a secretion lasting two to three hours is set up. A careful consideration of this experiment discloses its meaning at once. The juice poured out in the second case exactly corresponds to the "psychic" secretion, the energy of which we have already learned in the sham feeding experiment. This correspondence, however, no longer obtains when bread or boiled-egg albumen is eaten. Not more than one-half or even one-third of the juice secreted in these cases can be ascribed to the psychic effect. The source of the remaining portions remains as yet undiscovered. That, as a matter of fact, some other cause, some other excitant, must exist, follows from this, namely, that the juice of the second or third hour after the eating of the egg-albumen possesses no specially strong digestive power, while the psychic juice, as already stated, is of the most active kind. The most natural conclusion is, that during the elaboration of bread and egg-albumen by the psychic juice, a chemical agency comes into existence early in digestion, which sets the neuro-secretory mechanism of the stomach into activity. Probably it is a digestive product identical or similar to the substance which plays the *rôle* of exciter in the case of flesh.

In support of this explanation we are able to bring forward experimental data. If one obtains the fluid digestive products from the stomach of a dog which has eaten egg-albumen, and injects them directly into the main stomach of a dog with an isolated miniature cavity, a much stronger and more constant secretory effect is produced than is yielded by a like quantity of water or fluid egg-albumen (*Dr. Lobassoff*). The formation of this product cannot, however, be very active, because after the psychic secretion, which lasts two to three hours, comes to an end; the hourly quantity of juice poured out upon bread or egg-albumen is very small. Further, this statement is supported by the following experiment. When a secretion is already going on in the stomach, caused either by psychic effect or continued from the last period of digestion, the unobserved introduction of fluid egg-albumen, is always followed by a considerable augmentation of the secretion (*Dr. Chigin*). How is this phenomenon to be interpreted if one is not to suppose that at the commencement of egg-white digestion a body is formed which stimulates the mucous membrane? The same explanation which holds good for bread and egg-albumen may be extended and applied to the proteids of flesh. Part of the chemical exciting substance already exists in the meat; the remainder, however, is only formed during digestion.

This investigation brings under our notice a very special and exceedingly important property of the psychic or appetite juice. In the case of flesh this juice affords important assistance to the pre-existing excitant, and thereby determines a rapid digestion, shortening the stay of the raw product in the digestive canal. With other foods—for example, with bread—this juice is an indispensable condition to their digestion. If bread or egg-albumen be eaten without appetite, or introduced into the stomach unobserved, they lie there for a long time, just as stones would lie, without the least appearance of digestion. In such cases the appetite juice is the sole initiator of the secretory process and the necessary condition for its continuation. If started by its assistance, the digestion of these foods spontaneously proceeds. The psychic juice here plays the *rôle* of the igniting material which sets the stove ablaze, and for this reason it has been called "Igniting-juice" by Dr. Chigin. Probably it is also, on this account, that the psychic juice with every food possesses a uniform and tolerably strong digestive power.

It is obvious that when bread or egg-albumen is eaten without appetite; water, or still better, meat broth or meat extract, may be made to play the part of igniting material. I have been afforded an opportunity of verifying all these results in actual practice, and in this way to test whether our analysis of the secretory processes is correct. For the delivery of these lectures I had to repeat my experiment on the influence of vagus division on the secretory effect produced by sham feeding. The result was that a greatly disordered condition of digestion was set up in the dog, as I had anticipated from my own previous experience and also from the publications of other authors, especially Ludwig and Krehl. I resolved, in the light of our new discoveries, to try and aid the animal's digestion. Now, in dogs with divided vagi, the psychic secretion of gastric juice is wholly and for ever done away with. I therefore endeavoured to supply its place by some other means. Before each feeding we washed out the dog's stomach, then introduced 200–300 c.c. of meat broth and waited till it became strongly acid, that is to say, till the gastric glands were thrown into vigorous activity. Not till then did we introduce solid food. By this means the food, which otherwise began to decompose, was satisfactorily digested.

In dealing with the secretory processes, we have up to the present almost exclusively confined ourselves to the quantity of juice secreted upon the different foods. But from the second lecture, we know that the quality of the juice with the different kinds of foods also varies. How is this alteration produced? As we have already repeatedly stated, the psychic juice for all kinds of food possesses a uniform digestive power. Consequently, the variations of digestive power in the juice secreted during the later hours after the eating of food, must be produced by the dissimilar chemical influence of the different foods.

In our investigation we started from the fact that a much stronger juice is poured out on bread than upon flesh. On what does this difference depend? There were a whole series of possibilities. It might be due to the physical properties of the food, or to the special nature of the proteid substances of bread and flesh respectively, or finally to the amalgamation of starch with the proteid of the bread. The first supposition was easily set aside. Meat may be desiccated, or bread again moistened, without the relationships in the digestive powers of the juices being altered (*Dr. Chigin*). The third hypothesis was then tested (*Dr. Lobassoff*). We mixed flesh and pure starch paste in the same proportions in which the proteid and starch of bread are found, gave this artificial bread to our dogs to eat, and obtained, as a matter of fact, a juice of like digestive power to that secreted on ordinary bread.

Hour.	200 grms. bread. Expmt. May 25, 1894 (Dr. Chigin).		Mixture of 100 grms. starch, 100 grms. flesh, and 150 c.c. water. Expmt. May 10, 1895 (Dr. Lobassoff).	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1st .	11·9 c.c.	5·22 mm.	13·5 c.c.	7·88 mm.
2nd .	4·1 ,,	8·25 ,,	11·0 ,,	7·0 ,,
3rd .	5·7 ,,	6·69 ,,	8·9 ,,	6·13 ,,
4th .	4·5 ,,	3·56 ,,	4·9 ,,	5·63 ,,
5th .	4·1 ,,	3·62 ,,	4·3 ,,	5·0 ,,
6th .	1·6 ,,	4·80 ,,	1·9 ,,	6·5 ,,
7th .	1·8 ,,	5·50 ,,	1·2 ,,	6·0 ,,
8th .	0·8 ,,	5·62 ,,	—	—
9th .	0·6 ,,	—	—	—
Total.	35·1 c.c.	Mean 6·12 mm.	Total 45·7 c.c.	Mean 6·75 mm.

This brilliant confirmation of our third theory did away with the necessity of specially testing the second. But although the same results were repeatedly observed from the above experiment, and hence in themselves constitute a valuable enrichment of our knowledge in this field, the mechanism of their production required still further investigation. The combination of starch with the proteids of flesh, might produce its effects in various ways. It is conceivable that the paste may strongly stimulate the trophic nervous mechanism without affecting the true secretory. But another explanation is also possible. We know already, from the second lecture, that after a meal of flesh the juice from the second hour onwards continuously declines in digestive power till near the end of secretion, when it again becomes more effective; and since the psychic juice, which is present during the earlier hours after the taking of food, always possesses a fairly strong digestive power, the decline after the second hour must be ascribed to the less potent influence of the chemical excitant of the flesh. If this be so, it is possible that the starch paste may in some way restrain or prevent the depressing action of the meat constituents. The material in possession of the laboratory does not yet, however, enable us to settle this question positively; but nevertheless it argues considerable progress that we are able to raise it and take it experimentally in hand.

Whatever the answer may be, we have here before us a new fact, namely, that a material which of itself is unable to excite a gastric secretion can alter the work of the glands in a decided and special manner when combined with the active constituents of flesh.

With the question just discussed, as to how starch is able to influence the secretion of gastric juice, another one, namely, the similar effect of fat, stands in natural connection. As in the case of starch, fat also when tested by itself has no influence on the gastric glands, but it does not necessarily follow that it would remain ineffective if introduced as the forerunner of, or in conjunction with, other food materials. In the further investigation of the fat influence, a new fact came to light which is important towards a knowledge of secretory processes, just as the study of the mixture of starch and flesh revealed an interesting point in the effect produced by the former upon the properties of the juice.

One hundred cubic centimetres of Provence oil, which, as you already know, produces no secretion, were poured into the main stomach of a dog by means of the sound. Half an hour to an hour later, the dog was given its usual ration of 400 grms. of flesh, but a totally different curve of gastric secretion was observed to that obtained if the same food, without oil, had previously been given (*Dr. Chigin*). Instead of the usual five to ten minutes, we had to wait half an hour to an hour before the beginning of the secretion. When the flow at length commenced it was very scanty. In the space of two to three hours, instead of the usual 10 c.c. to 15 c.c. we collected only 3 c.c. to 5 c.c. per hour, and it was very much later when the normal quantities appeared.

A similar curve of secretion was obtained when the fat was introduced into the stomach immediately after the meal of flesh. The only difference consisted in this, that here the secretion began with normal energy at the usual time after feeding, and only later did the inhibitory influence make its appearance. Finally, the same results were obtained when the dog was given fat mixed with flesh to eat. In these instances (experiments of Dr. Lobassoff), besides the diminution of the juice, a lowering of its digestive power was also observed. I give here an example of one of these experiments, and also by way of contrast I give the normal flow after a meal of flesh without fat.

Normal secretion after a meal of 400 grms. of flesh :

Hour.	Quantity of juice.		Digestive power.
1st . . .	17·8 c.c.	...	6·25 mm.
2nd . . .	13·8 „	...	4·5 „
3rd . . .	12·0 „	...	3·75 „
4th . . .	8·5 „	...	3·38 „

Secretion, from the same ration of flesh, given after 75 c.c. of olive oil had been for one and a half hours in the stomach :

1st . . .	4·3 c.c.	...	4·25 mm.
2nd . . .	5·3 „	...	3·0 „
3rd . . .	4·5 „	...	1·75 „
4th . . .	3·8 „	...	1·75 „

A new and very striking fact is here before us. Fat depresses—that is, inhibits—the normal energy of the secretory process. How is this effect to be interpreted ? When one reflects upon our experimental arrangements, and remembers that the secretion was collected from the gastric *cul-de-sac*, it might be explained in two ways. Either the fat hinders the secretion directly in a mechanical way—for example, by covering over the mucous membrane of the stomach and preventing the excitation of its nerve endings—or else indirectly, by reflexly stimulating the inhibitory nerves of the glands, or the inhibitory centres of those nerves. After a careful examination of all the facts, we are compelled to adhere to the second hypothesis; for, as previously shown, the secretory activity after a meal of flesh always begins with the psychic juice—that is to say, with a flow of central origin, and it is precisely this secretion, above everything, which is inhibited by the fat, as may be clearly seen from the experiment quoted.

In view of the great importance of the inhibitory influence of fat, we took the greatest pains (*Dr. Lobassoff*) to vary the experiment in every conceivable way. On a gastro- and œsophagotomised dog a sham feeding of short duration (one minute) was carried out. The time at which the secretion commenced, the quantity, and the properties of the juice were accurately determined. Then 50 c.c. to 100 c.c. of oil were poured into the stomach of the same dog, and after a quarter to half an hour, or in some cases still later, the sham feeding was repeated precisely as before, both with regard to duration of the feeding and to the quantity of food. Occasionally we allowed the oil to flow out of the stomach immediately before the sham feeding. The secretion of juice in these cases was observed by means of a wide glass tube closed at its outer end, which we fixed into the fistula-tube. The specifically heavier juice thus collected at the bottom of the tube and was at once visible. In every case, without exception, a marked diminution of the psychic secretion was observed. Often there was none, and when it was present it began much later, the quantity was much less and the juice also much weaker. The experiment on the dog with isolated stomach and divided œsophagus was particularly convincing.

The sham feeding in this case lasted six minutes.

Hour.	Quantity of juice.	Digestive power.
1st	4·0 c.c.	4·75 mm.
2nd	1·0 ,,	
3rd	0·5 ,,	

One hundred c.c. olive oil were then poured into the stomach. After thirty minutes there was another sham feeding for six minutes. During the course of two hours nothing was secreted by the *cul-de-sac*. Once more a sham feeding for six minutes was made. During the course of an hour 1·8 c.c. of juice, with a digestive power of 4·5 mm., were collected.

It is of great interest to note that a prolonged sham feeding is able to overcome the inhibitory effect of the fat.

When the influence of such a powerful excitant as the psychic impulse can be diminished by fat, how much more must this hold good for the stimuli, which act directly on the mucous membrane of the stomach? Whether the covering of the mucous membrane with a layer of fat contributes in any way to the diminution of the secretion cannot be answered with certainty from the material to hand.

The action of fat, which we have just discussed, may possibly explain the slow progress of the secretion after the taking of milk, and also the low digestive power of the juice. Is the fat of the milk not to be credited with this? We hoped to have solved this problem by the administration of cream to our dogs—that is to say, milk with an increased amount of fat. If the fat is to be credited at all with the low digestive power of " milk juice," that secreted upon cream should be still weaker. This, as a matter of fact, is the case. The following table gives a comparison of the secretion with milk and with cream (*Dr. Lobassoff*).

Hour.	600 c.c. of milk.		600 c.c. of cream.	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1st .	4·2 c.c.	3·57 mm.	2·4 c.c.	2·1 mm.
2nd .	12·4 ,,	2·63 ,,	3·4 ,,	2·0 ,,
3rd .	13·2 ,,	3·06 ,,	3·1 ,,	2·0 ,,
4th .	6·4 ,,	3·91 ,,	2·2 ,,	1·75 ,,
5th .	1·5 ,,	7·37 ,,	2·2 ,,	2·0 ,,
6th .	—	—	1·8 ,,	1·38 ,,
7th .	—	—	2·5 ,,	1·88 ,,
8th .	—	—	1·5 ,,	1·62 ,,
Total .	37·7 c.c.	Mean 3·86 mm.	Total 18·9 c.c.	Mean 1·63 mm.

In addition to the above, we have recently compared the effects of milk by itself, with those of the same fluid when the fat has been removed by filtration (unpublished experiments of Dr. Wolkowitsch). The results were that the latter produced a greater quantity of juice in the earlier hours, with a more vigorous rate of flow for the whole secretion.

We have, therefore, discovered two reasons for the slow progress of the secretion after the taking of milk, and for the poverty of the " milk juice " in ferment, viz., the weak psychic effect and the inhibitory influence of the fat.

At this stage of my lectures I think it very desirable to discuss two important questions which have long been kept waiting. The one has already been raised in the first lecture, the other at the beginning of to-day's. The first concerns the right of our small stomach to be taken as representative of the large one in all secretory relationships, or, as Dr. Chigin has put it in his article, to serve as mirror for the activity of the large one. The second question is, whether it may be accepted as a fact that the different substances which excite a flow of gastric juice, or effect an enduring alteration of the secretion, act on the mucous membrane of the alimentary tract—that is to say, influence the peripheral terminations of its centripetal nerves. These questions are intimately connected with each other, and must be simultaneously dealt with at the present juncture. I begin with the former.

It must occur to every one who becomes acquainted for the first time with our investigations upon the secretion of gastric juice, that while the main stomach during digestion is filled in the ordinary way, the miniature stomach remains constantly empty of food. One might suppose that the contact of food in the one case, and its absence in the other, would involve an enormous difference in the working conditions of the two stomachs. After a careful investigation into the facts of the case, we may state with all positiveness that this apparently weighty consideration is, after all, of no moment. When juice flows at the beginning of the meal from the gastric *cul-de-sac*, its activity at the time must be accepted as identical with that of the large stomach. Such an assertion is incontrovertible when all the data of this and the two preceding lectures are taken into consideration. The secretion begins with the psychic excitation of the secretory nerve centres, and this excitation naturally spreads in identical fashion to all points of the mucous membrane and its glands, whether in the large or small cavity. But with this proved, we must (to preserve uniformity in our conception) admit a probability, that the nervous system acts in a similar way during the remaining phases of the secretory process.

The condition of matters has here radically changed when contrasted with former times, where notwithstanding the endeavours of several investigators, success was not attained in attempts to discover a nervous mechanism for the gastric glands. But such a mechanism has now been discovered, and indeed a complex one, to which a work must be assigned. If, then, the beginning of the secretory process is identical in the two stomachs; what is the condition, after the secretion has set in, which we assume has its causation in a local excitatory effect produced by the food; in other words, what occurs when the psychic influence has come to an end? At all events, we still see a flow from the small stomach after the psychic secretion has run its course, or even when it has not at any time been present; such, for instance, as happens when the food is placed unobserved into the stomach of the dog. These facts we shall take as the basis of our argument. How are they to be explained? How can local events in the large stomach produce an effect on the small?

The functional connection between the two stomachs can only be effected by one or other or both of two systems of the body—the circulatory or the nervous. One may, for instance, conceive that the chemical materials which excite the secretion are absorbed from the digestive canal, and carried by the blood either to the secretory centres which they excite or even to the glands themselves. This supposition is capable of being easily tested. If it be correct, we ought to obtain the same effect when the substances in question are introduced into the circulation in other ways than by means of the stomach. The results of experiments on this point speak most decidedly against the hypothesis. Many investigators have injected meat broth and solutions of Liebig's Extract *per rectum* into animals, but have never seen an indication of gland activity.

Dr. Lobassoff has also investigated this question with great care. He administered to his dogs, *per rectum*, much larger doses of meat extract than would suffice to induce a secretion if injected into the stomach. By washing out the rectum and investigating the wash-water both physiologically and chemically, he convinced himself that the excitatory material of the extract had disappeared. Hence we are driven by a process of exclusion to the imperative deduction that our miniature stomach, even in the later phases of secretion, is excited through nervous channels—that is to say, by reflex stimuli from the larger cavity. We also further conclude that secretion in the large stomach likewise depends on reflex events. But if these exist, it may be taken that, under the conditions of gastric digestion, the reflex must be a *diffuse*, and not a mere local one; that is to say, the excitation of a definite area of mucous membrane occasions a secretion not alone at this area but over the whole mucous membrane of the stomach. As a matter of fact, a localised response would have little meaning, since the food itself is in constant motion, and is rapidly moved from the point of stimulation to another. It is, therefore, quite natural that the effects of excitation of the inner surface of the large stomach should be constantly and accurately transmitted to the small one (which, after all, is only a piece of the large), if the nervous connections of the *cul-de-sac* have been preserved uninjured. These conclusions receive important confirmation when we compare the activity of a gastric *cul-de-sac,* isolated according to our method, with one made after the method of Heidenhain, in which the vagus fibres are severed. The dog operated upon by our method, now three and a half years ago, still manifests an exactly similar course of secretion in the two cavities under the same conditions. But the *culs-de-sac* formed by Heidenhain's method in the course of time have their secretory capabilities very essentially altered. In the beginning, they work very energetically: after a full meal their secretion is copious and lasts for several hours (*Heidenhain*, *Ssanozki*). If, however, the animals live long, a gradual decline of the secretion is noticeable, and a month or six weeks after the operation, even after a full meal, it lasts for only three to five hours, growing less and less from hour to hour. Furthermore, the dogs thus operated upon do not manifest the characteristic alterations in the work of the glands dependent on differences in the food, which we depicted in the second lecture. In such animals the variations are occasioned by differences in the water contents of the food eaten.

But these results do not constitute the only reasons which convince us of the reliability of our method. A complete parallelism between the work of the large and that of the small stomach, has been proved by direct observation, and at the same time evidence was obtained showing that the above deductions are fully justified. We have here only to recall the facts bearing upon the matter and to arrange them in order. In the fifth lecture we described a sham feeding experiment on a dog with an isolated small stomach, and divided œsophagus, in which the figures were given. As you may remember, the juices from both stomachs were in every way the same. The absence of the sham feeding effect in dogs with Heidenhain's isolated stomach is in perfect harmony with the fact that in animals with intact stomach but having the vagi divided in the neck, the sham feeding is also ineffective. The above similarity in the working of the two stomachs is also to be seen when those excitants which act immediately upon the mucous membrane are employed. Water produces a secretion both in the large and in the small organ. The same applies to Liebig's Extract, the solutions of which act more strongly on both stomachs than water. Egg-albumen and starch, whether in fluid or solid form, are ineffective on both cavities. Fat produces a secretion in neither, indeed manifests rather an inhibitory influence. In short, we know of no single instance where the secretory process takes a different course in the two stomachs. I think it is also essential to mention here that many of the facts, which were obtained on the dog with isolated stomach, have severally been repeated and confirmed on a number of œsophagotomised dogs with ordinary gastric fistulæ. Recently also, with a second dog, having a gastric *cul-de-sac* made according to our own method, the most important of the facts observed on the first animal, were reproduced in a veritably stereotyped manner.

It is not difficult to see that our second question concerning the seat of action of the exciting substances is also answered at the same time as the first. When it is shown, for instance, that the whole work of secretion is of nervous and, with the possible exception of the psychic effect, of reflex origin, it is simultaneously proved that the exciting substances act on the peripheral end-apparatus of the centripetal nerves, and, in consequence, upon the mucous membrane of the alimentary canal. This happens, however, only in definite situations. As we have seen, there is no reflex effect on the gastric glands from the rectum; on the other hand, recent experiments of my own, which are not yet published, show that such an effect arises both from the small intestine as well as from the stomach. In a dog which had an ordinary gastric fistula and also a duodenal one (provided with a metallic cannula), the stomach and intestine were separated from each other near the pylorus by a septum formed of mucous membrane in a way similar to that described in our operation for making the miniature stomach. In this dog a gastric secretion could be set up when the exciting substance was introduced either into the stomach or into the intestine.

But a remote possibility may still exist that the food (apart from its reflex effect) could act also in a more immediate and direct manner upon the glands. We must confess that this hypothesis, which formerly, when nothing was known concerning gastric innervation, was of necessity admitted, appears now quite inconceivable. To accept it, one had to admit that the food, in order to excite the gastric glands, was able to penetrate into the thick mucous membrane. How little physiological this idea sounds! Now, however, the supposition becomes all the more improbable since according to the latest investigations the absorbing capabilities of the inner surface of the stomach are very limited. Moreover, it must not be forgotten that even a long-sustained absorption might not of necessity lead to a penetration of the substances into the peptic glands. Nor can one even admit that the substances gain entry into the mouths of the glands, because during secretion the stream of fluid is directed from the lumen of the gland towards the cavity of the organ. In support of the view for which we are contending, the analogy of insect-eating plants has been brought forward, but this analogy is scarcely justified. In plants the nervous system has not yet been differentiated into a separate tissue or factor; its functions are shared by all the cells; in our case, however, the gastric glands have placed at their disposal the services of a very intricate nervous mechanism. Unfortunately, one cannot, so far as I see, disprove this improbable hypothesis by direct experiment. It will only gradually die out, by giving way before the discovery of other neuro-glandular phenomena, which certainly will attract ever more and more attention to themselves.

Now that I have shown you that the secretory activity of the stomach, as a whole, depends on nervous processes, I must present the matter once more to you as a working hypothesis of the innervation apparatus of the gastric glands. In the immense majority of cases gastric digestion begins with a strong central (automatic?) excitation of the secretory and trophic fibres of the glands. Sooner or later after the taking of food the influence of the reflex excitant comes into play, while the automatic psychic effect gradually dies out. If meat have been eaten, the secretory centre will still be strongly excited in a reflex manner from the stomach and intestine, whilst at the same time the trophic centre receives only weak impulses from the peripheral terminations of the nerves in question. When bread, however, is eaten, the reverse effects happen. After the cessation of the psychic stimulus, the secretory fibres are now only weakly excited through the end apparatus; the trophic, on the other hand, are strongly influenced. In cases where fat has been added to the food, reflex inhibitory impulses proceed to the centres which affect the activity both of the secretory and of the trophic nerves.

I have depicted the work of the gastric glands as we have seen it in our experiments, and as it has developed under our hands. Is the picture a new one? In its details, yes, but not in its fundamental features. However singular it may appear, the sketch of this picture was more than fifty years ago outlined by physiology. May this constitute another reason for our science relinquishing its characteristic shyness of new things and for its conversion to our interpretation of the phenomena under consideration!

The talented author of the *Traité Analytique de la Digestion*—Blondlot—spoke in plain words of the importance of the act of taking food, and of the specific excitability of the gastric mucous membrane. The facts adduced in the working up of his theory were naturally insufficient, but we must not forget that the first experiments on dogs with artificial gastric fistulæ had only just been performed. It is truly incomprehensible, that the researches of Blondlot and his views upon the secretion of gastric juice, have experienced during the last fifty years no completion, no additions, but, on the contrary, have passed out of sight, thanks to the faulty experiments and erroneous representations of later authors. Only in the works of a few writers—and these mostly French—has Blondlot's theory survived. Of other investigators, we must give mention to Heidenhain, who has enriched the physiology of absorption in general, but more especially in connection with the secretory work of the stomach, has discovered important facts and given birth to many fruitful ideas. From him proceed the subdivision of the secretory process according to periods and exciting agencies, as well as the suggestion that it would be important to investigate the individual food-stuffs in relation to the work of the stomach. Heidenhain's results are contained in his well-known article on the secretion of the cardiac glands of the stomach, published in the year 1879 in Pflüger's *Archives*. The work of Blondlot and the additions of Heidenhain comprise almost everything of importance which was accomplished by physiology in fifty years concerning the conditions and mechanism of the secretory work of the stomach during digestion. Full of moment, however, for our subject was the obvious error that mechanical stimulation constituted an effective excitant of the gastric glands, and this error was in its turn a result of faulty methods.

LECTURE VII.

THE NORMAL EXCITANTS OF THE NERVOUS MECHANISM OF THE PANCREAS: SUMMARY OF MATTERS DEALT WITH, AND PROBLEMS FOR FURTHER INVESTIGATION.

Acidity is a powerful excitant of the pancreatic gland—The specific properties of this excitant—The stomach contents on passing into the duodenum, excite the pancreas chiefly because of the acid reaction of the gastric juice—The acid reflexly excites the pancreas by acting on the duodenal mucous membrane—Probable significance of the relationship established by the acid between the gastric and pancreatic secretions—Starch does not augment the secretion of the pancreas, but does increase its content of amylolytic ferment. Fat is a reliable exciter of pancreatic secretion, and also increases the amount of fat-splitting ferment in the juice—Sleep does not hinder pancreatic secretion—Although psychic excitation of the pancreas may be accepted as existing, yet it plays only an unimportant *rôle*. Water is an independent exciter of the pancreas—Solutions of neutral and alkaline salts of the alkalies inhibit pancreatic secretion—Grouping of problems still to be investigated in connection with the work of the digestive glands—The definite establishment of a specific excitability of the digestive canal constitutes the fundamental result of all the experiments related—Summary of the results from a general point of view—Outlook and programme of future investigations.

GENTLEMEN,—In turning, in our lecture to-day, to the questions as to when, how, and by what means the nervous mechanism of the pancreas comes to be excited during digestion we must from the beginning expect to encounter both complicated relationships and unexpected facts. The secretion of the pancreas is richer in ferments than that of the stomach and, moreover, it is a supplementary fluid which works on food already affected by a previous agency, and which has consequently to adapt itself to peculiar chemical conditions. The difficulties of investigation which arise from these sources are, however, considerably discounted by the following advantage. The intestinal canal is completely separated from the lumen of the gland, and consequently there can be no question of a direct penetration of the food into the gland ducts.

We begin with a form of stimulus which aroused the attention of the laboratory in a very striking manner, just as did the discovery of the psychic excitation of the gastric glands. In the search for pancreatic stimuli we (*Dr. Becker*) tested, for particular reasons, on the one hand, the effects of solutions of neutral and alkaline salts of the alkali metals; on the other hand, water saturated with carbon dioxide gas. It resulted that a species of antagonism was found to exist between these substances in their effects upon the pancreas. The saline solutions proved to be weaker excitants of pancreatic juice than water, the carbon dioxide distinctly more energetic. These results directed our attention to the effects of acids, and we may now proceed to the important initial experiment of our investigations upon this subject. The dog which I bring before you possesses a permanent pancreatic fistula. As you see, the secretion at present is hardly worth mentioning, two to three drops in the minute, and even this is quite easily accounted for: the animal was fed fifteen hours ago. I introduce 150 c.c. of half per cent. solution of hydrochloric acid by means of the sound into the stomach. The dog remains perfectly still and makes no protest whatever against the procedure. Two to three minutes after the injection you notice that the drops fall faster. We can already count twenty-five in the minute, and the flow grows stronger and stronger. In order to meet the objection that water or the influence of fluids generally, acts here as the exciting agency, I bring into the stomach 500 c.c. of lime-water, and you see not only that the secretion does not increase, but, on the contrary, grows weaker and weaker, indeed almost stops. This powerful influence of acids upon the pancreas is one of the most securely established facts in the whole physiology of the gland. The acids are such strong stimulants to pancreatic flow that by their means one can excite the activity of the gland more effectively than by any other; so much is this the case, that in the laboratory, the effect of acids has become a crucial test of the normal condition of the alimentary canal in this respect. To illustrate the intensity of the juice-secreting influence of acids, I give here an example taken from the work of Dr. Dolinski, who had the investigation in hand.

The dog was fed twenty-two hours beforehand, and pancreatic juice no longer flowed. Two hundred and fifty c.c. of hydrochloric acid of the strength of the gastric juice were poured, by means of the sound, into the stomach. The quantity of juice secreted every five minutes is shown below:

6·0 c.c.	0·4 c.c.
9·5 ,,	3·4 ,,
9·5 ,,	5·4 ,,
9·5 ,,	2·4 ,,

8·5 c.c.	0·6 c.c.
7·0 „	1·0 „
8·0 „	0·2 „
7·5 „	0·8 „
7·5 „	0·4 „
7·0 „	0·0 „
2·0 „	0·2 „
0·5 „	0·0 „
In the 1st hour, 82·5 c.c.	In the 2nd hour, 14·8 c.c.

Thereupon 250 c.c. water were poured in ; no secretion followed for thirty minutes. Then another 250 c.c. of the same hydrochloric acid solution were introduced and the quantities of juice recorded every ten minutes :

1·5 c.c.	13·0 c.c.	3·0 c.c.
13·5 „	15·0 „	0·2 „
15·0 „	10·5 „	Secretion stopped
16·0 „	9·0 „	
13·0 „	7·5 „	
15·0 „	10·5 „	
In the 1st hour, 74·0 c.c.	In the 2nd hour, 65·5 c.c.	

No particular difference in the exciting effect of various acids was noticed. The acids investigated were phosphoric, citric, lactic and acetic, in addition to the hydrochloric.

The constancy and intensity of the acid influence stands out as a very remarkable, indeed, an exceptional fact. The idea, therefore, at once occurred to us that we had discovered in acids the specific excitant of the pancreatic gland, and simultaneously we remembered that the contents of the stomach normally possess an acid reaction. It, therefore, appeared to us that this acid reaction probably serves as a connecting link between two neighbouring compartments of the alimentary canal. But all these interesting and pregnant suppositions had to be proved and established experimentally. In the first place, the effects of increasing strengths of hydrochloric acid (from 0·05 to 0·5 per cent.) were tried and with the following results :

Into the stomach 250 c.c. of HCl of the following strengths were poured :

	0·5 per cent.	0·1 per cent.	0·05 per cent.
Pancreatic juice secreted per hour.	70·8 c.c.	—	—
	79·5 „	25·7 c.c.	—
	82·5 „	26·8 „	20·5 c.c.
	89·4 „	32·5 „	—

It was conceivable that in the employment of 0·5 per cent. acid we had not yet reached the highest degree of gland activity. On the other hand, so far as one can judge from experiments not systematically carried out, the sensitiveness of the pancreas is about as great as that of the organs of taste, for a fluid which just tastes acid acts distinctly as an excitant of the gland. The proportionate nature of the effects, and the great sensitiveness to the influence of acids, confirmed us in the belief that they behave not merely as general and indiscriminate exciters, but as specific stimulants of the pancreas. This conclusion appeared all the more forcible since the gastric glands remained perfectly indifferent to the same acids. We have, however, even more convincing proofs. We have often compared the effects (*Prof. Schirokich*) of such stimulating substances as pepper and mustard with those of acids. With the former we could perceive no trace of exciting effect. Decoctions of red pepper and mixtures of oil of mustard and water were used as strong as they could be employed without producing vomiting. The solutions caused distinct burning on the tongue but not the least indication of a stimulating effect on the pancreas, while weak solutions of acids invariably caused a flow of the juice at once. The experiments of Dr. Gottlieb, which were performed on rabbits, with the same substances, pepper and mustard, and which gave contrary results, must be interpreted in a different way to that which the author indicates. Obviously there must have been an injury to the mucous membrane, caused by the large doses of the substances in question, and the centripetal nerves themselves (not their terminal apparatus, which alone possesses specific irritability) were in consequence excited. It appears to me that these data suffice to give a positive answer to the question as to whether acids are specific exciters of the pancreas or not. As a logical sequence to the above, came the further conclusion that the gastric contents must have an exciting effect on the gland by virtue of the acid reaction which they possess. It naturally was not difficult to test this supposition. To begin with, we convinced ourselves that pure gastric juice was just as powerful an excitant of the gland in question as an acid solution of equal strength. Solutions of different sugars, of peptone, and of ovalbumen proved, when introduced into the stomach, to be excitants of the pancreas only when they possessed a strong acid reaction. If neutral or alkaline, their secreto-motor effect was no greater than that of water, in some cases even less. Finally, our hypotheses became fully established when we succeeded in destroying the exciting effect of the gastric contents by neutralisation of the mixture. When at the height of digestion, with a free secretion of pancreatic juice, one introduces into the stomach of an animal by means of the sound, or through a fistula, solutions of soda, or lime-water, or pancreatic juice, after a few minutes, one always observes a diminution of the normal secretion—a diminution which often lasts for a long time. I give here one experiment as an example:

The secretion was recorded every five minutes.

5·6 c.c.	1·4 c.c.
6·6 „	1·0 „
7·2 „	1·0 „
7·4 „	1·1 „
7·2 „	1·5 „
6·8 „	1·6 „
Of the dog's own pancreatic juice 70 c.c. were here poured into the stomach.	5·0 „
	6·8 „
	6·0 „
5·6 c.c.	5·7 „ and so on.
2·2 „	

We see in the above an instructive instance of how the work of one segment of the alimentary canal is connected with and dependent upon that of the previous one. Thus, the saliva which moistens everything dry, is able to act as an exciter of gastric secretion by virtue of its content of water. In the stomach itself it is in this way ensured, that the psychic secretion which is the forerunner of digestion is continued by the influence of the saliva. The acid of the gastric juice acts in its turn as an excitant of the pancreatic gland, and thus the mutual influence which the digestive glands exert upon each other is clearly manifested.

We are, therefore, justified in saying that the acid is a specific exciter of the pancreatic gland. Where, however, is its point of action? There are two possibilities. The acid works either locally by exciting the peripheral end-apparatus of the centripetal nerves in the mucous membrane, or else it is absorbed into the blood and stimulates either the secretory centre or the gland cells directly. If we analyse the facts already communicated, together with the results of some new experiments, we must decidedly accept the first hypothesis.* Let us attentively consider the facts of the acid effect. The question as to how these substances could act in the blood is very simple, namely, by reducing its alkalinity. If, therefore, pancreatic juice is expelled, as soon as acids are introduced from without, the alkalinity of the blood must thereby be reduced, and this can be the only alteration which

* Bayliss and Starling have recently shown (*Proceedings Royal Society, London*, vol. lxix. 1902, p. 352, also *Centralblatt f. Physiologie*, Bd. xv. 1902, p. 682) that the exciting agency is not the acid itself, but a substance produced by its action upon the mucous membrane of the duodenum and of the upper jejunum. This substance, which they term "*secretin*," is effective when injected into the blood stream, after extirpation of the solar plexus and destruction of all nervous filaments passing to the isolated loop of intestine, also after the injection of atropin. Hence they conclude that its action is not a reflex one through nervous channels. The substance is not destroyed by boiling or neutralisation of the acid extract of

happens in the fluid. In normal digestion, however, the alkalinity of the blood is increased. The food of the stomach, by virtue of its hydrochloric acid, calls forth the secretion of pancreatic juice, which in its turn is derived from the blood. The increased alkalinity of the blood during digestion is also in harmony with the well-known fact that the alkaline content of the urine is greater during the same period, consequently diametrically opposite changes would occur in the blood, according as the pancreas is excited to action by acids introduced from without or by that prepared in the stomach. From these theoretical considerations alone we are therefore unable to admit an acid effect through the medium of the blood. But we are in possession of direct experiments which speak in the same direction. When acid solutions are injected into the rectum the pancreas remains in perfect rest. In the same way, acids do not act on the pancreas if they continue in the stomach without entering the intestine. This fact was first indicated by Dr. Gottlieb, but the question has since been more fully investigated by Dr. Popielski. Here is one of his experiments on a dog with a permanent pancreatic fistula:

Time.		Juice.
11 h. 37 m.	. . . . . .	0·0 c.c.
11 „ 43 „	. . . . . .	0·75 „
11 „ 48 „	. . . . . .	1·0 „
11 „ 50 „ to 11 „ 57 „	200 c.c. of HCl, 0·25 per cent. strength, injected into the rectum.	
12 „ 0 „	. . . . . .	0·25 „
12 „ 15 „	. . . . . .	0·0 „
12 „ 25 „	. . . . . .	0·0 „
12 „ 37 „	. . . . . .	0·25 „
12 „ 50 „	. . . . . .	0·0 „
12 „ 50 „	100 c.c. of the same solution poured into the stomach.	
12 „ 53 „	. . . . . .	0·0 „
12 „ 54 „	. . . . . .	0·75 „
12 „ 59 „	. . . . . .	9·0 „
1 „ 4 „	. . . . . .	7·75 „
1 „ 8 „	. . . . . .	6·0 „
1 „ 10 „	. . . . . .	2·0 „
1 „ 15 „	. . . . . .	4·25 „
1 „ 20 „	. . . . . .	1·0 „
1 „ 25 „	. . . . . .	0·0 „

the mucous membrane, and is not obtained from the ileum. A saline extract yields an inactive precursor of the substance, "*prosecretin*," which becomes effective when treated with acid. Popielski, Wertheimer and Lepage had previously shown that the acid was effective after severance of the duodenal and pancreatic nerves.

In addition we have had a dog (*Dr. Popielski*) whose stomach was divided into two parts near the pyloric region, into each of which a fistula-tube was brought. If now acid were introduced into the larger segment the pancreas remained at rest. On the other hand, when acid was poured into the pyloric portion, a secretion of pancreatic juice appeared, but only when the acid passed on into the duodenum. This is in harmony with the fact that the flow of pancreatic juice rises and falls in undulatory fashion, obviously from its connection with the entry of the acid food mixture into the intestine. One must be very partial to forced conclusions, who interprets the action of acids upon the pancreas as anything else but reflex. We may mention here once more, that in the case of the pancreas, the necessity is completely removed of discussing a direct penetration of food materials into the lumen of the gland.

The interesting question remains of how we are to account for the fact that the acid has an effect. The substance, as we have already said, forms a connecting link between gastric and intestinal digestion. This fact is undisputed, but why does the acid and not something else serve as the connecting link? Naturally, we cannot as yet claim to have solved this question scientifically, we can only bring forward some hypotheses. As is known, the pancreatic ferments act best in an alkaline medium. When weakly acid their effect is less, and with any pronounced degree of acidity it soon becomes nil. Hence it may be conceived that the pancreatic juice comes in to neutralise the acid which causes it to flow, and thus to provide a suitable medium for the activity of its ferments. At the same time the pancreatic juice protects itself against the destructive action of the pepsin, for which a neutral or alkaline medium is very unsuitable. Thus the fruitful idea of Brücke that the bile arrests the action of pepsin in the duodenum and provides favourable conditions for intestinal digestion may also be extended to the pancreatic juice. At the same time another important significance of this relationship lies near. For a peculiar and as yet not quite obvious reason, the gastric juice is secreted with the most concentrated strength of hydrochloric acid possible. This hydrochloric acid, according to the present teaching of physiology, is prepared from the sodium chloride of the blood. An excess of alkali thus arises in the blood, and this must, in order to preserve the mean chemical composition of the fluid, be removed from it. The hydrochloric acid, however, after fulfilling its function in the alimentary canal, would again be absorbed, and thereby in turn lead to a marked diminution of the alkalinity of the blood. Consequently the reaction of this fluid would suffer great variations in both directions during digestion; but as we know, this is a factor the constancy of which is of great importance to the chemical processes which transpire in the organism. These difficulties are all removed when we consider the relationships of the digestive juices just discussed. The acid gastric juice causes secretion of pancreatic fluid by its acidity and in direct proportion to it; that is to say, while the acid constituent of the sodium chloride is taken up by the peptic glands and then passed on into the cavity of the stomach, the basic element, the sodium, serves for the preparation of pancreatic fluid. And thus the two constituents of the sodium chloride meet again in the alimentary canal and reproduce the salt. Recently this explanation has received support from the experiments of Dr. Walther. If the acid excites a flow of pancreatic juice, with the object amongst others, of neutralising itself, we should in consequence expect to meet with variations in the alkalinity of the juice, apart from the content of ferment, and determined by the acidity of the exciting fluid; and this is indeed the case. Determinations of the amount of ash, as well as titration both of the ash and of the unaltered pancreatic juice, have incontestably shown that a connection exists between the nature of the secretory excitant and the amount of inorganic substance in the pancreatic fluid. The juice excited by acid solutions shows a very unimportant amount of organic substances with a maximal content of inorganic; in fact, the quantity of the latter is two or three times as great as that of the former. It shows also a very high degree of alkalinity both in the ash and in the juice itself. Thus the rapidity of the secretion has no decided influence, the "acid" juice retains its characteristic properties even when the hourly quantity of secretion varies. This occurrence is perfectly analogous to one previously described. In the first lecture we saw that the ferments of the juice adapted themselves to the kind of food ingested at the time being. With bread the amylolytic ferment, and with milk the fat-splitting ferment, was found to be increased. Likewise here, an acid-exciting substance evokes the production of alkali, while the organic constituents which are not required are extraordinarily reduced. The juice, however, which is poured out on acids is never wholly deprived of its ferment-properties. This shows that the relationship just mentioned is only one of relative importance. The juice is always produced for digestive purposes, and never merely for the neutralisation of acids.

By a fuller study of the alkalinity we shall probably soon be in a position to indicate that part of the general flow of pancreatic fluid which is evoked by the acid, or, in other words, to know if the acid always plays a part in the production of the juice. It appears, for instance, that "flesh juice" secreted by the pancreas during the first hours after partaking of this food approaches very nearly in inorganic constituents to the "acid juice." This harmonises beautifully with the fact that in the early hours after a meal of flesh a very vigorous secretion of gastric juice takes place, the acid of which appears to be at the same time the chief exciter of pancreatic flow.

Consequently, a non-nutrient substance, namely the acid, has proved itself to be the strongest excitant of the neuro-secretory apparatus of the pancreas. This does not, however, preclude the possibility that there may also be other exciters, either identical with those for the gastric glands, or different therefrom, since the field of action is wider in the case of the ferments of the pancreas. Hence the natural question arises whether starch and fat may not also be exciters of the pancreas, for, as we know, the gland has special relations to these substances. So far as our experiments go, we were unable to prove an exciting effect on the part of starch. Solutions of starch of varying concentration expelled the juice no more energetically than water alone. The question, however, requires still further investigation, for it is quite possible that the minutiæ of the requisite conditions for the starch effect may for the time being have escaped our observation. It may, for instance, happen here, as in the case of gastric juice, that the starch exercises only a trophic influence—that is to say, augments the quantity of the ferment without increasing the total quantity of juice. Some experiments of Dr. Walther furnish a basis of fact for these hypotheses. When he fed a dog with bread, the pancreatic fluid possessed a much stronger amylolytic action than the juice obtained at a corresponding period, and with the same rate of flow, after a meal of flesh. It is particularly interesting that in the same specimens of juice the fat-splitting ferment behaved in just the opposite way—the flesh juice revealed a greater, the bread juice a lesser degree of fat-splitting action.

Finally, the possibility is not excluded that the progress of starch digestion may be dependent on some other condition—for example, the continued production of lactic acid from the carbohydrate constituents of the food. Possibly this is the explanation of the chemico-physiological fact in question, the meaning and importance of which have as yet been but little cleared up. Science has not attempted, and could not up to the present venture, to reproduce a synthesis of real digestion—that is to say, to combine the often conflicting interests of the different food-stuffs among themselves with those of the digestive canal and of the organism as a whole. Here I beg to remind you of the relationships of fat to gastric digestion, and of the probable importance of the acid effect.

The experiments dealing with the influence of fat upon the pancreatic gland yielded much more positive results and were much simpler. Indeed, the mere comparison of known facts made it very probable that fat is an independent exciter of the pancreas. Fat restrains the secretion of gastric juice, and consequently we could not fancy that, under ordinary conditions, a pancreatic secretion after fat is indirectly caused by the acid of the gastric juice. Dr. Dolinsky poured fluid oil into the stomach of dogs, and constantly observed a more or less considerable flow of pancreatic juice. Bearing in mind the strongly inhibitory effects of fat on gastric secretion, the constancy of this result afforded good assurance that we had here to deal with a direct influence of fat upon the pancreas. A confirmed sceptic might, however, reply that possibly an acid fluid had accumulated in the stomach before our experiment, or, as we previously indicated ourselves, that a strong psychic effect might have overcome the inhibitory influence of the fat. But here is an experiment instituted by Dr. Damaskin which complies with the strictest requirements. A perfectly healthy dog, having two fistulæ —one a gastric, the other a pancreatic fistula—was last fed twenty hours before the experiment. Beneath the orifice of the pancreatic duct a metallic funnel and graduated cylinder were fastened. The gastric fistula was closed by a cork through which a glass tube was led, and which in turn was connected with an india-rubber tube and funnel. The funnel was hung up at a suitable height, and contained 110 c.c. to 115 c.c. of oil. The india-rubber tube was also provided with a T-piece, the transverse arm of which was connected with a second india-rubber tube. At the beginning of the experiment the connecting tube was clamped between the funnel and the T-piece with a Mohr's clamp, so that the oil could not leave the funnel. The tube at the end of the transverse arm of the T-piece remained open to allow the gastric contents to escape freely. Often at the beginning of the experiment the stomach secreted a clear acid fluid—the psychic gastric juice. More rarely it contained only a little alkaline mucus. The experimenter secluded himself in a separate room with the dog and quietly waited. The animal gave up the hope of receiving anything to eat, and finally slept. When the acid secretion from the stomach ceased, the experimenter then cautiously closed the outflow tube and opened the clamp on the oil funnel. So long as the stomach cavity remained unclosed, either no pancreatic juice, or at most 0·5 c.c. to 1·0 c.c. in fifteen minutes, was secreted, but three to five minutes after the pouring in of the oil the flow was quite distinctly increased, and after fifteen to thirty minutes attained a rate of 7 c.c. to 10 c.c. in fifteen minutes. At the same time only a very small quantity of alkaline mucus collected from the stomach in the lower division of the india-rubber tube; consequently, the secretion of pancreatic juice after the administration of fat takes place even when every trace of acid contents is absent from the stomach. Sometimes the experiment was varied in the following way. Fifteen to thirty minutes after the introduction of the oil, the clamp on the lower india-rubber tube was opened and the contents of the stomach emptied out. For the most part it contained only 15 c.c. to 20 c.c. of oil, and 3 c.c. to 5 c.c. of alkaline mucus, while later only mucus mixed with small quantities of oil flowed out. In other cases, together with this mucus, either early or late, some bile or bile-stained fluid escaped from the stomach. This latter fluid contained suspended fat, reacted alkaline, and was obviously driven into the stomach by anti-peristaltic action. Nevertheless, during the whole of this time pancreatic juice freely flowed from the fistula. These facts exclude the immediate idea that an acid reaction is rapidly set up in the intestine by cleavage of the fat, and then acts as an exciter of the pancreas. The intestinal contents, in the course of an hour or still longer, showed no trace of acid reaction. The experiment affords us adequate grounds for concluding that fat is an independent exciter of the pancreatic gland. The investigations of Dr. Walther go still farther, and show undoubtedly that fat excites not only a free secretion of pancreatic fluid, but also leads to an increase of the fat-splitting ferment. In the first two hours after a meal of milk a juice is furnished which is uncommonly rich in fat-splitting ferment. If the milk, however, be deprived of its fat by filtration, the juice presents a very low fat-splitting power, without any other alteration in the progress or rate of the secretion. When, however, the milk filtrate is again mixed with fat—that is to say, when the milk is synthetically reconstructed—the fat ferment in the pancreatic juice increases to the previous amount, which is characteristic of "milk juice."

And now, as regards the seat of influence of the fat. We might suppose, from the experiments related, that the stimulus acts on the mucous membrane of the duodenum. Thus we have often observed a strong and lasting secretion of pancreatic juice, even when the stomach had been perfectly emptied of fat. But the mechanism of pancreatic excitation by means of fat scarcely requires a special discussion. When it is borne in mind that fat is a chemically indifferent substance, an effect through the blood can scarcely be thought of. But the fat may well excite the peripheral end-apparatus of the nerves which are specially adapted to react to every possible influence, such as chemical, mechanical, and the like.

I now wish to introduce some remarks relative to the experiments with the oil described above. An emulsion-like fluid, as has been stated, flows for one to two hours from the stomach. This fact, possibly, suggests the idea that the duodenum forms a cavity, bounded somewhat like the stomach, and that the contents of this cavity are continuously driven from one end to the other. In our case the contents consist of fat mixed with the fluids—bile and pancreatic juice—which act upon it. Under their influence it is emulsified and split, and it is a fact that after one or two hours the emulsified fluid becomes acid. It is also possible, in the case of an empty stomach, that the duodenal cavity may expand at the expense of the former. The second remark concerns the sleeping of the animal during the experiment. As I have previously stated, sleep does not exercise the least influence on the secretory work of the gastric glands. With regard to the pancreas, however, the distinct statement went forth from the laboratory some years ago that sleep almost completely arrests the secretion of pancreatic fluid, even when it is in full progress. Further observations have shown that this was an error, and the origin of the mistake is not without interest. The investigator who made it was, apparently, perfectly right. When the animal slept the secretion abruptly declined and fell to nil. But why? Instead of the connection which was assumed, it was found that a purely extraneous circumstance explained the relationship between the sleep of the animal and the arrest of the flow. The dog in this case was retained in a frame by a special arrangement of leather supports which we named "boots." When the animal slept, it naturally assumed an easy, passive position, and allowed its body to hang in the straps of the boot. In this way the skin was differently stretched, in many parts being displaced from its ordinary position, and at the same time the duct of the pancreas which passes through it was kinked and pressed upon. Thus a distinct but purely extraneous and accidental connection came to exist between the sleeping of the dog and the arrest of the pancreatic flow. This fact is further evidence of the necessity for constant watchfulness over the minutest details in the performance of physiological experiments.

We shall now pass on to the other exciting agencies which proved to be effective in the case of the secretion of gastric juice. Will they not also have an influence on the pancreas? I refer to the psychic effect, together with that of water and also of extractive substances. Theoretically, the answer might be either a positive or a negative one. If the feeling of appetite and the presence of water are necessary to ensure a beginning of gastric secretion, the same might also apply to the flow of pancreatic fluid, although the secretion is essentially dependent (through the acid) on gastric digestion. In affections of the stomach the pancreas might remain without its chief exciter, but we know of pathological conditions where the hydrochloric acid was absent from the gastric juice for months, and yet digestion as a whole proceeded tolerably well. In the interests, therefore, of a greater degree of independence for the pancreas, we should be inclined to admit the activity of the above-named exciters. But facts must decide the case. We have intentionally deferred this question till near the end of the lecture because its solution is intimately connected with previously established relations. The experiments which concern the excitants special to the pancreas are, as we have seen, very simple, but it is quite otherwise with those agencies which are at the same time excitants of gastric juice. They will naturally also be indirect excitants of the pancreas through the acid of the latter. But this does not solve the actual question in hand. It is necessary to determine whether they are not also capable of acting independently and directly, apart from the acidity of the gastric juice. And this, indeed, is not easy to decide.

Dr. Kuwschinski showed long ago that tempting a hungry dog with food at times called forth a very lively secretion of pancreatic juice. His conclusion, which was at that time perfectly justified, was that the nerves of the pancreas can be excited by psychic influence, but this obviously now requires further examination. Are we not dealing with a stimulating effect of the gastric juice collected in the stomach under the effect of the psychic impulse? It was necessary to repeat the experiment in a manner which eliminated the intervention of the gastric juice. In the beginning we placed our hopes on a complicated operative procedure. We performed œsophagotomy on a dog, and also made both gastric and pancreatic fistulæ. We then submitted the dog to a sham feeding, with the gastric fistula open, and were able to observe the onset or augmentation, as the case might be, of pancreatic flow. The result, however, of this experiment is ambiguous. It would have been decisive if no juice had flowed. Now, however, we may draw divergent conclusions. It may be that, even with an open gastric fistula, part of the juice obtained entry into the duodenum. But there was another way by which the matter might be decided, viz., the determination of the latent period of sham feeding for the pancreas. The latent period of the gastric secretion in dogs has a sharply marked lower limit, and is never less than four and a half minutes. The pancreatic juice, on the contrary, begins to flow two to three minutes after the application of the exciting agency—for example, an acid. In the experiment of teasing the animal by offering it food, the pancreatic flow also generally begins after two to three minutes. This appears to me to point to a direct psychic influence through the secretory nerves of the pancreas, such as has long been established for the secretory mechanism of the stomach. And with this, probably, a phenomenon is connected, which one may often notice when the flow of pancreatic juice is observed in a fasting animal. After a rumbling sound in the abdomen a more or less active secretion often sets in; the gastric glands, however, remain in perfect rest. One is at liberty to conceive that a passing desire for food has thrown the centres for the motor nerves of the intestine, and also for pancreatic secretion, into action, while the impulse is not sufficient to excite the more inert gastric glands, which, as we know, have a longer latent period. It is, moreover, possible that the centre for the nerves of the pancreas—in agreement with the fact that the gland belongs to the abdominal set of digestive organs—should be more or less closely associated with the centre for the motor nerves of the intestine. The psychic excitation of intestinal movements is, however, a universally recognised fact, and has even become a byword when, for instance, it is said that in severe hunger the stomach yearns. In any case, the question of psychic excitation of the pancreas requires further investigation.

Similar considerations to those in the case of psychic excitation have to be borne in mind with regard to the relationship which exists between water and pancreatic secretion. When water is poured into the stomach the result is a secretion of pancreatic juice. But how? Is it because it independently excites the gland, or because it has led beforehand to acidification of the gastric contents? In the experiments to decide this question the same method was adopted (*Dr. Damaskin*) as in the case of oil. When 150 c.c. of water are poured unnoticed into the stomach of a dog, the glands of which are resting, one sees after two or three minutes that the secretion of pancreatic juice either begins or becomes distinctly increased. If one waits for a minute or two longer, and then empties the stomach, some water, or rather a neutral or possibly alkaline fluid, is generally still found. Occasionally the secretion of pancreatic juice continues for a time after the emptying of the stomach, although no secretion whatever may have occurred in the latter, or may only have appeared after the lapse of ten minutes. The conclusion is clear and free from objection, namely, that water is an independent and direct exciter of the nervous mechanism of the pancreas.

Finally comes the question, How do other chemical excitants of the gastric glands behave, namely, those which we have found in the extractives of flesh? The experiments on this point were arranged in the same way as those with pure water, and gave precisely the same results. When solutions of meat extract were poured in, the secretion began after the same length of time as with water, and was in no case greater.

If we now sum up these facts, we are in a position to say that there are some excitants common to the gastric glands and to the pancreas. Amongst these probably the psychic effect, the strong craving for food and water, is to be included. But, in addition, both organs have their own specific stimuli; for the gastric glands, the extractive substances of meat; and for the pancreas, acids and fat.

We must, however, dwell a little longer on the inhibitory phenomena which became evident in certain cases during the activity of the pancreatic gland. As we have already related, solutions of alkalies and of alkaline salts of the alkali metals not only do not excite a flow of pancreatic juice but even exert an inhibitory action. I will describe the experiment more exactly. The secretory influence of the solutions in question was compared with that of water, and in every case the flow of pancreatic juice was considerably less with the former. I give here some figures taken from the article of Dr. Becker.

The fluid was collected and recorded every half-hour.

250 c.c. water poured into the stomach.	2 grms. of $NaHCO_3$ given in 250 c.c. of water.	250 c.c. water poured into the stomach.
5·6 c.c.	4·2 c.c.	18·0 c.c.
9·9 ,,	0·6 ,,	7·3 ,,
6·2 ,,	1·0 ,,	—

The inhibitory effect was also investigated in another way, in which it was particularly observed how long such influence lasted. The solution to be investigated was poured into the stomach of a dog by means of the tube. An hour later the animal received its ordinary meal and the resulting secretion was compared with the normal. In every case a marked diminution of the secretion was to be seen. Once more I give an example from Dr. Becker's article.

The secretion was recorded every hour.

The dog was given 1200 c.c. milk and 2 lb. of meat.	Two hours before the feeding the dog was given 400 c.c. of Essentucky water.	The same food without the Essentucky water.
46·6 c.c.	32·2 c.c.	42·3 c.c.
45·4 ,,	56·3 ,,	62·1 ,,
53·5 ,,	21·5 ,,	46·4 ,,
18·1 ,,	15·7 ,,	21·4 ,,
22·4 ,,	12·0 ,,	14·5 ,,
18·7 ,,	14·4 ,,	13·9 ,,
Total 204·7 ,,	Total 152·1 ,,	Total 200·6 ,,

And here I ask you to recall to mind what I said to you in the first lecture, concerning the effects of a continued addition of sodium bicarbonate to the food. Such an addition for a length of time markedly depresses the secretory activity of the pancreas, which comes down to an unusually low point.

Hence the fact that some substances diminish the secretion of pancreatic juice is very striking, and certainly deserves our consideration. How we are to interpret the mechanism of inhibition remains still obscure. It is at present difficult to decide whether we have only a local effect on the peripheral terminations of the reflex-transmitting nerves, or whether an influence is also produced through the blood. That the local effect in any case is not confined to these substances is apparent from the fact that the inhibitory influence is not confined to them, but belongs also to other bodies readily soluble in water (*Dr. Damaskin*). One gathers the impression that certain substances which are easily soluble in water diminish its ordinary properties and prevent it from acting as a local stimulant.

Such are the facts which this laboratory has collected concerning the normal excitants of the pancreatic gland. We believe we are justified in characterising them as new, although the idea of a special stimulating effect caused by acids and by the acid chyme was long ago expressed. However, it is a long way from the mere expression of an opinion to a clear and precise statement of facts. And that the idea obtained no general recognition, because it was not founded on any definite basis, is shown by this, that in recent articles and text-books only a stimulating effect of the food as a whole is mentioned.

I have now, gentlemen, completed the part of these lectures which deals with gastric and pancreatic secretions, but I am far from believing that the subject is thereby in reality exhausted. Much, very much, has still to be achieved before we are able to congratulate ourselves on a final conquest of our territory. That which is gained is already very valuable, because it may serve as a sign-post to guide future research. We have now many more open questions before us than we had a short time ago, and all these questions mean progress in our investigations, because they testify to the existence of a wide field of inquiry which we have studied from a general point of view, but which we now wish to submit to exhaustive research. The questions are so many that we must group them together for discussion.

In the second lecture we learned of the great complexity, but at the same time great constancy and accuracy, of the work of the gastric glands and of the pancreas. It is now necessary to seek an explanation for every step of this complicated process, and in doing so the requirements of the individual food constituents, and the conditions necessary for the welfare of the digestive canal, and for the organism as a whole, must be borne in mind. In particular we must answer the following questions: Why at any given moment a certain quantity of juice and not any other is secreted? Why has it certain properties and not any other? In what way do its quantitative and qualitative variations advance the digestion of the food? How are they of service to the healthy condition of the digestive canal and of the organism as a whole? To these questions others are linked, such as, how do all these variations of gland activity come about?

We have previously spoken of the foods and subdivided them into their separate component materials, but we have not by a long way brought all their real constituents under consideration. We must naturally have a knowledge of all of these and determine their importance. It is from the effects of the elementary constituents that each separate point of the curve of secretion which we observe after a complex meal, must be explained. In order to solve this problem we must successively combine the individual constituents with each other, must synthetically build up the food step by step, and, moreover, must submit the properties of the juice at each phase to an exact analysis. In the case of a complex food we shall then be in a position to draw conclusions from the properties of the juice as to what is the effective excitant. Thus from the degree of alkalinity of the pancreatic juice one could decide whether its secretion was caused by acids or not. A correspondence in the results obtained by both methods—the analytic and the synthetic—furnishes the best assurance of their reliability.

The systematic investigation of the elements of the food must undoubtedly lead to the discovery of many unexpected relationships between the food-stuffs on the one hand and the digestive glands on the other. A complete answer to the two groups of questions, why and in what way gland activity varies, will only be obtained when an exact investigation of the contents of the digestive canal is joined hand in hand with observations upon secretory activity; when, for instance, for any given period of digestion, and for every point of the digestive canal, we know precisely where a certain constituent of the food is to be found, and what alterations it is at that moment being subjected to. The latter group of questions concern, on the one hand, the effects of the elementary food constituents, that is to say, their seat of action, their mode of working, and the combined results of the local specific excitants. On the other hand, they deal with the chain of phenomena in the central nervous system, determined not only by peripheral impulses from the digestive canal, but also by impulses from other organs as well. The questions in these two groups are, of course, interwoven in the closest manner. It is probable that the same questions likewise apply to those digestive fluids, such as the bile and the succus entericus, which have not as yet found place within the limits of our subject, because their physiology, from the point of view of these lectures, has not been sufficiently worked out. Recent experiments of Dr. Bruno, carried out in the laboratory upon the entry of bile into the intestine, have shown quite as exact and intimate a connection between this event and the nature of different sorts of food as we have already learned for the gastric and pancreatic juice. Although much more remains to be done, we have reason to be satisfied with what has been accomplished. Our results, I hope, have at once and for ever done away with the crude and fruitless idea that the alimentary canal is universally excitable, without distinction, by every mechanical, chemical or thermal agency, independent of the speciality which attaches to each single phase of digestion. According to the prevailing view of matters, the pronounced action of those agencies could serve merely as favouring or restraining influences, and not as normal definite guiding factors in the secretory work of digestion. Instead of a crude indefinite scheme, we see now the outlines of a skilled mechanism which, as with everything in nature, proves itself to be adapted with the utmost delicacy and in the most suitable manner to the work which it has to perform.

An essential advantage to the digestive process is derived from the instinctive craving for food; for, in addition to the impulse to seek out and partake of food, the instinct is at the same time the first and strongest exciter of several digestive glands. The fluids of varying reaction, secreted under its influence, convert a considerable part of the food into a soluble half-fluid condition, and thus allow the chemical constituents of the food-mixture to take effect. In consequence of this, the initial rate of gland activity is modified to harmonise with the altered constituents of the food, which are now in such a condition that they are capable of acting directly upon the end organs of the neuro-secretory apparatus. In the interest of all the constituents a certain equilibrium is established, in regard both to the quantity and strength of the digestive fluids as a whole; the one ingredient is promoted, the other to a certain degree restrained: a species of contest for the ingredient needed is fought out between the several components of the food. The secretory work which began with the ingestion of food is thus propagated farther and farther along the alimentary canal, thanks to a suitable interlinking of the several processes.

In my address before the Association of Russian Medical Men, to which I referred in the beginning of these lectures, I expressed the opinion that in ten years we should have as good a knowledge of the chemical work of the digestive canal as we have now of the physical apparatus of the eye. Since then two years have fled, and, when I look back upon their results, I see no reason to retract my words. Even in the Far West a lively interest is taken in our researches, and with the assistance of numerous European colleagues together with our workers here, the investigations, when once started on the right way, will rapidly lead to a complete accomplishment of the task. We are not dealing with questions concerning the nature of life or the physics and chemistry of the cell. The working out of these presumably will furnish, for a long series of generations, a theme of engrossing but ever-insatiable interest, before the final solution of the problem is arrived at. In our department of life, however, that is, in organ physiology, as we may say in contrast to cell-physiology, one may reasonably hope that there are many territories where the reciprocal relations of the individual component parts of a system (for example, the digestive canal) and the bearing of the whole towards objects of external nature (in this case to the food) will receive a complete explanation. At the very portals of organ-physiology we find such questions as, What is the peripheral end-apparatus of a centripetal nerve? How does it perceive this or that form of excitation? What are the nervous phenomena by which reactions and molecular changes in the secretory cell lead to the formation of this or that ferment, or to the preparation of this or that reagent? We have hitherto taken these properties and elementary functions as granted, and investigated the rules and laws of their working in the apparatus as a whole. We have learned how this or that apparatus may be set into activity; that is to say, within certain limits we have been able to understand it.

LECTURE VIII.

PHYSIOLOGICAL ACTION AND THE TEACHING OF INSTINCT: EXPERIENCES OF THE PHYSICIAN.

It would be desirable, in the interests of medicine, that the methods described in these lectures should be employed in experimental investigations into the pathology and therapeutics of the digestive canal on the lines laid down—The fact that the beginning of the secretory work in the stomach depends upon a psychic effect harmonises with the experiences of everyday life, namely, that food should be eaten with attention and relish—To restore the appetite has from all ages been the endeavour of the physician—The indifference of the present-day physician towards appetite—Probable causes of this—Curative remedies based upon a restoration of appetite—The therapeutic effects of bitters depend upon the excitation of appetite—The usages of the mid-day meal are in agreement with physiological requirements—Physiological reasons for certain instinctive customs and empirical regulations—Importance of an acid reaction of the food—Dietetics of fat and its therapeutic application—The peculiar position of milk among food-stuffs is based on physiological reasons—Explanation of the curative effects of sodium bicarbonate and sodium chloride—The causes of individual differences in the work of the digestive glands—Participation of the inhibitory nerves of secretion in the production of pathological effects.

Gentlemen,—To-day we shall endeavour to bring the previously communicated results of our laboratory investigations into reconciliation with the customs observed in the ingestion of food, and with the regulations prescribed by the physician in disorders of the digestive apparatus. To bring our knowledge to full fruition, and so secure for it the most useful application, the same methods should be applied from the same standpoint to the experimental investigation of the pathology and therapeutics of the alimentary canal. Nor should we be likely to encounter insuperable difficulties. Thanks to the advances of bacteriology, many of the pathological processes can now be experimentally produced in the laboratory. Moreover, we would, in a sense, have to deal with external ailments, since our present methods enable us to obtain access to any desired part of the inner surface of the digestive canal. In such pathological animals the functional diseases of the apparatus could be studied in a precise and detailed manner; that is to say, the alterations of secretory activity, the properties of the fluids, and the conditions under which they appear could be examined. On such animals therapeutic remedies could also be tested, the whole process of healing and the final result experimentally observed, while the conditions of secretory activity during every phase of the healing process could be investigated. It can hardly be doubted that scientific, that is to say ideal, medicine, can only take its proper position as a science when, in addition to an Experimental Physiology and Pathology, there has also been built up an Experimental Therapeutics. A proof that this is possible is furnished by the recent vigorous strides made by the science of bacteriology.

I have already described one of such pathological therapeutic experiments, namely, on the dog whose vagi nerves were divided in the neck. Other similar cases I can also call to mind. Our dog with the two stomachs suffered at one time from a slight and transitory gastric catarrh. It was then very interesting to observe that the pathological process (which we were usually able to wholly guard against) spread from the large to the small stomach. It manifested itself here in an almost continuous slimy secretion of very slight acidity, but of strong digestive power. At the beginning of the ailment, indeed before it became fully established, the psychic stimulation was remarkably effective (that is to say, still furnished juice in appropriate quantity), while local excitants almost completely failed. One may conceive that the deeper layers of the mucous membrane with the gastric glands were still healthy, and thus easily thrown into activity by central impulses, whilst the surface of the membrane with the end-apparatus of the centripetal nerves was already distinctly damaged. I mention these, which I may call impressions rather than precise observations, because I wish to point out what a fruitful field awaits the investigator who wishes to study, with the aid of our present methods, the pathological conditions of the digestive organs and their treatment. Such an investigation is all the more desirable, because clinical study of the same subject (notwithstanding the zeal devoted to it during the last ten years and the results derived therefrom), has to contend with serious difficulties. We must not forget that the sound or stomach-tube, the chief clinical instrument, is more uncomfortable than the ordinary form of gastric fistula which was previously practised on animals, and yet the physiology of the stomach, even with the aid of the latter, made no material progress for many long years. Nor is this difficult to understand. The investigator obtained through the fistula a mixture of substances from which it was difficult, or even at times impossible, to decide anything.

Hence the exact scientific study of therapeutic questions in this region still belongs to the future. But this does not exclude the probability that the newer acquirements of physiology may fruitfully influence the work of the physician. But physiology naturally can make no pretence to guide the field of medicine, since the knowledge at its disposal is incomplete, and is much more restricted than that of the broad world of clinical reality. As a recompense for this, however, physiological knowledge is often able to explain the causation of an illness and the meaning of empirical curative methods. To employ a remedy the mode of action of which is not clear, is quite a different thing from knowing precisely what we are doing. In the latter case, the treatment of the diseased organ will be more effective, because it will be better adapted to the special needs of the case. It is thus that medicine, being daily enriched by new physiological facts, will at length grow into what it ideally must become, namely, the art of repairing the damaged machinery of the human body, based upon *exact* knowledge, or, in other words, applied physiology.

We may now return to our subject. If it be at all admitted that human instinct is the outcome of an everyday experience, which has led to the unconscious adoption of the most favourable conditions for life, it is particularly so with regard to the phenomena of digestion. The expression that physiology merely confirms the precepts of instinct is justified here more than anywhere else. It appears to me also that, in relation to the foregoing facts, instinct has often made out a brilliant case when brought before the tribunal of physiology. Perhaps the old and empirical requirement, that food should be eaten with interest and enjoyment, is the most imperatively emphasised and strengthened of all. In every land the act of eating is connected with certain customs designed to distract from the business of daily life. A suitable time of day is chosen, a company of relatives, acquaintances or comrades assemble. Certain preparations are carried out (in England a change of raiment is usually effected, and often a blessing is asked upon the meal by the oldest of the family). In the case of the well-to-do, a special room for meals is set apart; musical and other guests are invited to while away the time at meals—in a word, everything is directed to take away the thoughts from the cares of daily life, and to concentrate them on the repast. From this point of view it is also plain why heated discussions and serious readings are held to be unsuitable during meal times. Probably this also explains the use of alcoholic beverages at meals, for alcohol, even in the lighter phases of its action, induces a mild narcosis, which contributes towards distraction from the pressing burden of the daily work. Naturally this highly developed hygiene of eating is only found in the intelligent and well-to-do classes, first, because here the mental activity is more strained and the various questions of life more burning; and secondly, because here also the food is served in greater quantity than is required for the wants of the organism. In the case of the poorer classes, where mental activity is less highly developed, the greater amount of muscular activity and the constant lack of more than sufficient nourishment ensure a strong and lively desire for food in a normal manner, without recourse to any special regulations or customs. The same conditions explain why the preparation of food is so choice in the case of the upper classes and so simple in that of the lower. Further, all the accessories of the meal, which are foretastes of the actual repast, are obviously designed to awaken the curiosity and interest, and to augment the desire for food. How often do we see that a person who begins his customary meal with indifference, afterwards enjoys it with obvious pleasure when his taste has been awakened by something piquant or, as we say, appetising. It was here only necessary to give an impulse to the organs of taste, that is, to excite them, in order that their activity might be later maintained by less powerful excitants. For a person who feels hungry such extra inducements are, of course, not necessary. The quelling of hunger in his case affords of itself sufficient enjoyment. It is not, therefore, without reason that it is often said that "Hunger is the best sauce." This dictum, however, is only right up to a certain point, for some degree of appetising taste is desired by everybody, even by animals. Thus, a dog which has not fasted for more than some hours will not eat everything with equal pleasure which dogs usually eat, but will seek out the food which it relishes best. Hence the presence of a certain kind of spice is a general requirement, although naturally individual tastes differ.

This short discussion as to how different people behave with regard to the act of eating is of itself testimony that care should ever be taken to keep alive the attention and interest for food and to promote enjoyment of the repast—that is to say, that care should be taken of the appetite. Every one knows that a normal, useful food is a food eaten with appetite, with perceptible enjoyment. Every other form of eating, eating to order or from conviction, soon becomes worse than useless, and the instinct strives against it. One of the most frequent requests addressed to the physician is to restore the appetite. Medical men of all times and of every land have held it to be a pressing duty, after overcoming the fundamental illnesses of their patients, to pay special attention to the restoration of the appetite. I believe that in this they are not only animated by an endeavour to free their patients from troublesome symptoms, but also by the conviction that the return of appetite of itself will favour the restitution of normal digestive conditions. It may be said, that to the same extent to which the patient wishes back his appetite, the physician has effectively employed measures to restore it. Hence we have not a few remedies which are specially named "gastric tonics," and whose action is to promote appetite. Unfortunately medical science has latterly deviated from this, the correct treatment of the appetite, and that which corresponds to the real conditions. If one reads current text-books on disorders of digestion, it is remarkable how little attention is paid to appetite as a symptom or to its special therapy. Only in a few of them is its importance indicated, and then merely in short parenthetic phrases. On the other hand, one may meet statements in which the physician is recommended to adopt no special means for counteracting so unimportant a subjective symptom as a bad appetite! After what I have said and demonstrated to you in these lectures, one can only designate such views as gross misconceptions. If anywhere, it is precisely here that symptomatic treatment is essential. When the physician finds it necessary, in disorders of digestion, to promote secretory activity by different remedies, this object can most certainly and completely be achieved by endeavouring to restore the appetite. We have already seen that no other excitant of gastric secretion, so far as quantity and quality of the juice are concerned, can compare with the passionate craving for food.

To a certain degree we can understand—and this contributes to an explanation of matters—how medical science of our time has come to regard so lightly the loss of appetite as a special object for treatment. Now, however, the experimental method has penetrated more and more into medical science, with the result that many pathological factors and therapeutic agents are judged of according to whether they hold good in the laboratory or not—that is to say, they are valued only in so far as they can be verified by laboratory experiments. Naturally we do not doubt that a movement in this direction indicates a great advance, but even here, as with every undertaking of mankind, things do not proceed without mistakes and exaggerations. We must not consider an event to be a mere picture of the imagination because it is not realisable under given experimental conditions. We often do not know all the essential conditions for the production of the phenomenon in question, nor are we yet able to grasp the connection between all the separate functions of life as fully as may be desired. Thus in the clinical treatment and pathology of digestion assistance was sought for in the laboratory, but nothing was there met with which had a relation to appetite, and consequently this factor was overlooked in medical practice. As stated above, the psychic gastric juice obtained only cursory mention in physiology, and this not even by all authors; and when it was noticed it was related more as a curiosity. Great importance was, on the other hand, assigned to the mechanical stimulus, the efficiency of which, now that our knowledge is more complete, has been shown to be purely imaginary. Each of the contending factors has at length been assigned its proper place, and if clinical medicine maintains her worthy desire of following out the experimental investigation of her problems, she must in actual practice accord to appetite its old claim for consideration and treatment.

But notwithstanding the indifference of physicians to appetite in itself, many therapeutic measures are based on the promotion of it. And in this, the truth of empiricism makes itself irresistibly felt. When the patient is enjoined to eat sparingly, or when he is restrained from eating at all till the physician expressly permits, or again, when he is (for instance, during convalescence) removed from his ordinary surroundings and sent to an establishment where the whole life, and particularly the eating, is regulated according to physiological needs—in all these cases the physician seeks to awaken appetite, and relies upon it as a factor in the cure. In the first case, where the food is prescribed in small portions, in addition to preventing the overfilling of a weak stomach, the oft-recurrence of appetite juice, which is so rich in quantity and so strong in digestive power, is of great importance. I ask you here to call to mind one of our experiments in which food was given in small portions to a dog, and thus led to a secretion of much stronger juice than if the whole ration had been eaten at once. This was an exact experimental reproduction of the customary treatment of a weak stomach. And such a regulation of diet is all the more necessary, since, in the commonest disorders of the stomach, only the surface layers of the mucous membrane are affected. It may, consequently, happen that the sensory surface of the stomach, which should take up the stimulus of the chemical excitant, is not able to fulfil its duty, and the period of chemical secretion, which ordinarily lasts for a long time, is for the most part disturbed, or even wholly absent. A strong psychic excitation, a keen feeling of appetite, may evoke the secretory impulse in the central nervous system and send it unhindered to the glands which lie in the deeper, as yet unaffected layers of the mucous membrane.

An instance of this, taken from the pathological material of the laboratory, I have already related at the beginning of this lecture. It is obvious in these cases that the indication is to promote digestion by exciting a flow of appetite juice, and not to rely upon that excited by chemical stimuli. From this point of view the meaning of removing a patient, the subject of chronic weakness of the stomach, from his customary surroundings, is also plain. Take, for instance, a mentally overstrained individual, or a responsible official: how often does it happen that he cannot for a moment distract his thoughts from his daily work. He eats without noticing it, or eats and carries on his work at the same time. This often happens, particularly in the case of people who live in the midst of the incessant turmoil of great cities. The systematic inattention to the act of eating prepares the way for digestive disturbances in the near future, with all their consequences. There is no appetite juice, no "igniting juice," or, at most, very little. The secretory activity comes slowly into play; the food remains much longer in the digestive canal than is necessary, or passes, for want of sufficient digestive juices, into a state of decomposition which irritates the mucous membrane of the alimentary canal and brings it into a condition of disease. No medicinal treatment can help such a patient while he remains surrounded by his old conditions. The fundamental cause of his illness still continues in progress. There is only one course to pursue, namely, to take him completely away, to free him from his occupation, to interrupt the interminable train of thought, and to substitute for a time, as his only object in life, the care of his health, and a regard for what he eats. This is attained by sending the patient to travel, or by placing him in a hydropathic establishment. It is the duty of the physician to regulate not only the life of individual patients according to such rules, but also to have a care that in wider circles of the community a due conception of the importance of eating should be disseminated. This is particularly so with the Russian physician. It is precisely in the so-called intelligent classes of Russians that a proper conception of life generally is often found wanting, and where an absolutely unphysiological indifference towards eating often exists. More methodical nations, like the English, have made a species of cult of the act of eating. It is, of course, degrading to indulge excessively and exclusively in culinary enjoyments, but, on the other hand, a lofty contempt for eating is also reprehensible. As so often is the case, the best course here also lies between the two extremes.

With the establishment of mental effect upon the secretion of juice the influence of condiments enters upon a new phase. The conclusion had already been empirically arrived at, that it was not alone sufficient for the food to be composed exclusively of nutrient substances, but that it should also be tasty. Now, however, we know why this is so. For this reason, the physician, who has often to express an opinion upon the suitability of the dietaries of different persons, or even of whole communities, should constantly bear in mind the question of psychic secretion; that is to say, he should inquire after and learn how the food has been eaten, whether with or without enjoyment. But how often do the people who have charge of the commissariat pay attention solely to the nutritive value of the food, or place a higher value on everything else than taste? We must, further, in the interest of the public weal, direct attention especially to the feeding of children. If this or that inclination of the taste ultimately determines the relation of grown-up individuals towards food, a matter with which the commencing phase of digestion is closely linked, it would seem undesirable to habituate children solely to a nicety and uniformity of gustatory sensations. Such might affect their capabilities of adapting themselves to other conditions in after life.

The question of the therapeutic influence of the so-called bitters, it appears to me, bears the closest connection with that of appetite. After a long period of high repute these substances have been almost expelled from the list of pharmaceutic remedies. When tested in the laboratory, they were unable to justify their old and valued reputation; when directly introduced into the stomach, many of them were unable to produce a flow of gastric juice. Consequently, in the eyes of the clinician, they became greatly discredited, so that many were quite ready to discard their use altogether. Obviously, the simple conclusion was drawn, that a weak digestion could only be assisted by a remedy which directly excites secretory activity. In this, however, it was forgotten that the conditions of the experiment possibly had not corresponded with the actual state of affairs. The whole question of the therapeutic importance of the bitters, however, acquires a different significance when we link it with another question, such, for instance, as how do bitters affect the appetite? It is the universal opinion of the earlier and later physicians that bitters increase the appetite, and if this be so everything is said. They are, in consequence, real secretory stimulants, since the appetite, as has many times been repeated in these lectures, is the strongest of all stimuli to the digestive glands. It is, however, not by any means strange that this had not previously been observed in the laboratory. The substances were either introduced directly into the stomachs of normal dogs or else injected into the circulation. But their action is chiefly bound up with their effect upon the gustatory nerves, and it was not, therefore, without some reason that this large group of remedies, consisting of substances of the most varied chemical composition, were grouped together mainly on account of a certain bitter taste common to them all. A person who suffers from digestive disturbance has, moreover, a blunted taste, a certain degree of gustatory indifference. The ordinary foods, which are agreeable to other people, and also to himself when in health, now appear tasteless. They not only arouse no desire for eating, but may even cause a feeling of dislike; there is no sense of taste, or at best a perverse one. It is necessary, therefore, that the gustatory apparatus should receive a strong stimulus in order to restore a normal sensation. As experience teaches, this object is most quickly attained by exciting sharp, unpleasant gustatory impressions, which by contrast awaken the idea of pleasant ones. In either case there is no longer indifference, and this is the foundation upon which an appetite for this or that kind of food may be awakened, and here a general physiological law is illustrated. The light appears brighter after darkness, a sound louder after silence, the enjoyment of blithesome health more intense after illness, and so on. This explanation of the appetising effects of bitters proceeding from the mouth does not exclude the possibility of some such similar influence coming also from the stomach. As has been already stated in the fifth lecture, there is some reason for believing that certain impulses from the cavity of the stomach are likewise necessary for the excitation of appetite. It is possible that bitters not only act directly on the gustatory nerves in the mouth, but that they also act on the mucous membrane of the stomach in such a way that sensations are generated which contribute to the passionate craving for food. As a matter of fact, it has been confirmed by many clinicians that after the administration of bitters some such special sensations do arise in the stomach. The effect of these remedies consists, therefore, not merely in the generation of a simple reflex, but in the production of a certain psychic effect, which indirectly excites a physiological secretory activity. The same probably applies to other substances, such as condiments. In any case, whether our explanation corresponds to the actuality or not, the question of the therapeutic effect of bitters is settled in the affirmative the moment we acknowledge that these substances awaken appetite. The problem, therefore, of an experimental investigation of bitters consists in establishing the fact that they have an effect upon the appetite. The question is a difficult one, and has not hitherto been attempted in the laboratory. It is not sufficient to hand over clinical observations to the laboratory as experimental proofs. One must have, in addition, the assurance that the investigation has been correctly carried out; that is to say, that it dealt exactly with the point under consideration. It is interesting to observe that the connection between appetite and gastric juice is by many physicians, and in many text-books of medicine, exactly reversed. Thus it is represented that some medicinal remedy calls forth a secretion of gastric juice, and this, by its presence in the stomach, awakens an appetite. Here we have to deal with a false explanation of a true fact, and that because it was not recognised that a psychic effect could by any possibility be a powerful excitant of secretory nerves. The customs of the chief meal of the day also correspond with our physiological results. After this or that *hors d'œuvre*, perhaps also with a liqueur of brandy (especially customary in Russia), both of which are designed to awaken the appetite, the repast proper begins, and, in the majority of cases, with something hot, consisting mostly of meat broth (*bouillon*, different soups, and so on). After this comes the really nourishing food—meat of different kinds served in various ways, or, in the case of poorer people, stews made with vegetables, and therefore rich in carbohydrate material. This sequence of foods, from the standpoint of physiology, is quite rational. Meat broth, as we have already seen, is an important chemical excitant of gastric secretion. An attempt is therefore made in two ways to secure a free secretion of gastric juice to act on the chief food; first in the excitement of the appetite juice by the *hors d'œuvre*, and secondly in the promotion of the flow by the action of the meat broth. It is in this way that human instinct has made provisions for the digestion of the chief meal. A good meat broth can only be afforded by well-to-do people, and consequently with the poorer classes a less expensive, and, indeed, also a less effective, chemical excitant is used for awakening the early secretion. For example, *kwas* * serves in this way with the Russian population, while in Germany, where the price of meat is high, different kinds of soups are used, consisting of water mixed with flour, bread, &c. It is further to be borne in mind that the quantity of the digestive juices in general stands in close connection with the content of water in the organism. This has been shown by the experiments of Dr. Walther for the pancreatic juice and by my own for the gastric juice. If this sequence of foods, therefore, holds good for healthy people, it must be even more strictly adhered to in pathological conditions. Thus, when a person has no appetite, or only a weak one, he has no psychic juice or only very little; consequently, the meal must in every case be begun with a strong chemical excitant—for example, with a solution of the extractives of flesh. Otherwise solid foods, particularly if they do not consist of meat, would remain long in the stomach without any digestion whatever. It is, therefore, in every way desirable to prescribe meat juice, strong broth, or meat extract to people who have no appetite. The same applies also to forced feeding, for instance, of the insane. It is true that the method of introduction in this case necessarily secures the presence of a chemical excitant, since the food can only be introduced in a fluid form. In any case the addition of meat extract would be very useful. If one arranged the ordinary fluid foods in descending order, according to the influence of the chemical excitants, the following would be the series: first, the preparations of the flesh, such as meat juice and the like; secondly, milk; thirdly, water.

The usual termination of the repast is also, from the physiological standpoint, easy to be understood. The chief meal is generally ended with something sweet, and everybody knows that sweets are

* *Kwas* is a favourite Russian drink, prepared from water, bread or meal, with malt and yeast. It contains a considerable quantity of lactic acid, some acetic acid, and other products of fermentation.

pleasant. The meaning of this is easy to guess. The repast, begun with pleasure, consequent on the pressing need for food, must also, notwithstanding the stilling of hunger, be terminated with an agreeable sensation. At the same time the digestive canal must not be burdened with work at this stage, it is only the gustatory nerves which should be agreeably excited. After thus dealing in general with the usual arrangement of our meals, we may now speak of some special points.

Above all comes the acid reaction of the food. It is apparent that acidity enjoys a special preference in the human taste. We use quite a number of acid substances. Thus, for example, one of the commonest seasoning substances is vinegar, which figures in a number of sauces and such like. Further, many kinds of wine have a somewhat acid taste. In Russia, *kwas*, especially in the acid form, is consumed in great quantities. Moreover, acid fruits and green vegetables are used as food, and they are either of themselves acid, or made so in the preparation. In medicine this instinct is likewise often made use of, and acid solutions, especially of hydrochloric and phosphoric acids, are prescribed in digestive disturbances. Finally, nature itself constantly endeavours to prepare lactic acid in the stomach in addition to the hydrochloric acid. The former arises from the food introduced, and is consequently always present. These facts are all physiologically comprehensible when we know that an acid reaction is not only necessary for an efficient action of the peptic ferment, but is at the same time the strongest excitant of the pancreatic gland. It is even conceivable that in certain cases the whole digestion may depend upon the stimulating properties of acids, since the pancreatic juice exerts a ferment action upon all the constituents of the food. In this way, acids may either assist digestion in the stomach where too little gastric juice is present, or bring about vicarious digestion by the pancreas where it is wholly absent. It is easy, therefore, to understand why the Russian peasant enjoys his *kwas* with bread. The enormous quantity of starch which he consumes, either as bread or porridge, demands a greater activity upon the part of the pancreatic gland, and this is directly brought about by the acid. Further, in certain affections of the stomach, associated with loss of appetite, we make use of acids, both from instinct as well as medical direction, the explanation being that they excite an increased activity of the pancreatic gland, and thus supplement the weak action of the stomach. It appears to me that a knowledge of the special relations of acids to the pancreas ought to be very useful in medicine, since it brings the gland—a digestive organ at once so powerful and so difficult of access—under the control of the physician. We could, for instance, intentionally discard digestion in the stomach, and thus transfer it to the bowel by prescribing substances which do not excite the gastric glands. On the other hand, by lessening the acidity of the gastric juice we could reduce the activity of the pancreas, and these are matters which might be made use of in various special diseases, or even in some general disturbances of the digestive apparatus.

No less instructive is a comparison of the results of our experiments upon fat, with the demands of instinct and also with the precepts of dietetics and therapeutics. Everybody knows that fatty foods are heavy, that is, difficult of digestion, and in the case of weak stomachs they are usually avoided. We are now in a position to understand this physiologically. The existence of fat in large quantities in the chyme restrains in its own interest the further secretion of gastric juice, and thus impedes the digestion of proteid substances; consequently, a combination of fat and proteid-holding foods is particularly difficult to digest, and can only be borne by those who have good stomachs and keen appetites. The combination of bread and butter is less difficult, as might *à priori* be inferred from its wide employment. Bread requires for itself, especially when calculated per unit, but little gastric juice and but little acid, while the fat which excites the pancreatic gland ensures a rich production of ferment both for itself and also for the starch and proteid of bread. Fat alone does not count by any means as a heavy food, as may be seen from the fact that large quantities of lard are consumed in certain districts of Russia with impunity. This also is comprehensible, since the inhibitory influence of the fat in this case does not prevent the digestion of any other food-stuff, and is conducive to the assimilation of the fat itself. There is no struggle in this case between the several food constituents, and therefore no one of them suffers. In harmony also with daily experience, the physician, in cases of weakness of the stomach, totally excludes fatty food and recommends meat of a fat-free kind, for example, game, &c. In pathological cases, however, where an excessive activity of the gastric glands is manifested, fatty food, or fat as emulsion, is prescribed. And here medicine has empirically brought to its aid the restraining action of fat, which we have so strikingly seen in our experiments.

Amongst all the articles of human food, milk takes a special position, and this is unanimously recognised, both in daily experience and in the practice of medicine. By everybody milk is considered a light food, and is given in cases of weak digestion as well as in a whole series of severe illnesses, for example, in heart and kidney affections. The extreme importance of this substance, a food prepared by nature itself, we can now well understand. There are three properties of milk which secure it an exceptional position. As we already know, in comparison with nitrogenous equivalents of other foods, the weakest gastric juice and the smallest quantity of pancreatic fluid are poured out on milk, consequently the secretory activity requisite for its assimilation is much less than with any other food-stuff. In addition, milk possesses a further important property. Thus, when it is introduced unobserved into the stomach of an animal it causes a secretion both in the stomach and also one from the pancreas, consequently it appears to be an independent chemical excitant of the digestive canal, and in this action it is remarkable that we perceive no essential difference in the effect when the milk is brought unnoticed into the stomach from that which occurs when it is given to the animal to lap. Although flesh is a better chemical excitant, it is by no means a matter of indifference how it gets into the stomach. It must, therefore, be accepted that milk excites not only a really effective, but at the same time a very economic, secretion, and also that the appetite is unable to stimulate this secretion into a more active or abundant flow. The secret of the relation of milk to the secretion of the digestive juices can, unfortunately, at present be submitted to no further analysis or investigation. We are at liberty, however, to suppose that the fat on the one hand is of importance for the inhibition of the gastric glands, and the alkalinity on the other for the restraint of the pancreas. Thus the gastric glands and the pancreas, notwithstanding the presence of excitants, are maintained by milk at a certain but not too high degree of activity, a matter which is in every way desirable in consideration of the easy digestibility of its constituents. Finally, the third characteristic which is observed to belong to milk, and which is probably only an expression of the first, consists in the following. When one administers to an animal equivalent quantities of nitrogen, in the one case as milk, in the other as bread, and afterwards estimates the hourly output of nitrogen in the urine, it results that the increase during the first seven to ten hours after the milk (compared with the excretion beforehand) amounts only to from 12 per cent. to 15 per cent. of the nitrogen taken in, while after bread, it amounts to 50 per cent. If the hourly rate of absorption and the extent to which milk and bread are respectively used up be taken into consideration, it has to be admitted that these augmentations of urinary nitrogen which appear soon after feeding, must be expressions of the functional activity of the digestive canal itself, and that this activity in the case of bread is three or four times greater than in the case of milk (*Experiments of Prof. Rjasanzew*); consequently, in the case of milk a much larger fraction of its nitrogen is free to be used up by the organism at large (irrespective of the organs of digestion) than in that of any other kind of food. In other words, the price which the organism pays for the nitrogen of milk, in the form of work on the part of its digestive apparatus, is much less than that for other foods. How admirably, therefore, the food prepared by nature distinguishes itself when compared with all others!

The facts just related bring forward a new aspect from which the relative nutritive values of different foods may be judged. The older criteria must frankly make room for the new or else be displaced by them. Experiments upon the utilisation of food-stuffs, in which what remains undigested is determined, as well as what is absorbed into the body fluids, cannot alone be trusted to solve the question in a satisfactory manner. Suppose, for instance, that in the digestion of a given food the alimentary canal has been given a certain work to perform; if it be in health, the work will be accomplished in the best possible manner, that is to say, with complete abstraction of everything nutrient. You will thus learn how much nutrient material was contained in the food, but the question of its digestibility remains as obscure as before. In your experiment you do not know how great an effort it has cost the alimentary canal to extract all the nourishment from the food. Nor can artificial digestion experiments settle the question of digestibility, for experiments in which food is normally partaken of are quite different from those in the test-tube, where we have to deal with only one juice, and not with the interaction of different juices and different food constituents. That one must here, as a matter of fact, make a distinction, is clear from the observation of Dr. Walther in our laboratory. Fibrin, which is regarded by all as the most easily digested proteid, proved, when compared with a nitrogen equivalent of milk, to be a much stronger excitant of the pancreas, although milk contains, in addition to nitrogenous substances, a good deal of other non-nitrogenous material. The digestibility and nutritive value of foods must obviously be decided by an estimation of the real work which they entail upon the digestive apparatus, both in regard to the quantity and quality of the juices poured out on a given amount of nutrient material. The energy used up in gland metabolism must be deducted from that of food taken in. The remainder will then indicate the value of the food to the organism, that is to say, will give the amount available for use by all the other organs exclusive of the digestive apparatus. From this point of view those materials must be taken as less nourishing and less digestible, which are in large part used up to make good the expenditure entailed by their digestion on the part of the alimentary canal; that is to say, those food-stuffs are less useful whose nutritive value little more than covers the cost of their digestion, consequently it is of great practical importance to compare from this aspect the same foods, differently prepared—for example, boiled and roast meat, hard and soft-boiled eggs, boiled and unboiled milk, &c.

A discussion of some further medical questions may here be taken up. The first concerns the therapeutic use of the neutral and alkaline salts of sodium. In clinical, pharmacological, and physiological text-books it is stated now, as ever, that these salts promote a flow of gastric juice. We may look in vain, however, for any experimental foundation to support this doctrine. The experiments brought forward cannot be regarded as conclusive. When Blondlot sprinkled sodium bicarbonate upon flesh, or Braun and Grützner introduced sodium chloride solutions directly into the blood, they began with methods either false in themselves, or far removed from normal conditions. In this case, however, the gaps in the experiment were happily made good by the clinician, for the experiment appeared to be confirmatory of clinical experience. That sodium salts (the chloride and bicarbonate) are useful in disorders of the digestive apparatus there can be no doubt. How do they act, however? It appears to me that here, as in some other cases, medical science has fallen into error. When we know that an effect takes place it does not by any means imply that we know the mechanism by which it occurs, and although medicine is broad enough and comprehensive enough to make free use of empiricism in practice, yet it often thinks in narrow grooves when it turns to the explanation of facts. It frequently tries to explain complicated healing processes in the simplest way, on supposed physiological data. And this is true in the present case, which affords an example of prevalent medical reasoning; the alkalies work favourably in digestive disturbances; therefore, they are succagogues. Naturally the stomach, under the influence of alkalies, sometimes begins to secrete a greater quantity of juice. This means, however, that it has recovered from a disordered state, and has returned to normal conditions. Consequently, the effect is due to the fact of recovery, and not to a direct influence of the alkalies. This latter, however, must be specially proved. The assistance afforded by the alkalies to the organism might be capable of another explanation: for example, that which is ordinarily given. In this case, however, I venture to offer a reason for the effects of sodium chloride, and of the alkaline salts of sodium, which is exactly the opposite of that generally accepted. We were unable to convince ourselves of any succagogue influence on the part of these salts. Indeed, both on the stomach and pancreas they proved in our hands to have an inhibitory effect. In addition to the experiments which I previously brought forward concerning the relation of alkalies to gastric and pancreatic juice, I may relate the following observation: A dog which fortunately had survived the performance, one after the other, of a gastric fistula, a pancreatic fistula, and an œsophagotomy, received daily during the course of several weeks an addition of soda to its food. The animal enjoyed good health and had an excellent appetite. When the first sham feeding experiment was carried out, the relatively small effect of this otherwise very active juice-exciting procedure at once struck us. At the same time we observed that the pieces of flesh which fell from the upper end of the œsophagus, contrary to the ordinary rule, were hardly at all insalivated. In this dog, therefore, a greatly lowered activity of several digestive glands, viz., of the gastric, pancreatic, and salivary glands, simultaneously existed. With regard to the salivary glands, the circumstance was naturally submitted to closer investigation. I believe that the inhibitory influence of the alkalies on the digestive glands, which was here proved experimentally, may furnish a basis for the following representation of their mode of action in producing healing effects. Catarrhal affections of the stomach are characterised by an incessant or very protracted secretion of slimy, weakly acid gastric juice. Further, in many cases the affection begins with a hypersecretion, that is an abnormal excitability of the secretory apparatus which makes itself evident in a superfluous and useless flow. The same must be conceived to happen in disorders of the pancreatic gland: at least, such a condition sets in after operations performed for physiological purposes. It is, further, justifiable to suppose that, when an affection is once set up by this or that cause, it may later maintain itself independently, for continuous activity has undoubtedly a harmful influence on the glands. The due nourishment, and the restoration of organs after activity, proceeds best during rest. In the normal course of events, after a period of active work follows a pause, during which the latent work of restoration is accomplished. When, therefore, a remedy effectively restrains the excessive work of a diseased organ, it may in this way contribute to the removal of the pathological condition, and thus to a restoration of the normal state. In this consists, in my opinion, the healing effects of the alkalies. One might draw a parallel between the action of these substances in digestive disturbances and that of digitalis in compensatory disturbances of the heart. An uncompensated heart beats rapidly, and thereby only aggravates its condition. Its time of rest, that is, of recovery, of restitution of the organ is shortened. A vicious cycle is set up. The weak action of the heart lowers blood pressure; the lowering of this leads (from known physiological causes) to an increase in the number of beats, the quickening leads to weakening of the organ. Without doubt the digitalis aids by breaking through this vicious cycle in that it greatly slows the pulse, and thereby gives new power to the heart. With our explanation of the action of the alkalies harmonises the further circumstance that, with the use of the salts in question, a strict diet is generally prescribed, which means that a certain amount of rest is secured for the digestive glands. It is interesting that in clinical investigations with the stomach-tube, after a period when the alkalies were looked upon as succagogues, a new phase has also set in, mention being now more frequently made of a restraining effect.

The cause of the erroneous belief that alkalies promote a flow of juice obviously lies in this, that people omitted to compare the effects of the saline solutions with those of like quantities of water (*Dr. Chigin*).

The second point which we may consider is the following. The chief difficulty of the physician who wishes to regulate the diet of patients when they suffer from digestive disturbances consists in the fact that idiosyncrasy plays a very important *rôle*. In one and the same illness, different patients react to the same diet in wholly different ways. That which is agreeable to one, and is well borne and useful, may be rank poison to another. Consequently, the golden rule in dietetics is to give no directions with regard to food till one has made inquiries concerning the inclinations and habits of the patient. What does all this indicate? Till now physiology had no experimental answer to the question. But our facts, it appears to me, contribute to a clearing up of the situation. Every food determines a certain amount of digestive work, and when a given dietary is long continued, definite and fixed types of glands are set up which can only slowly and with difficulty be altered. In consequence, digestive disturbances are often instituted if a change be suddenly made from one dietetic *régime* to another, especially from a sparse to a rich diet, such, for instance, as happens after the long Russian fasts. These disturbances are expressions of the temporary insufficiency of the digestive glands to meet the new demands made upon them.

Finally, it may be of some use to relate the following here: There are often cases of sudden and unaccountable digestive disturbances From the standpoint of modern physiology they might be explained by an activity of the secreto-inhibitory nervous system, which from some cause or other has been excessively and abnormally stimulated. In any case, this system is now a factor of which the physician has to take due account.

LECTURE IX.*

LATER RESEARCHES — THE COLLABORATION AND MUTUAL RELATIONSHIPS OF THE DIGESTIVE JUICES — BILE AND SUCCUS ENTERICUS — MOVEMENTS OF THE STOMACH—PATHOLOGY AND EXPERIMENTAL THERAPEUTICS OF DIGESTION — THE METHOD OF EXPERIMENT IS THE ONLY ONE ADEQUATE TO PRESENT-DAY MEDICAL REQUIREMENTS.

Later researches on the digestive glands—The physiology and psychology of salivary secretion—New method for the separate study of gastric secretion —The multiplicity of functions attributed to the bile is an indication of our lack of knowledge of the physiology of this secretion—Method of studying the biliary secretion—The entry of bile into the intestine is dependent on the presence and the nature of the food—The true digestive function of the bile is to augment the activity of the ferments of pancreatic juice—The *succus entericus* has also the same function—A ferment of ferments, the ENTEROKINASE—Mechanical excitation effects a secretion of *succus entericus*, but only of its watery constituents—Pancreatic juice is a specific excitant of the kinase—The favouring influence of *succus entericus* upon the trypsin of pancreatic juice depends upon the transformation of the zymogen into trypsin—The amount of trypsin in the form of zymogen depends on the nature of the diet—The spleen and the pancreas—The propulsion of food along the digestive canal ; its functional adaptation thereto—Experiments on the movements by which the stomach is emptied of its contents—The passage of chyme into the intestine is regulated by impulses generated in

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* This lecture was delivered at the anniversary meeting of the Society of Russian Medical Men five years later than those preceding. It was also dedicated to the memory of S. P. Botkin in the names of Professor Pawlow and the following collaborateurs : J. O. Lobassow, A. N. Wolkowitsch, J. C. Soborow, J. C. Sawriew, A. A. Walther, L. B. Popielski, A. R. Krewer, G. G. Bruno, N. N. Kladnizki, S. H. Wulfson, W. W. Nagorski, D. L. Glinski, N. P. Schepowalnikow, A. S. Serdjukow, P. O. Shirokich, E. A. Hanicke, and A. P. Sokolow. The lecture was afterwards published as a separate pamphlet under the title, "The Experimental Method — An indispensable Requirement of Medical Research." (*Translator.*)

the mucous membrane of the duodenum—Reflex closure of the pylorus by acids, its significance and importance—The pathology of the stomach as studied by our experimental methods—The protection of the mucous membrane of the stomach—Physiological function of the epithelium of the gastric mucous membrane—Experimental production of gastric asthenia and of a condition the reverse of this—The point of attack of the round ulcer of the stomach—Substitution of the small stomach for the large in our physiological and pathological experiments—Nervous inhibition in affections of the stomach—Experimental therapeutics of the stomach based on our investigations—Survival of vagotomised dogs—Treatment of gastric hyper-secretion by alkalies.

Gentlemen,—Since the delivery of the preceding lectures, now five years ago, our investigations into the physiology of digestion have been carried on without interruption, and our later results have even a closer connection with the practice of medicine than the former. At that time I could only theoretically discuss the pathology and therapeutics of digestion, but now these subjects have been made matters of direct research. The results of the several investigations have in nearly all cases been communicated to this society; consequently, the facts concerning which I am about to speak will be already known to many of you. However, I think it desirable to bring them all under consideration. It is only in this way that the general bearing of the investigations can be made clear, and that each single piece of work will find its proper place in the whole scheme.

It may well be understood that even at this stage, purely physiological questions have taken the first place in our researches, but our field has naturally grown ever wider and wider. My former lectures dealt mainly with the more important of the digestive organs, the gastric glands, and the pancreas. During the last five years we have worked still further at the physiology of these glands, but in addition we have included that of the remaining digestive secretions, namely, the saliva, the bile and the succus entericus. Further, we have also made observations on the movements of the food along the digestive canal.

In the case of the gastric glands and the pancreas we were able to disregard the question of the main physiological import of their secretions, since this was already fully known. We were therefore free to direct our whole attention to an investigation of the factors which determined the normal activity of these glands. But in the case of the latter fluids, it was necessary to establish at the outset their functional importance.

With regard to the glands of the stomach and also the pancreas the investigations of the past five years have confirmed our fundamental deductions while they have also added a greater completeness to them. The beautiful adaptation to the requirements of the food undergoing digestion, which we saw then to be an essential characteristic of the work of these glands, has been even more clearly expressed in our later experiments, especially in connection with the pancreatic secretion. The ferment activity of the pancreatic juice harmonises in the most beautiful manner with the nature of the food to be digested. Thus, with a diet containing a large proportion of fat, the fat-splitting ferment predominates, and so on. (*Experiments of Dr. Walther.*) Further, we have gained a better knowledge of the mechanism of this adaptation; we have discovered new factors in the nervous machinery of these glands—nerves which restrain their activity. (*Experiments of Dr. L. B. Popielski.*) We have determined the relationship of each individual element of the food to the receptive part of the nervous apparatus of the glands. And in this way we have convinced ourselves by direct experiment that the special nature of the gastric juice poured out on bread, with its strong digestive power, is determined by the fact that starch is mixed with the proteid. (*Dr. J. O. Lobassow.*) Similarly, we have been able to explain nearly all the quantitative and qualitative changes in the secretions of the digestive glands which occur during the whole period of activity. It is also very gratifying to me to be able to state that both Russian and foreign representatives of clinical medicine have made use of the results of our physiological investigations and with good effect. Further, all our hypotheses and discoveries have gained wide recognition in foreign lands, and this encourages us to extend our work.

I now come to a new subject in our researches, in which we see that what is true of science generally is likewise true of every individual scientific problem. Everything does not mean advance; we often meet with a standstill, sometimes even take a retrograde movement. A striking example of this is shown in the investigation of the salivary glands.

About the middle of the last century, after the appearance of the classical work of Mitscherlich, a number of talented investigators, such as Claude Bernard, Schiff, and others, endeavoured to solve the interesting and natural questions of how much and what kind of saliva is poured into the mouth under different conditions, such as the act of mastication, the entry of foods of different tastes and different degrees of dryness, &c. It resulted—and the same is to be expected from every organ in the body—that the work of the salivary glands is capable of adapting itself to given conditions, that is to say, bears a definite relationship to the requirements which must be fulfilled by the saliva produced. And yet we read in modern text-books of physiology, which purport to sum up the achievements of our science, that every form of stimulus applied to the cavity of the mouth, be it mechanical, chemical, thermal, or otherwise, excites the activity of the salivary glands in one and the same way. Only in the case of a few authors has the state of dryness of the food received mention as a special factor in the case. But, as to the why and the wherefore of all this, not one word, as a rule, is said! One is led to suppose that the work of the salivary glands is of no import, and that they respond in haphazard fashion to every form of stimulus. Obviously the fruitful ideas of the earlier authors had passed into complete oblivion. This could not be ascribed to the occasional discrepancies in the observations of these different authors, because, in spite of such, a kernel of truth always remained. The utter inadequacy of any hypotheses to the contrary must, however, be clear. How could it come about that the work of the salivary glands should be robbed of its adaptation? Where is the reflex that could determine this, especially when we bear in mind the accuracy of a sensation so finely differentiated as that presided over by the nerves of taste? In the case of the deeper-lying glands, namely, those of the stomach and the pancreas, we had previously learned many facts pointing indubitably to adaptation, and we could not readily give our assent to the contrary representation. The experiments concerning salivary secretion had, therefore, to be repeated.*

We easily convinced ourselves that it was by no means the case that every form of mechanical and thermal stimulus, without distinction, excited a flow of saliva. Thus if a handful of small quartz pebbles be thrown from a certain height into the dog's mouth, so that the mechanical stimulus is fairly strong, the dog will gnaw them, move them backwards and forwards, sometimes swallow a few of them, and yet no saliva flows, or at most only one or two drops. Again, if ice-cold water be poured into the mouth, or snow thrown in, no saliva will be seen. Obviously it is not required in these cases. But cast in some sand, and the saliva flows in quantities, because the sand cannot otherwise be got rid of than by a free stream of fluid. Upon all substances which the dog rejects—for example, acids, salts, bitter and caustic substances—saliva, will likewise be poured, because these require to be neutralised, diluted, or washed out of the buccal cavity. This explanation is fully confirmed by the absolutely constant and striking fact that a thin watery saliva, containing mere traces of mucin, is poured out by the mucous salivary glands upon every substance, without exception, which requires to be removed, while upon eatable substances a slimy mucin-holding fluid is

* These experiments were begun by Dr. D. L. Glinski and afterwards continued by Dr. S. H. Wulfson. They were performed on dogs in which the normal orifices of the salivary ducts were displaced outwards. During the experiments a small funnel (with a cylinder for collecting and measuring the saliva) was attached to the skin around the orifice. The secretions of the sub-maxillary and sub-lingual glands were jointly collected, that of the parotid separately.

secreted which lubricates the food bolus and facilitates its descent through the œsophagus. Further, the quantity of saliva secreted is closely related to the dryness of the food. The drier this is, the more saliva flows—a striking proof that the first of the digestive glands adapts itself to the physical conditions of the food. Of special interest is the peculiar relationship between the parotid secretion and acids. For these, a saliva is always secreted which is particularly rich in proteids. This peculiarity is still without an explanation. Perhaps it concerns some antitoxic precautionary measure.

Since ptyalin is almost absent from the saliva of the dog, we unfortunately could make no observations upon the "adaptation" of this ferment. I, therefore, proceed to another aspect of the question which is in the highest degree interesting. In the course of our experiments it appeared that all the phenomena of adaptation which we saw in the salivary glands under *physiological* conditions, such, for instance, as the introduction of the stimulating substances into the buccal cavity, reappeared in exactly the same manner under the influence of *psychological* conditions—that is to say, when we merely drew the animal's attention to the substances in question. Thus, when we pretended to throw pebbles into the dog's mouth, or to cast in sand, or to pour in something disagreeable, or, finally, when we offered it this or that kind of food, a secretion either immediately appeared, or it did not appear, in accordance with the properties of the substance which we had previously seen to regulate the quantity and nature of the juice when *physiologically* excited to flow. If we pretended to throw in sand, a watery saliva escaped from the mucous glands; if food, a slimy saliva. And if the food were dry—for example, dry bread—a large quantity of saliva flowed out, even when it excited no special interest on the part of the dog. When, on the other hand, a moist food was presented—for example, flesh—much less saliva appeared than in the previous case, however eagerly the dog may have desired the food. This latter effect is particularly obvious in the case of the parotid gland.

Thus, in a quite unexpected way, the physiology and psychology of the salivary glands have come to be associated together; or, even more than this, the psychology has in many cases displaced the physiology. For example, the psychological influence, in some cases, can be unhesitatingly accepted where formerly only pure physiological relationships were thought of; whereas the physiological influence, as such, must now be proved by special experiments designed to exclude the play of psychological factors. In the psychology of the salivary glands, as it has displayed itself to us, we find all the elements of what we usually attribute to "mental activity"—namely, sensation, choice, dispassionate consideration, and judgment with respect to the substance introduced into the buccal cavity. These latter facts are of such importance that I should like to go more fully into two conclusions to be drawn from them —the one of a more practical, the other of a more theoretical nature.

It is quite clear that the activity of even such apparently insignificant organs as the salivary glands penetrates unconsciously into our everyday psychical conditions through sensations, desires, and thoughts which in their turn exert an influence on the work of the glands themselves. We see no reason why the same should not apply to the other organs of the body. It is, indeed, by means of such unconscious impressions that the usual physiological processes of our bodies are guided. Viewed from this aspect, the rationale is at once apparent which underlies the prevalent conviction that a deep and lasting sorrow, which seizes hold of one's whole mental existence, reacts upon the body and renders it an easy prey to every form of disease. On the other hand, a cheerful disposition tends to develop and strengthen the body by increasing its susceptibility to every invigorating emotion of life, to every beneficial influence which acts upon the physical and psychical being.

Further, it is clear that the adaptation of the salivary glands is a phenomenon of the same order as that, for example, of the pancreas. Hence, if we could analyse step by step the adaptation in the latter organ, and if it be open to us to regard the process in the salivary glands as the more primitive form, we have here a clear physiological scheme for the study of the development of psychological phenomena.

Thus a way is open to us, even here, towards a synthetic study of the whole indivisible life.

In order to definitely settle some new as well as old problems relative to the secretion of gastric juice, we found it necessary to perform still more complicated operations upon our dogs than we had heretofore done. Thus the following operations were successively carried out on one and the same animal. In the first place an ordinary gastric fistula and then an isolated *cul-de-sac* of the stomach were formed. Further, a duodenal fistula (provided with metallic cannula) was made, and finally the cavity of the large stomach was shut off from the duodenum by a septum formed in the region of the pylorus of mucous membrane only. To permit of the dog being fed daily in the ordinary way, the gastric and duodenal fistulæ were connected externally by means of glass and indiarubber tubes. Dogs thus operated upon are exceedingly convenient to experiment upon. (*Investigations of Dr. A. P. Sokolow.*) With such animals it can easily and conclusively be decided that the second or chemical period of gastric secretion is determined by a reflex proceeding mainly from the inner surface of the stomach. If chemical excitants (solutions of meat extract and so on) be alternately introduced into the large stomach and into the duodenum, a full secretory effect is only obtained from the small stomach in the former case. In the latter the secretion is very scanty.

On the other hand, the inhibitory effect of fat originates chiefly from the surface of the duodenal mucous membrane and not from that of the stomach.

With the same dogs we were able, without difficulty, to demonstrate a new form of auto-regulation on the part of the stomach, which concerns the secretion of hydrochloric acid. It appears that the acid prevents the further secretion of gastric juice when it has accumulated in any considerable quantity within the cavity of the organ. It is moreover of the greatest interest that other acids, for example, phosphoric, &c., do not exert this inhibitory action. Butyric acid, on the contrary, strongly excites gastric secretion, a matter which is probably connected with the fact that hydrochloric acid strongly inhibits butyric acid fermentation. What could be more striking as an instance of the selective excitability of the mucous membrane of the stomach?

I have only brought forward a few of the results which we obtained by our new method, and would merely remark, in addition, that the experiments on such dogs were characterised by an astonishing degree of accuracy and constancy in the results. It might seem that the cutting out of the influence of the movements of the food, and of the effects of the different exciting substances, from these parts of the digestive canal, would make it otherwise, but this was not so.

I turn now to the bile. You all know, gentlemen, that the greater the number of remedies recommended for a disease, the less is the real efficacy of any one of them. The reason of this is quite plain. When we possess a really good remedy we want no other. The same criterion may be applied to our knowledge of the organs of the body. When a number of insignificant functions are assigned to any organ, it means that we do not know its real function or have not properly appreciated it. So it is with the bile. In every text-book one can straightway learn the functions of the gastric juice, of the pancreatic juice, and so on. But when we come to the bile we have to read whole series of sentences about its supposed uses, and perhaps will not even then learn its chief function. Mention will be made of the emulsification of fat, of the moistening of the intestinal wall, of the promotion of peristaltic action, of the disinfection of the intestinal contents, of the excitement of the intestinal villi, of the precipitation of the proteid bodies, and so on. Are all these correct, however? In how far is the one essential and the other not? To such questions you will find no satisfactory answer. Further, the academic teacher will have little or nothing clear and incontestable to *demonstrate* concerning the bile, a fluid the appearance and composition of which are so special. And yet we cannot doubt that the bile is necessary for digestion, that it plays an important *rôle* in this process, otherwise it would not be poured into the intestine at such a remarkable situation, namely, where the acid peptic gives place to the alkaline pancreatic digestion.

But how are we to set about determining what the digestive functions of the bile are? One of the most direct ways consists in examining how much and what kind of bile is poured into the digestive canal. It is remarkable that this method has never been correctly applied, although numbers of physiologists have worked at the subject. The bile has been collected from the most widely different animals, both during digestion as well as in fasting, but always by means of a fistula leading into the gall-bladder, a receptacle where the bile (continuously formed by the liver) is temporarily stored up till required for use. Experiments performed on dogs with an artificial opening into the common bile duct differ little from the foregoing, since, although the bile in the first instance enters the duct, it is conducted from thence into the gall-bladder. The experiments have led the authors to very different conclusions. In all cases, the bile continuously flowed from the gall-bladder whether the dog had been fasting or fed. And this is easy to understand, since the formation of bile in the liver and its employment during digestion are naturally two different things. It is because of this that a special reservoir is provided for it in the shape of the gall-bladder. Consequently, in order to determine what the function of the bile during digestion is, one must observe how it enters the alimentary canal and not how it accumulates in the gall-bladder. It was on these lines that we proceeded, after deviating the natural orifice of the bile duct (with a piece of the surrounding mucous membrane) towards the exterior.* A study of the results showed that the entry of bile into the intestine is regulated by the same laws that govern the flow of the other digestive juices. (*Experiments of*

* The operation is not an easy one. After some preliminary trials we adopted the following procedure. In the first instance the orifice of the duct, with a piece of the surrounding mucous membrane, was cut out of the intestine and transplanted upon its serous coat, where it was fastened with sutures. This done, the loop of intestine at the point in question was stitched into the abdominal wound, where it healed. See Fig. 18 (*a*, *b*, *c*,).

Dr. G. G. Bruno and Dr. N. N. Kladnizki.) In the fasting animal not a drop of bile entered the intestine. But when the dog had eaten, the flow began at a certain definite time afterwards. This time is different for the different kinds of food. The fluid continued to flow as

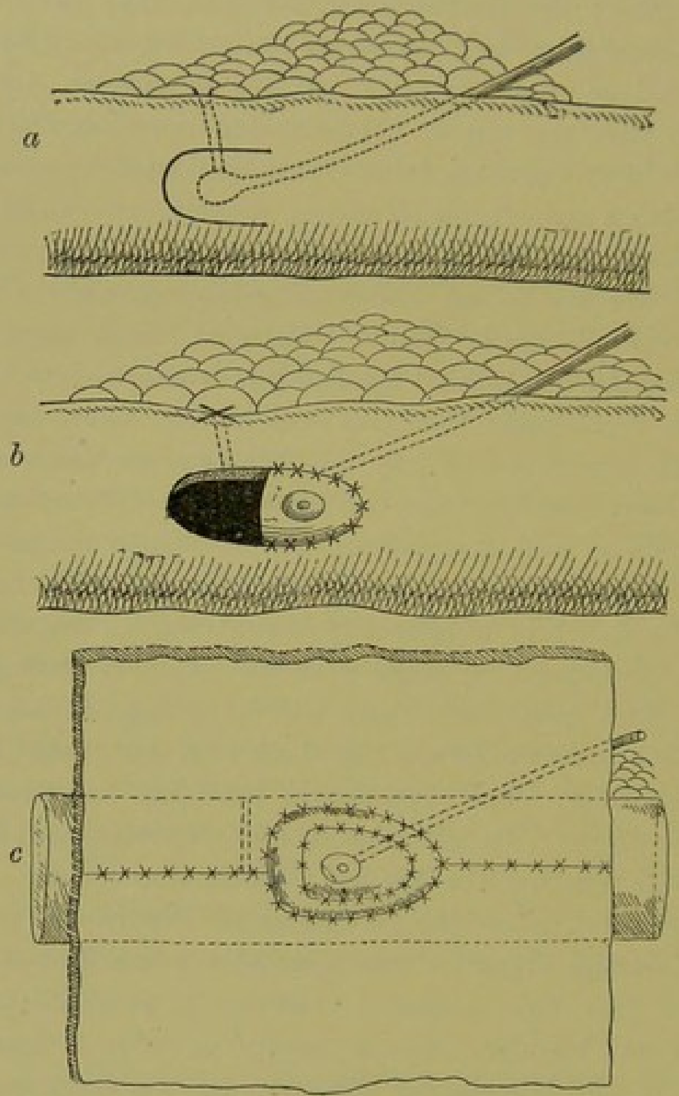

FIG. 18.—Showing the different stages in transplanting the orifice of the bile duct outwards. In (*c*) a flap of skin is represented *in situ* over the bowel.

long as the digestion lasted, but with definite fluctuations in quantity and quality, dependent upon the nature of the food. One cannot resist the idea that the bile has quite as important a part to play in the chemical elaboration of the food as any of the other digestive juices. Hence we proceeded further in our investigations, and gave the ingredients of the food separately to the dog to eat, or brought them directly into the stomach. It resulted that neither water, acids, raw egg-albumen nor boiled starch paste, whether in solid pieces or as a thin fluid, caused a flow of bile. Fat, on the other hand, as well as the extractives of meat, and the products of the digestion of egg-albumen, set up a free discharge of the fluid. The bile, therefore, resembles other digestive juices in that it possesses its own particular combination of excitants, which have the effect of causing it to flow into the intestine.

But in what does the work of the bile consist? In order to answer this question, which now took a definite shape, we adhered to certain facts which, it must be admitted, do not enjoy great popularity amongst physiologists. The lack of esteem from which they suffer is shown by the fact that in many text-books of physiology they are consigned to small print. The bile possesses only a weak direct chemical action upon the food constituents. Different investigators have long ago shown that it has a slight amylolytic action. In addition, during the past year, Dr. Gegaloff discovered in this laboratory that the bile of carnivora also contains a proteolytic ferment, but its action is only a weak one. We are now engaged, however, in systematically examining the variations of this ferment and the relationships which they bear to digestive activity.

There remains the possibility of a chemical effect upon the other digestive juices with which the bile mixes in the intestinal canal. It has long been known that the ferments of the stomach and pancreas manifest different degrees of digestive activity, according to the chemical properties of the medium in which they work. Further, there are very old experiments which point to an inhibitory action of the bile upon the ferment of the gastric juice. But, on the other hand, investigations, begun originally by Professor Nencki in his Berne laboratory and carried on by Heidenhain, Rachford, Williams and Martin, have shown that the bile has a favouring action on the ferments of the pancreatic juice. The majority of these experiments dealt, however, with extracts of the pancreas, and consequently in the main with zymogen and not with the ready-made ferment. It was open, therefore, to doubt whether they would hold good for the actual conditions of digestion. Rachford alone carried out experiments with ferments, but not with all of them, and only with those of the pancreatic juice of the rabbit. We shall see that in the favouring action of bile upon the ferments of pancreatic juice we have discovered the main feature of its digestive importance. Numerous experiments on dogs, systematically carried out, have shown us that when a definite quantity of bile, which varies for the different ferments, is added to pancreatic juice, it produces a constant and decided accentuation of the activity of its enzymes. The effect was most pronounced on the fat-splitting ferment, the action of which was increased two to three fold, less on the other two, which were only increased about twofold. Further, it was observed that this augmenting action showed adaptive variations dependent upon the nature of the food. The bile, indeed, proved itself to be a constant and powerful auxiliary of the pancreatic juice, a fluid which is of such importance for digestion and in itself already so complicated.

I am also able to bring forward another striking proof of the close relationship between the bile and the pancreatic juice. I pray you to examine the following curves in which the hourly rate of the secretion of pancreatic juice is compared with the entry of bile into the

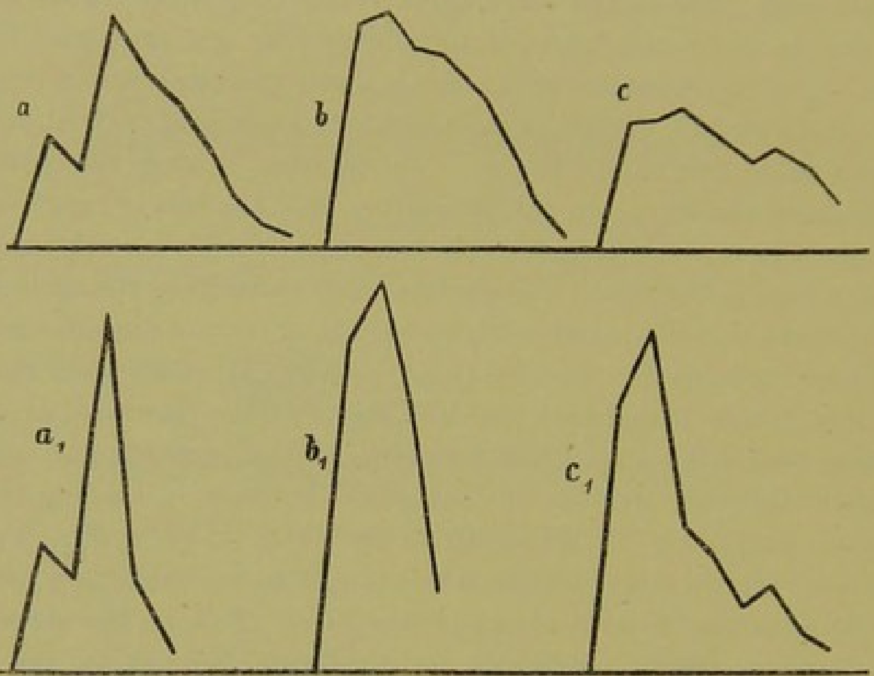

Fig. 19.—Curves representing in each case the hourly rate of pancreatic secretion (upper series) and the entry of bile into the intestine (lower series) ; a, a_1, after the ingestion of milk ; b, b_1, after flesh, and c, c_1, after bread. In comparing the curves, their general form only is to be taken into account. The scale of the ordinates was different in the different cases.

intestine under the same conditions of diet. Their similarity is most striking.

Is it not obvious that the two fluids have a reciprocal chemical relationship towards each other, and in consequence must act hand-in-hand? Their discharge at the same place into the intestines of many animals, or, as is often the case, their mixture beforehand in a common excretory duct, is not without a purpose.

The experiments dealing with the inhibitory action of bile on pepsin have also been repeated and confirmed by us. We have further determined the extent of this influence, using for our purpose pure gastric juice, and have come to the conclusion that it must have a definite physiological significance. When we link all these facts together we may with certainty conclude that the chief duty of the bile is to facilitate the transition from gastric to intestinal digestion. It arrests the action of the pepsin, which is injurious to the ferments of the pancreatic juice, and favours the ferments of the latter; in particular the fat-splitting ferment.

Still more indefinite and unsatisfactory than the teaching concerning the digestive functions of the bile, was, until recent times, that regarding the physiology of the succus entericus. Judging from extreme opinions, its existence was even doubtful, or at least all digestive influence was denied to it. It may, indeed, be authoritatively said that there is not a single point connected with the physiology of the succus entericus which has not at some time been contested. Only in one particular are all investigators agreed—namely, that the digestive action of the fluid is supposed to be very slight, almost of insignificant importance. It was only considered to have a weak solvent effect on starch, and an inverting action on sugar. But quite recently it has been the good fortune of our laboratory (*experiments of Dr. N. P. Schepowalnikow*) at one stroke, to elevate to a high position, the importance of the succus entericus as a digestive fluid—a fluid long known to physiologists, but for which they had discovered no precise use. This research was started with the same question which proved to be so fruitful in the case of the bile. Does not the succus entericus also function as a second adjuvant to the pancreatic juice? This seemed all the more likely, since closer investigation showed very strikingly that in the favouring influence of bile upon pancreatic juice, the fat-splitting ferment was much more powerfully aided than either of the other two. It was, therefore, not unlikely that the succus entericus would be found to actuate one or other of the remaining ferments, in a similar manner to the way in which the bile influenced the fat-splitting. Our anticipations have been fully confirmed by facts. The succus entericus undoubtedly possesses the striking capability of augmenting the activity of the pancreatic ferments, and more especially the proteolytic. In the case of the latter, the increase often reaches to an astonishing degree. He who has once convinced himself of this by experiment will never doubt for a moment that this accentuating influence is the most important function of the succus entericus. In view of the novelty and importance of our discovery, I think it necessary to demonstrate to you the fact itself. Upon a screen the shadows of two vessels are thrown, the one contains pure pancreatic juice, the other a mixture of pancreatic and intestinal juice. Pieces of fibrin of equal size are placed in the two vessels. Now while in the second, three pieces of fibrin, one after the other, have been fully digested before your eyes, in the first vessel the solution of fibrin has only just begun. The application of the usual tests for ferment action —namely, destruction by boiling, activity in very small quantities, and so on—convinced us that in this case we were dealing in point of fact with a ferment. We had, therefore, discovered a ferment, not for this or that constituent of the food, but a FERMENT OF OTHER FERMENTS. I propose to give it the name of *Enterokinase* to distinguish it from other possible ferments of a similar kind.

I may remark that the activity of the fat-splitting and amylolytic ferments of the pancreatic juice is promoted equally well, both by the secretion of the duodenum and by that of other portions of the small intestine. The proteid ferment, on the contrary, is most increased by the duodenal secretion. Our preliminary experiments therefore afforded ground for hoping that in the study of the chemical action of the three united fluids, namely, the pancreatic juice, the bile and the succus entericus, a wide field was open to us in which we could study the most subtle problems of adaptation on the part of these combined fluids to the substances undergoing digestion.

The secretion of the succus entericus seems also to follow laws of its own, in so far that it is a purely local secretion. A flow follows only in that segment of the alimentary canal which is immediately stimulated. This fact has obviously a rational significance. Since the food mass, especially in some cases, moves very slowly forwards along the digestive canal, a secretion of succus entericus would be unnecessary at a place where the food could only arrive some minutes or even some hours later.

Why the mechanical stimulus should here prove to be efficient, was a puzzling question which long troubled us. From cur previous experience the fact appeared quite extraordinary. Wherein lay the specific nature of the stimulus? A review of all the facts, of everything that we had learned in connection with the other secretions, taught us to steadfastly believe in this specific character, and the belief has not deceived us. Indeed, the two fundamental features of digestive activity, namely, adaptivity and response to a specific stimulus, stood out more prominently in connection with the succus entericus than with any other fluid. Thus, it was found (*experiments of Dr. Sawitsch*) that when a tube was introduced into the fistula, and the succus entericus afterwards collected in separate portions, the amount of kinase in the secretion became steadily less and less; obviously the tube excited a secretion mainly of water and not of kinase. For the latter, a specific stimulus had to be sought, and this stimulus was ultimately discovered in the ferment constituents of the pancreatic juice. When the secretion produced in an isolated loop of intestine under the stimulus of the cannula is studied for several consecutive hours, and when at length the juice contains little or no kinase, if now a few cubic centimetres of pancreatic juice be poured in and left for half an hour, a fluid will afterwards be secreted having much kinase. Boiled pancreatic juice has not this effect. I must further add that this peculiar physiological reaction to the ferments of the pancreatic juice (whether to one only, or to all of them, remains an open question) is extraordinarily sensitive. From the facts here communicated one must therefore conclude that in the case of the succus entericus, the secretion of the fluid part is more sharply separated from that of the ferment than anywhere else. With regard to the watery constituents, we may take it that every cannula which is introduced into the fistula, acts as a crude indigestible foreign body, and excites a secretion of water, merely with the object of being washed along the intestine. We have already learned of analogous phenomena in the case of the salivary glands. One may further assume that the severe diarrhœa which occurs in certain acute forms of enteritis results as a consequence of some powerful impulse to this water-secreting and cleansing function of the intestinal glands. The flow is here excited by the extreme irritation of the mechanical or chemically injurious contents of the bowel.

Hence the bile and the succus entericus have revealed themselves to be adjuvants of the pancreatic juice. And in their action the essential fact appears that their assistance is variable, being now greater and now less. What is the meaning of this assistance, and why is it so different and inconstant? It was long ago observed that pancreatic juice, secreted immediately after the formation of a fistula, often acts very weakly or not at all upon proteids. It was therefore conceivable that the operation might have caused some injury to the gland and have brought about an abnormal condition in it. But, as has already been related in the second lecture, Wassiljew and Jablonsky likewise saw a very weakly acting juice in normal animals, under the influence of certain diets. In this latter, there was obviously a purposive physiological relationship. It was remarked in the experiments of Schepowalinkow that the kinase worked all the more energetically the weaker in general was the pancreatic juice. It was therefore concluded, that the proteolytic ferment in these cases, for some reason or other, was secreted in the form of a zymogen. The experiments of Dr. Lintwarew, who started with this idea, have fully confirmed the hypothesis. A pancreatic juice, obtained from a temporary fistula in an "acute" experiment, only dissolved fibrin after four to six hours in the thermostat, and had not even attacked coagulated egg-white after ten hours. But on the addition of some succus entericus the fibrin was dissolved in three to seven minutes, and the coagulated egg-white in

Mett's tubes in from three and a half to six minutes. That is to say, the juice was an extremely active one. The same result was obtained with the juice which first flowed from a permanent fistula. Our interest in the normal variations of digestive power of the juice and in their possible dependence upon diet, therefore, became still greater, because in this way we hoped to be able to discover the meaning of the remarkable relationships in question. As a matter of fact, we found that, in dogs fed exclusively on flesh, the zymogen condition of the ferment almost wholly disappeared after a short time. The juice contained then only *trypsin*, and the succus entericus had no augmenting effect. Indeed, on the contrary, for some reason or other it often slightly diminished the proteolytic action of the fluid. With dogs, however, which were fed chiefly on starch and fat (bread, milk, and so on) the gland furnished a juice with a very weak initial effect upon proteids, the action of which was rendered very energetic by an addition of succus entericus. Obviously the zymogen stage of the ferment predominated here. Consequently, the appearance of the proteolytic ferment under different forms depends upon definite conditions. The idea at once occurred to us that, in the case of starchy and fatty foods, the proteid ferment is excreted in a latent form, with the object of protecting the amylolytic and fat-splitting ferments, which might possibly be injured by the other in its ripe and very active form. The experiments of E. A. Hanicke have, indeed, confirmed this. A juice, mainly containing zymogen, preserves the activity of its ferments even after several hours in the thermostat, while one which has been actuated by succus entericus, or contained trypsin to begin with, has its ferments, especially the amylolytic and fat-splitting, very easily destroyed. It is significant that such a protection of the ferments is chiefly required in the gland-lumen and along the passage to the digestive canal. In the bowel, however, where the proteid ferment is made active by the kinase, new conditions arise which protect the fat-splitting and starch ferments; namely, the presence of proteid food and of bile. This latter was proved also by the experiments of E. A. Hanicke.

It was further shown that the promoting effect of bile upon the fat-splitting ferment likewise depended on definite conditions of diet. The relationships of the amylolytic ferment were, however, less obvious in this respect. Additional experiments are also desirable, and indeed necessary, to investigate the fact that an antagonism was often observed between albumen on the one hand, and the actuating influences of the succus entericus and the bile on the other.

Thus, the newly discovered kinase soon found useful employment. But whether, under similar circumstances, the augmenting action of spleen extract upon infusions of the pancreas—first observed by Schiff, then more exactly investigated by Herzen, and still more recently confirmed by Pachon—has any significance, I am unable to say. I wish only to remark that the importance which is ascribed to it by Herzen, especially in his latest contributions, is without doubt exaggerated, and does not correspond with the facts of the case; for, as has already been shown by Dr. Popielsky with the aid of proteid in tubes, and by myself in the digestion of fibrin, the freshly collected pancreatic juice from animals previously deprived of their spleens (dogs and cats) contains large quantities of proteolytic ferment in the form of trypsin. My esteemed colleague, Herzen, who firmly believes the contrary, must, I think, be convinced of this when I say that the pancreatic juice of a splenectomised animal digested a quantity of fibrin in thirty to forty minutes at thermostat temperature, which filled a test-tube fifteen centimetres high and 1·5 centimetres in diameter. Naturally these new results concerning the interaction of the digestive juices compel us to repeat all our earlier experiments upon the quantitative production of the pancreatic ferments under different conditions.

Hence the chemical agencies of digestion form an alliance of a complicated nature in which the individual members are linked together mutually to relieve and support each other. The discovery of this relationship, and the possibility which it affords of a real synthetic construction of digestive processes, I would like to designate as the most important general result of the work of our laboratory. Might I at the same time venture to indicate that a method of procedure similar to that which underlies our own work, if employed in other departments of physiology, would probably be very applicable, and lead to fruitful results. It is only when we are able to bring into view the whole train of normal occurrences in this or that portion of the organism, that we can at once distinguish the accidental from the essential, the artificial from the natural; find out new facts, and quickly detect bygone errors. To constantly remember that all parts of the organisms work together sheds a bright light over the special field under review.

In our analysis of the curves of secretion of the different digestive juices, the question of the PROPULSION OF THE FOOD ALONG THE ALIMENTARY CANAL became more and more pressing. In order fully to understand the variations in the curves it is necessary to know where, in what amount, and in what condition, the food is to be found at any given moment. But what was the known physiology of the motor functions of the digestive canal able to do for us in this connection? How extensive is this section of physiology? How many methods have been employed in its investigation? How many nerves have been stimulated and how numerous the forms of stimuli employed? And yet this great mass of work could not in the smallest degree answer our question. It offered to us the analytical consideration of a long series of facts without any inner connection. But as to why the one kind of food is held back while the other is moved forwards, or why the one is moved quickly and the other slowly, there was no reply; and yet is not the complex food mixture somehow separated into its components during the onward movement? All these processes must, as a matter of fact, take place, because upon the food, which is a mixture of different substances, the various juices are poured out in different parts of the alimentary canal, and in varying combinations, both quantitatively and qualitatively. Why, therefore, and from what combination of separate elementary conditions is this propagation of the food effected, and with the purposiveness of a delicate and ingenious mechanism? The synthesis of the actual progress, and the mechanism of the movements, have been till recently as little brought under investigation as had the synthesis of the secretory work of the digestive apparatus. The credit of having begun this synthesis belongs to two German investigators (Hirsch and v. Mering), who simultaneously discovered that the passage of food from the stomach into the intestine is quantitatively regulated from the upper segment of the latter, in such a way that the expelling movements of the stomach are temporarily inhibited by a reflex from the duodenum, which closes the pylorus each time after a portion of the stomach contents has passed into the intestine. Our investigations have been carried on along the same lines, and have already yielded interesting results. In the first place, it was discovered (*experiments of Dr. A. S. Serdjukow*) that the duodenal mucous membrane, apart altogether from the fulness of the tube, regulates the passage of food from the stomach into the intestine by its behaviour towards the acid reaction of the gastric contents. When one continuously injects, through a duodenal fistula, either small quantities of acid solutions, or of pure gastric juice, a solution of soda which had previously been introduced into the stomach may be kept there for an unlimited time. If, however, no acid be injected into the duodenum, the solution of soda generally leaves the stomach very quickly. This cannot be accounted for by a reflex mechanically called into play, for if all the other conditions remain unaltered, and a solution of soda be poured into the duodenum, the escape of the solution from the stomach is not prevented. On the other hand, we have observed that the passage of acid solutions out of the stomach is remarkably slower in the case of dogs with a pancreatic fistula than in those without one. Each time that the intestine receives a portion of the acid contents of the stomach, a reflex act is set up which temporarily occludes the pyloric orifice and at the same time inhibits the propulsive movements of the organ. The acid food mass allowed through by the pylorus causes in turn an increased secretion of pancreatic juice, and is thus gradually neutralised. It is only when this has been achieved that the escape of a further portion of acid contents from the stomach is permitted. This regulatory action prevents disorder in the progress of digestion, and at the same time ensures regularity in the transition from the acid gastric digestion to the alkaline intestinal. If it were otherwise, and the acid contents of the stomach passed without control into the duodenum, the bile, on mixing with it, might arrest or greatly weaken the action of the pepsin, while the insufficient reduction of acidity would hinder the activity of the pancreatic ferments. The digestion of the food might thus, under certain circumstances, be completely arrested. But as matters stand this cannot happen. The injurious effect of pepsin upon intestinal digestion is arrested, while owing to the neutralisation of the food mass, together with the entry of those powerful excitants of the pancreatic juice, namely, the bile and the succus entericus, the ferments of the pancreas are afforded the opportunity of unfolding their activities in the most unrestrained manner.

Although, in the paper of Dr. Hirsch, clear and direct references are made to the fact that acid and alkaline fluids pass from the stomach into the duodenum at different rates, neither this author nor the other investigators who have worked at the subject (v. Mering and Marbaix) appreciated the nature of the acid reflex which regulates the passage of the food contents into the intestine. On the contrary, they misinterpreted it by thinking exclusively of a mechanical reflex discharged from the duodenum and acting upon the pyloric orifice of the stomach.

In other experiments (*Dr. P. O. Schirokich*), which dealt with the movements of the stomach itself, the following phenomenon was observed by us. In fasting animals, movements for emptying the stomach are from time to time discharged, probably as the result of a psychic impulse. If, now, without the animal perceiving it, neutral or alkaline solutions (*e.g.*, physiological saline, ½ per cent. solution of sodium bicarbonate, fluid egg-albumen, or milk) be poured through the fistula into the stomach, the fluids are all very rapidly—that is, in the course of a few minutes—largely passed on into the intestine. When, however, the stomach happened to be at rest to begin with, the fluids, introduced with the same precaution, remained several minutes in it without moving from the spot. These spontaneously occurring movements of the stomach can be repressed in a purely psychic manner, if the dog for instance, be greatly roused by the sight of food, or still better, if with an œsophagotomised animal a sham feeding be carried out. Consequently, when an ingestion of food is immediately to take place, or is actually happening, the evacuating movements of the stomach are arrested, clearly with the object of allowing the food to remain in the cavity and be worked up in a suitable manner. Thus milk lapped up by the dog, in contrast to that introduced unobserved through the fistula, does not pass at once into the duodenum, although evacuating movements may have been going on immediately before. The spontaneous movements also cease when acid fluids are poured into the stomach through the fistula, and this is a further confirmation of the relationship already mentioned. You see, gentlemen, that, in the study of stomach movements, and indeed at the very threshold of the subject, we have encountered the same characteristics which we saw in our earlier investigations—namely, the purposive nature of the phenomena and the intervention of psychical influences. I have one further remark to add, namely, that experiments of Dr. S Lintwarew have shown that fat also, when poured into the duodenum, regulates the emptying of the stomach in even a more striking manner.

In the foregoing I have given you a short summary of our later physiological experiments. I see quite well how much yet remains to be done. We are far from having the matter fully under control, but the next advances are clearly indicated, and we are justified in hoping that in the future our field of work will be even more accessible to investigation than in the past.

The animals employed in these researches, and which for the most part served for observation during many months or years, occasionally became ill, and sometimes the affected organ was that actually under investigation. At first such accidents annoyed us considerably, but it soon became evident that our discontent arose from an obvious misconception of the nature of the facts.

Why should a pathological condition of the digestive apparatus not appeal to us? What is a pathological condition? Is it not the effect produced upon the organism by the encountering of an unusual condition, or, more correctly said, an unusually intensified ordinary condition? Suppose one received a mechanical shock or became exposed to the effects of great cold or heat, or to the attack of pathogenic micro-organisms to a degree beyond the usual extent of these influences, a general struggle begins on the part of the organism against these agencies. The apparatus of defence is immediately called into play. This consists of parts of the body which, like the others, live within it, and share in the maintenance of the general equilibrium of the whole living organism. Consequently they are worthy objects for physiological investigation. But physiology learns of them only through illness; at other times their work is not to be seen. The struggle in question leads either to a repulse of the enemy, when the work of defence ceases, or it leads to a conquest by the enemy, which brings as a result the injury or destruction of this or that part of the body. But if an organ be destroyed, its function naturally ceases. Have we not therefore in this, a method which is quite commonly used in physiology for the investigation of the functions of a given organ, a method put into operation by nature with a delicacy which is quite unattainable by our crude technical measures? If the destruction be limited to a single organ, compensation for the loss of its function is gradually provided. A new condition of body equilibrium is established; other supplementary organs come into play. We learn in this way to recognise new and finer relations between the organs, and discover functions which were previously hidden. If, however, the injury be not limited to a single organ, but spreads still wider owing to the functional relationships between organs, we have again a method of recognising these relationships which, if followed up, may lead to the discovery of the cause, as well as the primary seat of action of the process by which continuity of function in the organism has been impaired.

Is not this from beginning to end true physiology, in which we seek to penetrate into the relationships between important parts of the body? Only an incurable scholastic could say that it is not part of our work. Nay more, it is precisely the physiologist who is most competent to decide upon the value of such investigation methods, and to logically apply them to the study of vital phenomena. The Physiologist is here, therefore, in his special field of research.

The experimental method indeed soon proved triumphant in our new field, namely, the Experimental Pathology of Digestion. Although only two workers in the laboratory have given special attention to it, I am already able to communicate some data which, it appears to me, are calculated to excite the interest of the whole clinical world. These at present apply only to the pathology of the gastric glands.

The method of isolating a gastric *cul-de-sac*, already known to the members of this society, has again proved to be of inestimable assistance in pathological investigations. It not only permits all the details of the diseased condition of the glands to be laid bare, but is invaluable in the analysis of the pathological condition. When pathogenic agencies (such as great heat or cold, various strong chemical reagents, &c.) were caused to act on the surface of the miniature stomach, the deviations of the activity of the gastric glands from the normal could be observed in an ideal manner. Every drop of the altered secretion of the mucous membrane could be collected. Every detail of the pathological condition, even the most minute, could be seen. The diseased state could be observed day by day or hour by hour from the very beginning to the end, while everything pursued its usual course in other portions of the digestive canal, without the intervention of complications of any kind, either from consecutive trouble in neighbouring parts of the digestive apparatus or from disturbances of general nutrition. The latter are excluded, since the miniature stomach takes no part in the general work of digestion. It acts upon no food, and no stimulus takes origin in it which reacts either on the large stomach or on the intestine, since it is always empty. An exception is, however, to be made of the short interval when the unusual stimulus, the pathogenic influence, operates on the walls of the small cavity. This might reflexly affect the remaining parts of the digestive canal. But in these experiments we are almost wholly concerned with a study of the pathological conditions of the peptic glands themselves, that is, of their cells. When, however, the large stomach is acted upon by noxious agencies, we are able on the one hand to see the reflex effects in the small cavity as well as to observe the disturbance provoked by a general disorder of digestive activity on the other. In this way it is possible to separately investigate the diseases of the reflex transmitting part of the surface of the stomach, as well as those of the glandular layer.

Our results were as follows: When powerfully acting substances, such as absolute alcohol, a 0·2 per cent. sublimate solution, a 10 per cent. solution of nitrate of silver, or a strong emulsion of oil of mustard, were introduced for a few minutes into the small stomach, they produced a more or less considerable, indeed, in many cases an enormous secretion of mucus. (*Experiments of Dr. J. C. Sawriew.*) One might think this was a serious pathological condition, an acute mucous catarrh. Is it, however, a condition of disease? In extreme cases, more than one hundred times the normal amount of mucus was secreted by the irritated surface. At times, only mucus instead of juice was obtained during the whole period of secretion, and yet I ask again, is it a morbid state? Often, after the lapse of an hour or two, the more or less copious secretion of mucus, which immediately appeared upon the application of the irritating substance, had wholly exhausted itself; or an enormous flow of mucus, which on the day of the experiment had completely suppressed the normal secretion of gastric juice, may, on the next day, to one's utter astonishment, have disappeared without leaving a trace behind. The contrast between the intensity of the phenomenon and its short duration is really striking. One cannot resist the idea that in the cases described no morbid condition had as yet been established, but rather that the pathogenic influences had been successfully battled with and conquered before our eyes. Has not the true physiological function of the surface epithelium of the stomach been here revealed—a function of which we could form no adequate conception in the normal course of affairs? By virtue of its wonderful power of secretion, a large quantity of mucous fluid is poured out which dilutes the noxious substance, or forms chemical combinations with it, and drives it away at the same time from the stomach wall. The surface epithelium thus wards off the danger which threatens the more important elements of the mucous membrane beneath.

That this explanation is correct is also shown by the fact that the peptic glands remain absolutely at rest, in striking contrast to the extreme activity of the surface epithelium.

The chemical substances mentioned stimulate therefore the one kind of epithelium only, leaving the other unaffected. A similar differentiation of stimulating effect we have already seen in the case of flesh, which when brought into the stomach excites only the cells of the peptic glands, leaving those of the surface quiescent. We have here before us, it appears to me, an unusually weighty fact—namely, that extraordinary stimuli which come in as pathogenic agencies, are at the same time specific excitants of the protective mechanisms of the organism —namely, of those forms of apparatus which are adapted to overcome the disease producing effects. I believe that this applies to all diseases, and that it gives a general indication of the adaptive mechanisms of the animal body, by which it is enabled to encounter pathogenic influences. Indeed, the intricate progress of normal life, with all its power of adaptation, is dependent upon the specific excitability of this or that apparatus.

Naturally the effects of the substances named, when of a certain strength, may also extend to the deeper layers of the mucous membrane, notwithstanding the energetic protection of the epithelium. We then see an altered form of activity in the peptic glands, which in its details may vary greatly, according to the nature of the causal condition, but which for the most part assumes a phasic character. In this way we succeeded in establishing different pathological conditions of the peptic glands, and, at the same time, furnished a rich contribution to the physiological characteristics of the gland cells. We have already a considerable store of remarkable observations, but I wish only to call your attention to the following. By the application of a 10 per cent. solution of nitrate of silver we have been able to produce a condition of *asthenia*, that is, of irritable debility of the peptic glands. (*Experiments of Dr. J. C. Sawriew.*) In the following two columns are given the hourly quantities of juice, secreted by the isolated miniature stomach, before and during the pathological condition experimentally provoked. The animal was fed each time on the same quantity (150 grms.) of flesh:

Normal secretion.	Pathological secretion.
6·5 c.c.	8·4 c.c.
5·3 "	3·5 "
4·3 "	2·5 "
4·4 "	1·2 "
2·8 "	0·0 "
4·4 "	—
Total 24·7 "	Total 15·6 "

You see, therefore, that in the diseased state the secretion assumed quite an unusual and special character. The quantity for the first hour markedly exceeded the normal; but in the second hour, an exceptionally steep decline to abnormally low values, set in. This continued in the third hour, and at length the secretion stopped prematurely, after much less than the normal amount of juice had been produced. The gland-cells had become more excitable than before, but at the same time they were extremely easily fatigued. The significance of this condition of the cell is at once clear. Obviously such a state is not merely a special result of the nitrate of silver, but must also appear under other conditions, and represents, therefore, a typical form of depressed cell activity. We may confidently anticipate that a knowledge of this condition will influence both the methods of clinical investigation, as well as the therapeutics of such diseases. So far as I know, this interesting fact has been first established by experiment in my laboratory, notwithstanding the infinity of cases where it might previously have been observed in the clinic. It is a striking confirmation of the fact that, in the analysis of morbid phenomena, clinical observation has to contend with much greater difficulties than is the case with experimental investigation in the laboratory.

Recently it has also been demonstrated (*experiments of Dr. Kasanski*), that exactly the opposite condition of the glands can be set up. This is seen in the following table, where the normal secretion is compared with that during the pathological state:

Hour.	Normal secretion.		Pathological secretion.
1st . . .	11·6 c.c.	...	6·2 c.c.
2nd . . .	8·4 "	...	11·6 "
3rd . . .	3·5 "	...	10·8 "
4th . . .	1·9 "	...	5·6 "
5th . . .	1·3 "	...	3·6 "
	Total 26·7 "		Total 37·8 "

The condition was produced by the application of intense cold. In it the gland-cell has become much more inert, more difficult to set in motion, and more tardy in its action when it begins, but once set going, it does more work than under normal conditions for the same amount of stimulation. We have, therefore, in all probability, two typical conditions of the living substances when thrown out of equilibrium—namely, an unstable and an inert.

It happened that in one of our dogs a ROUND ULCER formed in the gastric *cul-de-sac*, which steadily increased in size, gave rise from time to time to violent bleeding, and finally, after perforation of the stomach-wall, produced a secondary peritonitis. (*Observations and Experiments of Dr. A. N. Wolkowitsch.*) During the development of the ulcer, a continuous and increasing hypersecretion was observed, the flow finally exceeding the normal by three to four times. Of much greater interest, however, than this hypersecretion was the fact that a sharply pronounced deviation from the ordinary hourly rate of flow, appeared. This was especially marked after feeding with bread, as was first pointed out by Dr. P. P. Chigin. The normal secretion after bread is characterised by a copious flow during the first hour, then a great fall in the second to, as a rule, about half the former value. As in previous instances a further analysis revealed that two different periods of secretion were here sharply separated from each other, namely, a period of free psychic and centrally excited flow, and one of much weaker chemically excited secretion, brought about by reflex action. In our dog with the round ulcer the secretion of the first hour departed in no way from the normal, but in the second it remained at its previous height, instead of dropping to about one-half. In the succeeding hours also, the secretion was considerably greater than normal. The following are the figures in question :

Normal secretion.	Pathological secretion.
26·2 c.c.	26·2 c.c.
13·0 „	26·6 „
13·0 „	15·8 „

How is this deviation from the ordinary progress of secretion to be explained ? The following appears to me to be the most correct view. Since the centrally excited secretion of the first hour is normal, it shows that the glands, the centrifugal nerves, and the corresponding nerve centres are all in normal condition. Further, when an increased secretion in the second hour is observed, and we know that this secretion is a reflex one, it must be taken to prove that the augmented excitability of the secretory apparatus at this stage, has originated either in the centripetal nerves or in their nerve endings. Here, then, in all probability, is the special point of attack of the disorder; a matter which, so far as I know, has not hitherto been discovered or defined in the clinical investigation of the disease.

In the accidental illnesses of our experiment-animals we have frequently observed an augmented or a diminished activity of the digestive glands when contrasted with the normal. It has often occurred to us that these opposite conditions represented different phases of one and the same affection. Which of them, however, is to be regarded as the primary and which the secondary? Our experiments, in which diseased conditions of the large or small stomach were experimentally provoked, have shown with great regularity that the first reaction of the peptic glands to a powerful and unusual influence consists in a marked depression of their activity, lasting for several hours or even days. This depression is of a reflex nature. It is due to the influence of the inhibitory nervous system which is thrown into activity by the more than ordinary degree of stimulation. When one, for instance, pours ice-cold water, or a solution of nitrate of silver, into the large stomach (*experiments of Dr. J. C. Soborow*), the secretion which is subsequently produced by an ordinary meal is less than normal, more especially in the first hours. This happens not only in the large cavity but also in the small, the walls of which latter at no time come into direct contact with the injurious substance. The thought suggests itself that, as soon as the stomach encounters an unaccustomed stimulus, the activity of the peptic glands is at once inhibited by means of a special reflex, whose object is to protect the deeply lying cells still further against harmful influence. The only exception to this, is observed after the action of strong alcohol. When alcohol is poured into the large stomach, an extremely free secretion of gastric juice begins from the small cavity. Conversely, by acting on the latter, the alcohol is also able to set up an abundant secretion in the large. (*Experiments of Dr. J. C. Sawriew.*)

Further, in the disorders of the large stomach, which we several times produced, we have often distinctly observed that the isolated miniature organ, which here represents a healthy part of the large stomach manifested a striking compensatory activity. (*Experiments of Dr. J. C. Soborow.*) As soon as a diminution of secretion below the normal appeared in the large stomach an increase was seen in the small. On one occasion, especially when, by the application of very hot water, we had completely arrested the work of the large stomach, for several days, an enormous activity gradually developed in the small cavity, which finally produced as much secretion as the large did normally, at least for some kinds of food. As a general rule, the size of the small stomach, judging by the amount of secretion under normal circumstances, was about one-tenth of the large.

Hence in the above case, its secretory activity was increased tenfold. Conversely, when the work of the glands in the large stomach was augmented, the activity of those in the small organ became diminished. Thus, in certain pathological conditions of the large stomach, the small organ inversely reflects the activity of the large.

The relationship between the secretions of the large and small stomachs, under normal or pathological conditions of either, may be determined in different ways. In the case of fasting animals, if the fistula tube of the large stomach be opened, a secretion, which can be measured, may be excited in both stomachs by offering the animal food. Or, again, with the fistula tube open, flesh chopped up in small pieces, or, still better, in the form of mince-meat, may be given to eat for a certain length of time. Any of the food which does not of itself drop out at the fistula may be removed by washing, and then the juice from both stomachs collected. Occasionally, also, in the third or fourth hour of normal digestion, we opened the fistula of the large stomach, allowed the contents to escape, then washed out the interior, and compared the secretions from both cavities, which, in such cases, continues for some time. Or lastly, towards the end of the digestion we often found, on opening the fistula, that the large stomach was free from food while the secretion from both the large and small still continued. A comparison of the quantities of juice, then, gave, at once, the secretory relationships of the two stomachs.

The astonishing capabilities of the organs for vicarious activity drove us irresistibly to an analysis of the purely physiological problem —namely, of the mechanism by which these compensatory events are brought about. But I should like to indicate a certain importance which is, I think, to be ascribed to the facts of experimental pathology just communicated. It appears to me that, by investigations such as these, the conditions of disease are better differentiated, the physiological defensive arrangements more sharply defined from the purely pathological, while the pathological state itself is subdivided into phases, and accurately localised. I am firmly convinced that further endeavours along such lines will lead to still more important results, and that we shall in the end arrive at a knowledge of the processes of disease in the alimentary canal, as accurate and complete as that which we now possess of its admirably beautiful work under normal conditions.

Are we, as experimenters, however, to rest satisfied with this? I think not. When we see a deviation from the normal, and have grasped the mechanism of its causation, we naturally wish to come back and compare it with the normal. It is only by so doing that the final proof of our physiological knowledge being complete, can be furnished, and of our having mastered, in point of fact, the whole problem under investigation. Thus the necessity for an EXPERIMENTAL THERAPEUTICS spontaneously arises, disregarding for the moment its practical aims. The subject itself affords a new and fruitful method for the study of living events, since it presents the phenomena of life, which it is our duty to investigate, from a new side, and often reveals to us gaps in our physiological knowledge. The following example may explain my meaning. A mechanic only lays aside the study of a machine when he is able to take the parts asunder and put them back again in their original places. Physiology should be able to do much the same. No one can say that he fully comprehends the physiology of an organ till he is able to restore its disordered function to a normal state. Hence, experimental therapeutics is essentially a test of physiology.

I should wish, however, to avoid a misunderstanding. What I have said now about experimental therapeutics, and previously about pathology, is by no means new. It is only an expression of the prevailing opinion of medical science. Undoubtedly, the great honour of having, by the experimental method, united in reality the whole of medicine, is due to modern bacteriology. This science is at one and the same time physiology, pathology, and therapeutics. It proceeds from beginning to end along experimental lines. Bacteriology, the youngest and most vigorous branch of the series, is the only one which has developed to the natural and full extent of its own inherent capacity, unfettered by the traditional settings and mouldings which constituted, for the older investigators, lines of separation between the different fields of work.

Our own investigations in experimental therapeutics, to which I now proceed, are for the present not very important. But we may, I think, cherish a well-grounded hope of expanding this method of research in the future to an extent commensurate with the results of our investigations in physiology and experimental pathology. It is natural that upon our first entry into the new field we should allow ourselves to be guided by the experience of clinical therapeutics, but I am convinced that our new therapeutics will soon grow to be an independent source of experimental physiological and pathological knowledge. Then, the experimental therapeutics, born of the laboratory, supported by scientific knowledge, and in every way self-competent, will be able to give valuable indications to the clinician.

As the first example of our therapeutics, may I bring before you the treatment and care of the dogs in which the vagi nerves were divided in the neck. In these animals, from the sudden cutting-out of its most important secretory and motor nerve, almost every trace of digestive action on the part of the stomach disappears during the earlier periods. The ingested food soon undergoes decomposition, and this in its turn makes matters worse. But if each time, before the feeding, the normal psychic excitant of the gastric glands (which is now absent) be replaced by a chemical stimulant, and the stomach be freed, by systematic washing out, from the remnants of the previous meal, the difficulties are soon overcome, and a tolerably good condition restored. I should like here to transgress the narrower bounds of my subject, and once more expressly state,* that the question of the survival of dogs after vagotomy, which has been for so long a matter of uncertainty, has at length been answered in the affirmative by physiology, and this result is solely to be ascribed to the fact that the causes of the disturbances which set in after the operation, have been submitted to an exhaustive physiological analysis. In this, we have a striking instance of a rational therapy, founded upon laboratory knowledge, directed against a severe and fatal lesion of the organism, produced also, it is true, in the laboratory. Thus, if a gastric fistula be made in the dog, and its digestion regulated as above indicated (the cavities of the mouth and stomach having been severed by means of an œsophagotomy so as to prevent the gastric contents from passing along the gullet into the lungs, should vomiting occur), a double vagotomy in the neck ceases to have a fatal effect. Indeed, the operation is consistent with long life and an excellent condition of health. (*Experiments of Prof. J. P. Pawlow and Dr. P. E. Katschkowski.*)

We may return once more to digestion. In a series of dogs with well-marked hypersecretion, arising from spontaneous illness, or set up intentionally, we have used alkalies (a ½ per cent. solution of sodium bicarbonate) by way of treatment. The result was that we had the satisfaction of seeing the mode of action of alkalies, which I explained five years ago to this esteemed assembly, fully confirmed. It is one differing greatly from the current belief, which still holds sway in the clinic, with regard to the effect of these substances. In all the cases observed by us (*Prof. J. P. Pawlow* and *Dr. J. C. Soborow*) the hypersecretion proved to be readily amenable to the influence of alkalies. It diminished markedly, and the greatly exalted excitability of the glands was fully and permanently set aside.

It is to be observed that, with the experimental establishment of asthenia of the gastric glands, the indications for a rational employment of alkalies have been still further accentuated. In the irritable debility of the cell—that is to say, in the state of increased excitability which soon leads to exhaustion—alkalies, with their inhibitory effects, are more than ordinarily suitable. But naturally the mechanism of the alkali influence has still to be physiologically analysed.

* The author had already made several communications dealing with these investigations.

We have already taken up the question of how the individual kinds of food act upon the condition of hypersecretion (*Dr. Soborow*). These experiments are now being carefully pushed forward.

Judging from the material to hand, this condition of the gastric glands is readily amenable to treatment. The chief difficulty will, however, lie in effectively combating the different forms of hyposecretion.

We have further endeavoured to come to the aid of an enfeebled condition of activity of the gastric glands by supplying favourable conditions for the preparation of the juice. One of these favouring circumstances we discovered in the introduction of large quantities of water into the system. (*Experiments of Dr. Sawriew.*) We based this upon earlier facts (*experiments of Prof. J. P. Pawlow*), showing that the quantity of juice was strikingly dependent upon the amount of water in the organism. It is clear that the formation of juice by the glands consists largely in this, that the secretory cells attract water from the blood. In certain circumstances the blood opposes a considerable resistance to this abstraction. If sufficient water be not present, the cells could not withdraw an adequate quantity for the preparation of the juice. Hence we are able to assist a weakly acting cell, which only abstracts the water with difficulty, by intentionally diluting the blood with an excess of water, which the organism instead of holding back will, on the contrary, endeavour to expel. Our experiments have confirmed this hypothesis, but they are not as yet concluded.

Let us now turn to MEDICINE. It cannot be denied that biological processes are exceedingly complex when contrasted with other phenomena of nature, and that the difficulty of establishing a causal relationship which would give us control over them is very great. Nevertheless, it was ordained by the inevitable dispensations of life that medicine should hold sway over biological phenomena, and, indeed, long before they had become matters of scientific investigation.

And medicine has, at least to a considerable degree, accomplished that which was expected of her. Her task seemed endlessly large and hopelessly complex, but yet it is, at least in part, accomplished. She has fortunately arrived at many correct solutions of the problems which confronted her, notwithstanding the countless numbers of other possible ones. This unexpected result has only been made possible by the co-operation of two conditions. These are, that mankind from the earliest times constantly and passionately strove after the maintenance of life and health; and, secondly, that in this search after health numerous individuals—indeed, I might say all mankind—took part. But if the present achievements of medicine seem remarkable, it cannot be doubted that they are only very small in comparison with what she must ultimately accomplish. These future advances, however, will not be attained by merely calling in the results of increased knowledge in different branches of natural science, to assist in her diagnostic and therapeutic measures. So long as medicine devotes herself to practice only, she will never attain complete success, for, from the nature of the conditions, she is limited in the majority of cases to one implement of natural investigation, namely, *observation;* while the other implement, *experiment,* dare only be employed by her with great precaution, and within relatively narrow limits. Observation is a method, however, which only suffices for the investigation of simpler phenomena. The more complicated these become—and what is more complex than life—the more necessary is experiment. It is only by experiment, the development of which knows no other limits than the inventiveness of the human brain, that the crowning work of medicine can be achieved. Observation, for instance, encounters a number of individual phenomena in the animal organism which proceed together, and between which there is in one case an essential, in another only an indirect and accidental connection. The true character of this connection can only be guessed at by the observing investigator: he has to choose between a number of possible hypotheses. Experiment, on the contrary, grapples with the problem, the solution of which is sought for. It permits now one condition, now another, to come into play, and learns in this way, by artificial but simplified combinations, what the real connection of the phenomena is. In other words, observation collects what is offered to it by nature; experiment wrests from nature what it will. The power of biological research is immense. It has created in the short space of seventy to eighty years almost the whole of what must be described as the very comprehensive subject of the *organ* physiology of the animal body. If an educated man, not otherwise closely acquainted with biological science, should attend an ordinary, carefully conducted course of demonstrations in animal physiology, such as is at least read of by the medical student, he must certainly be astounded at the sovereign power with which modern physiology holds sway over the complicated animal organism. And his astonishment will further increase when he learns that this power has been acquired not in thousands or hundreds of years, but in a few decades.

And now we see the method of experiment extend its influence not only into the subject of pathology, but also into that of therapeutics. There is no reason why this influence should become less. It appears to me that the most remarkable advance of modern medicine consists in this, that the possibility is opened up of extending experimental investigation into all its important branches. This revolution has, again, for the most part been accomplished by bacteriology. Although for some time before the development of the latter subject, pathology was brought into the laboratory, yet the working up of the material was greatly restricted for want of knowledge of so important a factor in disease as micro-organisms. It was only after the discovery of pathogenic microbes that the experimenter had the whole field of pathological physiology opened up to him. One is now able to investigate almost every pathological phenomenon in the laboratory.

While clinical medicine has clearly distinguished the different types of diseases, and has given an almost perfect morphology of pathological conditions, and while macroscopic and microscopic anatomy in association with clinical investigation have, in recent times, collected an enormous amount of material concerning the finer processes of disease, and, indeed, still continue to do so, yet the possibility of a complete analysis of the whole course of a disease from its inception to its cure—that is, of a thorough knowledge of all the processes of a disease—was first attained by the method of experiment. Pathological anatomy provides too crude an instrument for this, and clinical observation without experiment is powerless in face of the complexity of the phenomena. It is laboratory experiment alone that is capable of unravelling in the organism the whole problem of disease, and of exactly differentiating the reparative from the compensatory events, the protective phenomena from the lesion itself. It is only by such experience that the interweaving of these latter can be detected, that it can be proved where the primary injury lies, and where the secondary which it has called forth. It is by such knowledge alone that appropriate and effective assistance can be rendered to the diseased organism. Then, and then only, will our interference be followed by no evil results, but on the contrary always bring help.

Again, it is only by experiment that we can ultimately discover the real cause of a disease and estimate its importance, since in it we always begin with a causal factor which is intentionally set to work. It is precisely here that the power of clinical medicine is least. Etiology, as is well known, is the weakest branch of medicine. As a matter of fact, the cause usually steals in, and begins to work in the organism before the patient becomes an object of medical care. But the recognition of the origin of disease is one of the most essential problems of medicine. For in the first place, one can only fight the etiological factor, with a proper knowledge of what is to be aimed at, when the cause is known. On the other hand, it is only under these conditions, and this is still more important, that one can forestall the cause of disease, and render it harmless before it has penetrated into the organism. It is only when the full etiology of disease is known that the medicine of our day can become the medicine of the future—that is to say, HYGIENE in its widest sense.

In view of the obvious justice and importance of these considerations, one cannot pass on without expressing a regret that pathology has not yet, or at least not everywhere, taken its proper place as an experimental science, namely, as pathological physiology. In the ordinary programme of academic instruction, it usually appears, either as an appendix of pathological anatomy, or is lost in the subject of general pathology. But the methods of pathological anatomy and of experimental pathology are too different to be combined under one representative, and in one laboratory, at least in a way that will afford justice to each, more especially if academic teaching be added to the duties. On the other hand, it appears to me that in the training to which we at present give the name of general pathology, the place of honour must be assigned to experimental pathology, to an experimental analysis of the phenomena of disease, and not to conclusions and abstractions drawn from special pathology, which often only amount to another grouping of its materials. No very important scientific advantage is likely to accrue from a purely theoretical treatment of general pathology at a time when the field of pathological investigation is becoming more and more dependent upon the laboratory, and when its thorough exploration promises to be so fruitful and so engrossing.

One can readily conceive himself in the difficult position of the physician who, in his measures against this or that disease, or in his use of this or that remedy against a given symptom, often does not know what the remedy in reality effects in the organism, or how it aids in a given case. How insecure and indefinite must his interposition often be, how much room for all sorts of chance occurrences! Hence, the endeavours of the clinician to grasp the mode of action of his remedies are easily to be understood. It was for this reason that therapeutics several years ago called in the method of experiment to its aid. Therapeutic measures were given over to laboratory investigation, and there their effects on the healthy organism were to be analysed. At first, chemical medicaments were experimented with, and from this experimental pharmacology sprang up.

The pharmacologists have, however, bit by bit deviated from their original goal, and now interest themselves but little, if at all, in the *healing* action of a given substance. Pharmacology has thus, by a natural process of development, grown to be a section of physiology. It investigates the action of chemical agencies on the animal body, and pursues its special theoretical aims. Against this in itself no objection can be raised. The connection, however, between the materials of pharmacology and the aims of practical medicine has thereby been damaged. For in spite of the fact that this connection formed an essential factor in the original working plan of pharmacology, and even still finds expression in the name of the science, yet in many cases it has grown to be very lax and purely nominal. Thus in the ordinary text-book, after the author has dealt with the physiological action of this or that remedy, the indications and contra-indications to its therapeutic applications are then related without any connection with the previously discussed physiological action. It is in consequence of this that many physicians are so little satisfied with modern pharmacology. In the mutual interests of both the experimenter and the practical physician, pharmacology should be completed by an experimental *therapeutics*. Then it will deal not alone with the healthy, but also with the diseased animal body. It will then study not alone the action in general, of the different remedies, but also their healing influence on the diseased organism. It will then in its own interests expand and deepen our knowledge of the reaction of the organism to chemical agencies, and, at the same time, our knowledge also of the organism itself. In the interests of the practical physician, it will, likewise make clear the real importance and mode of action of a therapeutic remedy. The necessity of studying the effect of such remedies on diseased animals has long been recognised, and corresponding requests have already been uttered. But an essential barrier to the fulfilment of these requests, lay in the difficulty of procuring the necessary diseased animals in the laboratory. This difficulty is now, in a large measure, overcome, thanks to the advances of experimental pathology. Indeed, it is only when pharmacology is blended with experimental therapeutics, as above indicated, that much therapeutic delusion will pass into long merited oblivion. On the other hand, the regrettable possibility will be avoided, of many remedies being undeservedly thrown aside solely because their pharmacological analysis, by experiments on healthy animals, has not been set about, or perhaps could not be set about, in the right way, simply because the animals were healthy. In the teaching plan of experimental therapeutics the experimental investigation of other remedial measures than the mere administration of chemically active substances, should also find a place. At present, in the comprehensive programme of medical teaching, they obtain no proper recognition.

One may hope, not without reason, that we are to witness an enormous awakening of the interest of investigators as soon as other pathological processes, not merely the bacteriological, are subjected in the laboratory to a bold and constantly controllable therapeutics, unfettered by extraneous considerations. Nay more, we may be convinced that the experimenter may reckon on not a few triumphs the moment he sets aside the exclusive point of view of the would-be expert, and takes upon himself the initiative of therapeutic treatment. Many have hoped to bring pharmacology and medicine more together by recommending and bringing about the establishment of clinical departments in pharmacological institutes. But it appears to me that laboratories for the study of experimental therapeutics would have had more scientific justification, and more prospect of a practical result, than special pharmacological clinics. It matters not what the clinic is called, the sick person in it can be made just as little the subject of experiment as elsewhere. Further, special clinical pharmacology would have no superiority in a systematic and competent handling of therapeutic remedies, since this competence is sought after by every clinical teacher. Thus without any special good to the science itself, either the experimenter will be lost in the clinician, or the clinician in the experimenter. A lasting and stable combination of these separate activities is scarcely to be achieved in practice.

And now for our conclusions: It is only when medicine is able to stand the crucial test of experiment that it can become what it should be, namely, in its whole extent a conscious and purposively acting medical art. We have an example in proof of this in modern surgery. On what are its brilliant results founded? Simply on its perfect knowledge of how to achieve its aims. Aided by the plasticity of the organism, and secured by asepsis and antisepsis against its arch enemy the micro-organism, it can now treat its subject from the purely mechanical standpoint, guided by a knowledge of the anatomical structure and physiological importance of the several parts of the body.

With unfeigned interest I now stop to ask myself in how far I have succeeded in convincing you of the extreme importance for practical medicine of the method of experiment, and in stimulating you to real activity? If I have succeeded at all, it is your duty to forward in every way the interests of biological experiment, not only by personally taking part in it to the fullest extent possible, but also by actively supporting experimenters in their efforts, because in the interests of biological, and also of medical science, suitable men, suitable conditions, and suitable means are necessary.

Do not forget, gentlemen, the following important difference between the representatives of clinical and of experimental medicine: The scientific representatives of practical medicine are drawn from the whole mass of practising physicians. Every physician who has the mind, the talent, and the energy, can take part in general scientific medical work, and ultimately become an important and ceaseless worker in this field. Experimenters, on the other hand, form an inappreciably small number of devotees, since it is only within the narrow range of the laboratory that they can be recruited. Because of this, it is your duty, both in the scientific institute, as well as in life generally, to encourage the beginners of laboratory work, since specialisation in the laboratory affords them, afterwards, many better chances in life.

It is known that clinicians, therapeutists, and surgeons in many cases turn to the fruitful method of experiment, whether it be to analyse a pathological process, to make clear the mode of action of a therapeutic measure, or to test a proposed surgical procedure. Such endeavours naturally are to be hailed with pleasure. The clinicians, even more than the physiologists, feel the necessity at the present time of working out the problems in the laboratory which they encounter in the hospital, whether they be of a pathological or therapeutic nature. Consequently, in by far the greater number of instances the initiative to investigations of an experimental pathological or experimental therapeutic nature at present proceeds from clinicians. This is to their great credit, and will ever remain so. Nevertheless, with the clinician, this kind of work has always to take a second place; it fills the leisure hours which his first duty, the care of the sick, leaves to him. Work in the laboratory, however, demands a full surrender; requires that the worker shall devote his whole energies to it. Hence, I maintain that our special departments of experimental pathology and experimental therapeutics (for, considered from a broad standpoint, they are in methods and conception nothing else than branches of physiology) should be given the most favourable conditions and the most independent position possible. In the curriculum of medical science there should everywhere be three chairs given to experimental physiology—one to normal, one to pathological, and one to therapeutic physiology.

And now to turn away from the fostering care required by science. Every human being will welcome the founding and erection of institutes of all kinds devoted to the care of the sick, whether they spring from private or public initiative. These institutes are, on the one hand, places for benevolent activity, for in them the sick, that is to say, persons who, in the struggle for existence, have encountered greater or less injury—persons sacrificed to the general conditions of life—are taken care of. On the other hand, these institutes are fields of work for people who in life are truly called upon to bear an excessive burden; to solve problems which are as yet insoluble. Gentlemen, I am making no misuse of my words, I have in mind *life* with all its great powers of adaptation, life as it concerns the majority of mankind; and this, after all, is what must engage our attention. Think of one who mentally grasps the unfathomable depths of his problem, and in his heart nurses a bitter feeling of impotence. Give him everything within your power and it will not be too much.

Moreover, gentlemen, our beautiful hospital buildings are only tributes which we pay to human misery and infirmity. All the more, therefore, should that in which mankind beholds its dignity and pride be likewise deserving of palaces, where the power of man and his strength of mind may be enlarged. Such palaces have been built by the great cultured nations. Thus, for instance, in Germany the scientific laboratories, especially the physiological, vie with each other in the splendour of their design and equipment. Unfortunately, of our laboratories, the same cannot by any means be said, with the one well-known exception, of the Institute for Experimental Medicine, which owes its existence to the lofty ideas and enlightened benevolence of Prince Alexander of Oldenburg. In many other scientific institutes a great want of accommodation makes itself felt, which is in striking contrast to the extraordinary growth of the problems biological experiment has to solve. For, in addition to a series of special rooms for the several experiments, a number of sufficiently large and suitably furnished compartments are now unavoidably necessary for the different animals under experiment. I have at present, in the laboratory of the Institute for Experimental Medicine, up to thirty dogs on which the physiology of digestion has been or is being studied, and which must be so kept that their state of health leaves nothing to be desired. Hardly any one would be so bold as to say that these animals have not been employed to good purpose, or that so great a number is not necessary. It is in fact the number of animals which has given security to our results, for in case of the least doubt or suspicion the laboratory can repeat and control its earlier observations. On the other hand, a large number of experiment animals favours the starting and solution of new problems. But these animals have been necessary solely for the study of physiological problems. How many more will be required for investigations in experimental pathology and therapeutics, where the events to be observed stretch out over months or years? That a fruitful field is open in the prolonged observation of experiment animals, I am convinced from various occasional observations during the last few years. I had by no means the intention at first to set up conditions of disease; I operated solely for physiological purposes, and kept my animals alive for months or years. How many and how profound pathological processes have, under these circumstances, come into existence before my eyes! I have seen, in connection with a disturbance of the functions of the liver, an enormous ascites develop; at another time an ascending paralysis of the central nervous system; or, again, a general lacerability of the blood vessels, and so on.

Biological experiment, to come back to it, requires therefore, institutes, which will cost hundreds of thousands of roubles. With us, however, this form of experiment has often met with the most bitter hostility. Private individuals and authorities give willingly to the building of new hospitals or clinics. But the needs and wishes of experimenters are mostly repulsed. They can neither find, nor reckon upon sympathy with their objects. Experiments on animals are often depicted in the most malicious way as animal torture. The underlying lofty idea is obscured, and the regrettable but unavoidable outward presentment is seized hold of. Investigators themselves, who pass their whole time in the laboratory, and have no regular intercourse with the outside world, cannot influence the opinion of the public with regard to experiments and experimenters. It is your duty, gentlemen—I appeal to the medical men in my audience—to assist us here. You move about every day amongst society, and come into contact with its highest and lowest grades. You are linked with it by the most intimate relationships. You take an active part in the greatest joys, and the keenest sorrows of mankind. Should you wish to speak in defence of our science, which serves the life and health of mankind, your words will be listened to. Therefore, it lies with you to spread the conviction amongst the public, that experiments upon animals are unavoidably necessary for the advancement of medicine, and of the greatest conceivable importance to it. You must make it understood that the greater the perfection attained by means of experiments upon animals, the more certainly will patients be cured, and the less frequently will they have to submit to trials between this and that remedy, with possibly serious consequences. Take, for example, the following instance. If more had been known by experiment upon animals concerning extirpation of the thyroid body, the early unhappy results of its removal from patients suffering from goitre, would not have occurred. There resulted, as you know, an incurable condition of cretinism. Make it manifest, there fore, to the public that modern medicine has passed the stage of the gruesome experiment upon man himself.

It is well known that medicine in its choice of therapeutic remedies, has drawn largely upon the experience acquired by their popular application. But this experience was gained at the expense of a great sacrifice of mankind. This can be judged of by instances, which even now are by no means uncommon, when, for example, in an out-of-the-way village, and, unfortunately, it is not confined to out-of-the-way villages, the patient succumbs to the revolting torture of uncalled-for attempts at healing on the part of some quack. And yet does not nature and religion tell us that animals are provided for the service of mankind, not, of course, to be unnecessarily or uselessly sacrificed?

But when large and specially fitted up apartments are required for experiments, these are naturally performed not only in the interests of science but also for the purposes of instruction. In this respect we are far behind our Western neighbours. The income of the only physiological laboratory in Russia—namely, that of the Institute for Experimental Medicine, exceeds by three-and-a-half times, the income of the physiological laboratory of such a colossal medical institute as the Military Medical Academy of St. Petersburg. But it only approaches the average for the corresponding institutes of the German Universities. How is it possible therefore, under present requirements, for an experimental chair to develop a tolerably extensive scientific and teaching activity, upon an income of a thousand roubles. Further, the parsimony is just as great in the *personnel* of the laboratory. For example, the physiological laboratory of the Military Medical Academy, has only one assistant. How can a department with so small a staff teach the students a course of practical physiology? And yet a direct acquaintance with the materials of physiology, and a schooling in physiological thought, is of the utmost importance for the physician of the future. Elsewhere, for example in England, such practical exercises are carried out on a large scale, and in the laboratories costly apparatus, for example, recording drums, &c., are provided in large numbers for the use of the students. With us, experimental research and experimental teaching must take comfort in the hope of better things.

Once more let it be repeated: The final triumph of medicine can only be achieved by laboratory experiment. With this conviction I venture to predict that in any given country, and in any given medical institute, whether it be devoted to scientific purposes or to teaching, the progress of medicine will go hand in hand with the care and attention paid to its experimental departments.

To-day I have set forth the work of our laboratory, its fundamental idea, and my own views with regard to the relationship of experiment to medicine, under the ægis of a great name, the name of the clinician whose memory we celebrate. Had I a right to do this? I should not have done so had I not been convinced of that right. I have had the honour of being associated, during the course of ten years, with the work of the departed clinician, so far as it concerned his laboratory. Ten other years have now fled since the death of S. P. Botkin, and yet his memory lives with us all. If anybody, it was the clinician who was thrown into astonishment by his rare gift of recognising a disease, and of finding the best remedy for it. His personality possessed for the patient a really magic power; a word from him, or even the mere fact of his visit often had an effect. How frequently have I heard the confession from his clinical pupils, that the same prescription which had worked wonders in the hands of the master, had remained without effect in theirs, in apparently identical cases. One might, perhaps, suppose that the celebrated clinician would have been satisfied both inwardly and outwardly with such results. But his deeper understanding, unalloyed by these triumphs, always sought in the laboratory, by the aid of experiment upon animals, the key to the great puzzle; "What is a sick man and how is he to be helped?" Before my own eyes he has directed many of his pupils to the laboratory. And this great appreciation of the method of experiment on the part of a clinician, in my opinion, does no less honour to the name of S. P. Botkin than his clinical activity, which is known to all Russia.

With this I close my lectures, gentlemen. Much of what has here been communicated will no doubt be welcome to the practical physician. He will often find in our physiological facts an explanation of pathological phenomena, and by a knowledge of the true state of affairs will be led to the employment of effective remedial measures. Physicians would, however, secure to themselves further advantage, if they imparted to the physiologists in what way the explanations, in their opinion, may need adjustment; and also if they further pointed out new phenomena in the subject of digestion which have cropped up in the broad world of clinical observation, but which have not yet entered the field of cognisance of the physiologist. My belief extends to this: That it is only by an active interchange of opinion, between the physiologist and the physician, that the common goal of physiological science and of medical art will be most quickly and securely reached.

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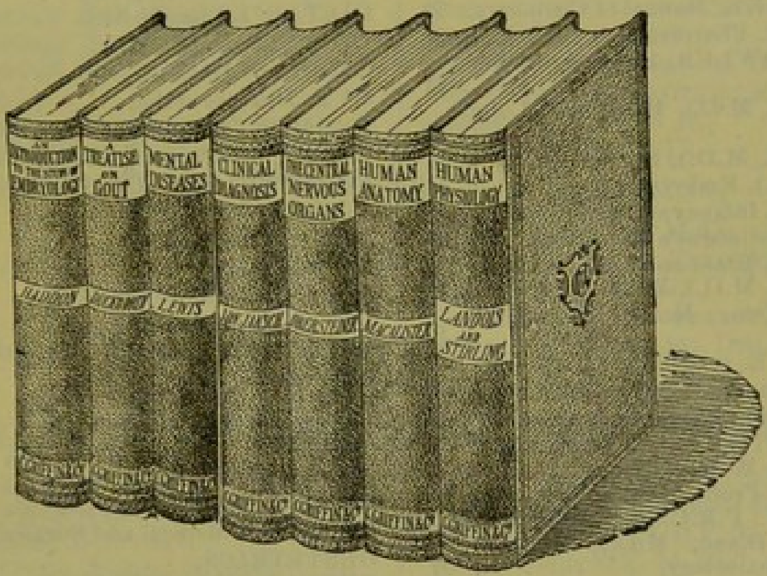

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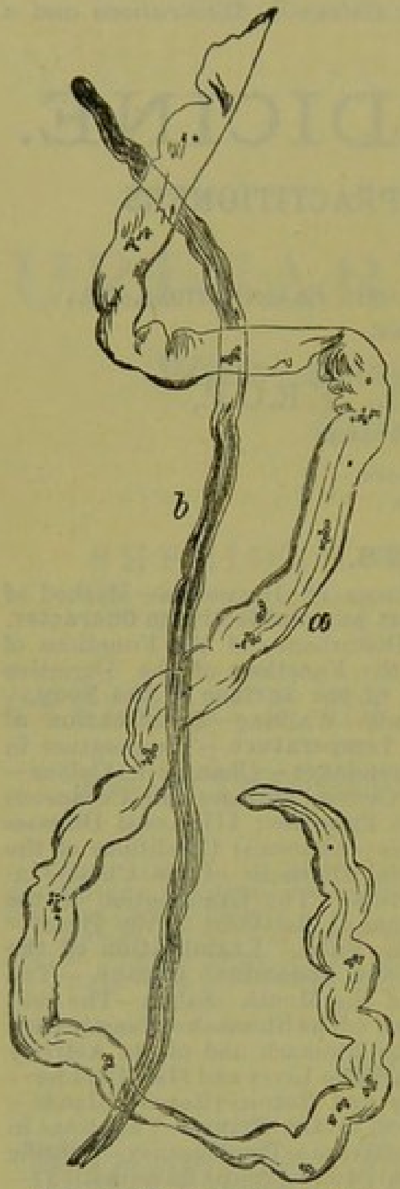

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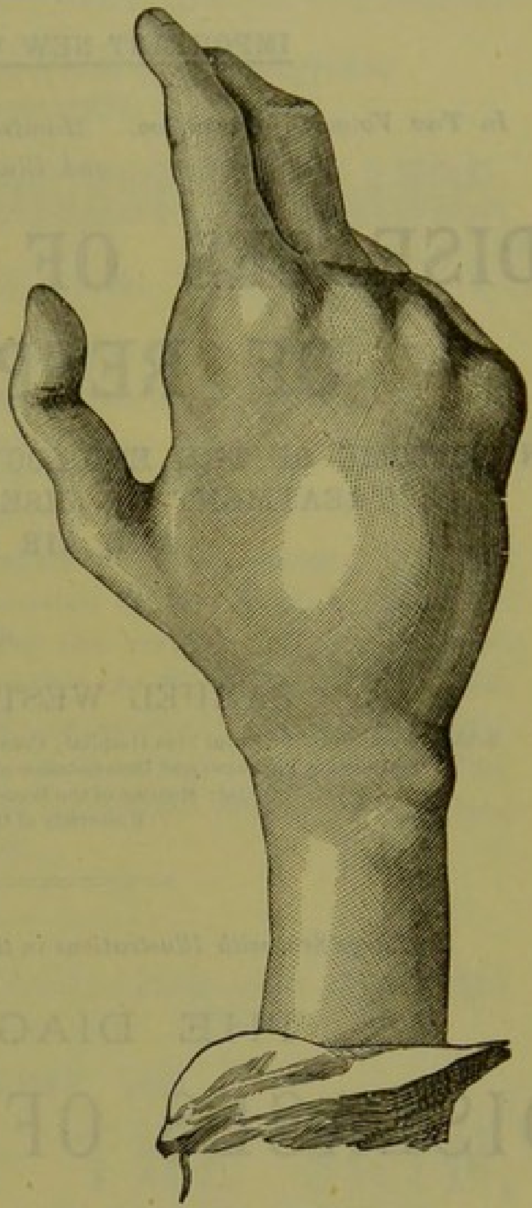

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