[SOLE AUTHORISED ENGLISH TRANSLATION]

THE WORK OF THE DIGESTIVE GLANDS

Lectures by

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SECOND ENGLISH EDITION

ILLUSTRATED

LONDON

CHARLES GRIFFIN & COMPANY, LIMITED

EXETER STREET, STRAND

1910

Printed by BALLANTYNE & Co. LIMITED
Tavistock St., Covent Garden, London

TO

THE MEMORY OF HIS FRIEND,

THE TALENTED PHYSICIAN

NIKOLAÏ PETROVICH BOGOIAVLENSKII

THE AUTHOR DEDICATES THIS WORK

PREFACE TO THE SECOND ENGLISH EDITION

IN preparing a second English edition of the WORK OF THE DIGESTIVE GLANDS the translator (with the permission of the author) has endeavoured to bring the subject-matter up to date without materially enlarging the scope of the work. The additions are chiefly culled from the results of investigations carried out along lines already indicated in the previous edition, by pupils or former pupils of the St. Petersburg Laboratory. With the exception of Lecture IV.—which is largely new and written from material supplied by Professor Pavlov—they are widely scattered throughout the book.

Two new chapters (X. and XI.) on the Muscular Movements of the Alimentary Canal have also been added by the translator. It is hoped they will increase the usefulness of the work. For the sake of uniformity they have been put in lecture form. Several new illustrations have been added, and grateful acknowledgments are made to Professor Starling and to Dr. Arthur Hertz for their permission to use certain of these as well as for the loan of some of the electrotypes employed in them.

One other change has been made in this edition. English equivalents of Russian proper names have been used for the most part throughout.

THE TRANSLATOR

SCHOOL OF PHYSIOLOGY,
TRINITY COLLEGE, DUBLIN.
June 1910

PREFACE TO THE ENGLISH EDITION

THE great importance of the results obtained by Professor Pavlov, 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 Pavlov 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

SCHOOL OF PHYSIOLOGY,
TRINITY COLLEGE, DUBLIN.
September 1, 1902

PREFACE [illegible]

The great importance [illegible]
first published in [illegible]
was soon [illegible]
over. [illegible]
in German and [illegible]

But the [illegible]
To place the [illegible]
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figures.

It is to be hoped, [illegible]
will be worthy of its distinguished [illegible]

School of [illegible]
Trinity College, Dublin.
[illegible]

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 dealing 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 investigator. 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 investigator. It is of essential advantage to the reader to see how a uniform guiding principle has developed, and taken shape in the form of consistent and harmonious 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 taken part individually; but it is a joint work, the result of the principle,

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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, is not by any means what has heretofore been represented in text-books, and consequently exists in the mind of the physician. A desire, therefore, to replace the older teaching by a fuller and more correct representation naturally arose. 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. But in the short space of one hour I could only give a general survey of the work of many years, and was unable to verify my statements by documentary references. In my present lectures I hope to make good these deficiencies and to be able to convince my hearers by the relation of actual experiments. The substance of the lectures is taken from work which for the most part has already appeared in print. But many unpublished facts possessed by the laboratory will also be referred to.

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

The digestive canal, from the chief function which it has to perform in the living organism, may be compared to a chemical factory, where the raw materials—the food-stuffs—are submitted to an essentially chemical process. In this factory the foods are 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. The factory consists of a series of compartments, in each of which the food, according to its properties, is either retained for a time or at once sent on to the next; and each single compartment is provided with suitable reagents. These reagents are either prepared in adjoining little workshops, burrowed into the walls of the laboratory itself, or else in distant and separate organs, connected, as in other large chemical factories, with the main workshop 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 product, endowed with definite chemical properties which enable it to act on certain portions of the food, this latter being ordinarily formed of a complex mixture of different ingredients. These properties are chiefly contributed by special substances in the reagents, the so-called ferments. The separate fluids, the digestive juices, as they are usually termed, attack in some cases only a single ingredient of the food, in others several. These latter combine the properties of several distinct 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 enzyme, it holds other substances 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 both singly as well as jointly when all are present together. Indeed, it is mainly upon knowledge so acquired that the teaching of the science with regard to the elaboration of the food, or, as we say, of its digestion, is based.

But our conception of the digestive process, which is essentially deductive, suffers from many and serious defects. Considerable divergence undoubtedly exists between the knowledge acquired in the above way and the physiological reality or even the empirical teaching of dietetics. Many questions remain to be decided, 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, combined with different reagents, in other juices? Are all the constituents of a particular fluid simultaneously poured out on the food, and does this happen indiscriminately 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 simply concern the composition of the fluid as a whole, or are the separate constituents altered 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 ingredient may require a special reagent the activity of which may interfere with that of other reagents on the remaining ingredients ? No one can deny that these questions are manifestly appropriate.

The mechanism of digestion can no longer be presented in the abstract manner current in recent physiological teaching. The differences and complexity of the reagents indicate that the work of the digestive canal in every single case is elaborately planned, beautifully executed, and above all especially adapted to the task in hand. 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 cannot, therefore, be a matter of surprise 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 fully to grasp his subject, include within the sphere of his observation the 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 a simpler nature.

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 digestive juices.

It is often said, and not without truth, that science advances by stages dependent upon the results accruing from particular methods. With each advance in technique we reach a higher level from which a wider field of view 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. It was necessary to know how the reagents were poured out upon the food brought into the 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, and also in *accurately measurable quantities*. Lastly, it was necessary that the *digestive canal should perform its functions normally*, and that the *animal under experiment should be in perfect health.*

It is but natural that these difficult problems have only been gradually solved by physiology, that not a little trouble has been spent in vain, and that numerous investigators have seen their efforts fruitless, in spite of the fact that many of the most distinguished physiologists have devoted their attention to this field.

We begin with a consideration of the pancreas, which presents a simple case. It may seem that here our problem is very light. Apparently we have 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 the fluid a free outflow 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 notwithstanding that digestion may be in active progress when the operation is begun, there is, as a rule, no flow of pancreatic juice from the tube, or if there be, 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 becomes evident that the gland is a very sensitive organ, and suffers such severe disturbance from the unavoidable conditions of the operation (narcotisation, opening of the abdominal cavity), that in the majority of instances not a trace of normal secretory action remains. This procedure is known under the name of the "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 after some time, when the disturbing influence of the operation had fully passed away. The fluid was therefore allowed to escape freely from the excretory ducts for a considerable time. This was

* Later investigations by Starling and others indicate that the absence of pancreatic secretion in the acute experiment is mainly due to the lack of an appropriate stimulus, and if this be supplied, a secretion is readily called forth. See Lecture vii., pp. 136, 137.

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 (*Ludwig's School*) in similar manner. These were named "permanent" fistulæ. Both modifications proved effective, but only for short periods, generally from three to five days, in exceptional instances for as long as nine days. After this 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 merely temporary fistulæ. But this was not the 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 changes 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 by which the duct could be kept open for any desired 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 is as follows: it differs slightly from Heidenhain's. From the wall of the duodenum, a piece, containing the orifice of the pancreatic duct, is cut out (Fig. 1), the bowel then stitched up, its lumen not being appreciably narrowed, and the isolated piece of intestine (with the mucous membrane outwards) sewn 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. The following are some of the details of the procedure. The incision in the abdominal wall is made either in the *linea alba* or at the outer edge of the right rectus muscle. It is 4–5 cm. long and begins above at the ensiform cartilage or margin of the ribs, as the case may be. The duodenum is sought out, brought to the surface and laid over towards the right side, so as to better expose the situation of the pancreatic duct. This latter is found 1½–2 cm. above the place where the vertical and lateral parts of the pancreas join. The duct is often concealed behind a blood-vessel, which must be ligatured and divided. It is sometimes difficult to find, in which case Mankovski recommends that a small vertical slit be made into the bowel on the

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

side away from the pancreas, and the orifice sought from the inside. When the duct is found, the gland immediately around it is separated from the duodenum and two grooved directors passed behind the latter (see Fig. 1). A rhomboidal piece, containing the orifice in its centre, is now cut out of the duodenal wall and transplanted into the skin wound. Previous to closure of the latter, two strong ligatures are passed behind the duodenum $1\frac{1}{2}$–2 cm. from the situation of the duct. These threads are brought through the abdominal wall at the wound and serve to retain the duodenum in position, thereby guarding against the tearing away of the duct orifice. They are removed next day. After two weeks the animals 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 collected either directly as it falls in drops from the mucous papilla, or by means of a funnel with its wide end upwards, if there be a tendency for the juice to flow along the abdominal wall. The two disadvantages which beset the investigators who employed "temporary" or "permanent" fistulæ are in this way avoided. The gland undoubtedly remains in a normal condition, but the difficulties of the experimenter are by no means ended. In a very short time the abdominal wall becomes eroded by the escaping juice, and even fairly large bleeding patches appear in places. These continuously irritate the animal and prevent the collection of pure juice by means of the funnel. What is to be done? Many things help—*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 to us 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 was seen: once more a portion of the wall was damaged. At the same time we noticed that the dog's abdomen was dry and the appearances of cutaneous irritation considerably reduced. We now realised the meaning of the circumstances. A bed of sand was in consequence prepared for the animal, after which the wall was no longer damaged, and the flow of juice gave no further trouble. We (Dr. Kuvschinski and I) acknowledged with gratitude that the intelligence of the animal had helped us as well as itself. It would be a pity if this fact bearing upon the psychology of the dog were lost. We thus overcame another difficulty, but our final goal was not yet attained.

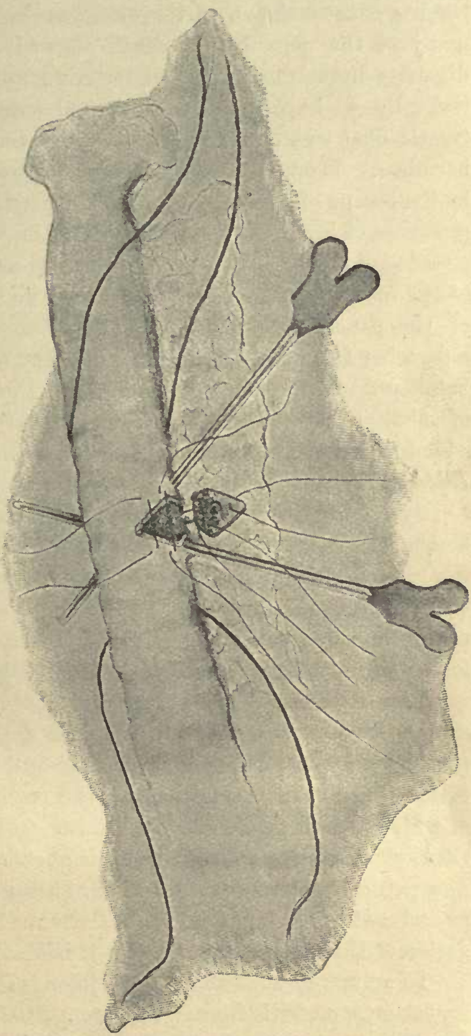


FIG. 1.—Method of making a Pancreatic Fistula.

Three to four weeks after the operation, the animals, previously to all appearance well, 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 we had here a peculiar form of ailment. Inanition was not the cause, for the animals often died with almost normal body-weight. The possibility of a septic post-operative illness, such as an insidious peritonitis, had also to be abandoned, since neither the condition of the animals before death nor the appearances *post mortem* afforded ground for such belief. Finally, the existence of an auto-intoxication due to the absorption of intermediate or abnormal products of digestion, such as Dr. Agrikolianski in his Dissertation has suggested might have arisen from the loss of so much pancreatic juice, was also excluded. In the first place, many of the dogs before death showed absolutely no symptoms of digestive disturbances; neither vomiting, nor diarrhœa, nor constipation. Secondly, we have found from special experiments, in which the pancreatic duct was ligatured and divided, that this operation is perfectly harmless. There remained only one supposition, viz., that the animals, by the escape of 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. Vasiliev) 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 keep animals for many months, or even years, in a fit condition for observation without the necessity of adopting any other special precautions. The difficulties encountered in the management of individual 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, the loss of which is so harmful to the organism, still remains 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 question, but as yet it has not been completed.

To return to our subject: the juice is collected by means of a glass or, better, a metallic funnel, so fastened to the abdomen by means of an elastic band or thin elastic tube brought round the body of the animal that its wide end receives the orifice of the pancreatic duct. Hooks are attached to the neck of the funnel, from which a graduated cylinder hangs, the animal being supported in its frame. These arrangements are very convenient for the observer, but at first less comfortable for the animal. for the dog quickly tires and becomes restless. Nevertheless, it soon learns to sleep excellently, even under such circumstances, especially if it be made more comfortable by providing a support for the head. When first used in the laboratory it is, however, better to collect the juice from the dogs in the lying posture. It is then 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 peculiar nature.

The solution of our problem is evidently not an ideal one. It would be in the highest degree desirable to possess a method which would permit us either to collect the juice from a portion of the gland only, or simply when desired during the experiments, allowing it to return to the intestine during the intervals. In either of these ways 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. The first object was attained in the dog, the pancreas of which has two ducts, by laying a fistula into the smaller instead of the larger. The fact that the bile-duct opens into the duodenum in common with the smaller duct introduces no appreciable difficulty. In cutting out the rhomboidal piece of bowel wall, the bile-duct is divided, but as the tube courses for a considerable distance through the wall, a new orifice can be provided by simply slitting through the overlying mucous membrane and coat of the duct at a slightly higher level than its old entry. In the single case in which this procedure was carried out, the quantity of juice obtained was very small and very irregular. Another method of achieving the same result was proposed by Dr. Sanotskii and carried out in my laboratory. A fistula was laid into the large pancreatic duct, and the portion of gland feeding it separated off by a transverse incision 1 cm. above the situation of the duct. To promote healing and prevent union with the remainder of the gland, the detached portion was stitched up in a fold of peritoneum. In this operation there is no difficulty in preserving the large vessels and nerves of the gland uninjured. They run longitudinally almost outside the gland, between it and the duodenum. The results obtained were fairly satisfactory, but the method cannot rank as one fully worked out.

A method which aimed at achieving the second object has been published by the Italian investigator Foderà * and theoretically

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

approximates to a perfectly faultless one. He succeeded in getting a special T-shaped metallic cannula to heal into the duct, so that at will, the juice could be either collected exteriorly 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 method, moreover, has not hitherto been adopted by other investigators.

Recently an improvement in the making of the permanent fistula has been introduced by Dr. Babkin, which appears to solve the difficulties successfully.

It has been shown by Delezenne and Frouin that the mucous membrane surrounding the fistular orifice retains the power of transforming the inactive trypsinogen of the pancreatic juice into the active trypsin, by virtue of the kinase which it secretes. Hence in order to obtain the juice in the inactive condition in which it is produced by the gland, it is necessary to remove the small oval piece of mucous membrane (usually 8 mm. by 12 mm.) from around the orifice of the fistula after the wound has healed. This is done by careful dissection, and the sides of the duct fastened to the edges of the new wound by four small sutures. When this latter wound heals a small cutaneous scar is produced, which constricts the orifice of the duct, so that ultimately little or no juice escapes at ordinary times. When an observation has to be made, a small cannula can, however, be introduced, and the fluid readily obtained in pure condition. The abdominal wall keeps normal, because the juice is inactive, and also because little or none flows out except during the observation. The method is apparently lacking in only one particular, namely, that during the observation, digestion has to be carried on with very little assistance from the pancreatic juice.

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 gastric fistula. In the year 1842, the idea occurred to one of our countrymen, Professor Bassov,* 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 the recovery of the patient, a permanent opening remained in the abdominal wall

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

† *Traité Analytique de la Digestion.* 1843.

which led directly into the stomach. An opening through the abdominal wall of a dog into its stomach was accordingly made, and a metal tube fastened in, which was closed exteriorly by a cork stopper. The tube healed firmly into the opening, and could be kept 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 moreover very difficult to obtain any idea of the rate of flow during digestion, or of the properties of the juice under different conditions. Voices were, therefore, loud in denunciation of the gastric fistula; it had justified none of the hopes, and had proved of little value.

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

In the year 1889, we (myself and Madam Schumova Simanovskaia) 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 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 several hundred cubic centimetres of gastric juice. In the next lecture I hope to explain why the gastric juice flows under such conditions, and what importance for the whole process 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 apparent injury to its health; that is to say, you can procure gastric juice from a dog almost as milk is obtained from a cow.

For experiments with pepsin we need no longer prepare an infusion of mucous membrane, since enormous quantities of the purest juice can now be obtained with much greater ease and rapidity from the living animal. The dog supplies us with 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. Konovalov, with solutions of commercial pepsin, and with natural gastric juice, as obtained from our dogs, showed that the latter was incomparably superior. 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 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 obviate 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. For several years past we have exported considerable quantities of the pure sterilised juice to foreign countries, where it is employed as a therapeutic remedy as well as a reagent for laboratory purposes.

I now come back to our methods. The problem of how to obtain pure gastric juice has been settled, but the method does not afford us the means of observing the rate of 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. What was quite simple in the case of the pancreas (where the gland duct is separate from the alimentary canal and its food contents) becomes, in the case of the stomach, a task of the greatest difficulty, since its glands are microscopic and are embedded in the walls around the food cavity.

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*, the open end of which he sewed into the abdominal wound. The idea was employed by Klemensievicz * 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, a little later succeeded in keeping an animal alive. He ‡ also isolated a portion of the cardiac end of the stomach, and formed it into a pouch which poured its secretion externally.

In this way the above requirements were fulfilled. When the food in the ordinary way reached the main stomach, 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 done, 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 in view we (myself and Dr. Khizhin) 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 portion, is carried in the longitudinal direction for ten to twelve centimetres, almost parallel to the long axis of the viscus, and divides both the anterior and posterior walls. A triangular flap is thus formed, the apex of which lies in the great curvature of the stomach. A second incision is made from the inside exactly at the base of this flap, but only through the mucous membrane, the muscular and peritoneal coats remaining intact. Thus the serous and muscular coats, and consequently the branches of the vagus nerve, pass uninjured from the wall of the main stomach into the flap of which the main pouch is to be formed (see Figs. 2 and 3). The technical points to be observed in the operation are as follows: The incision in the *linea alba* reaches from the ensiform cartilage downwards for 7–9 cm. Before opening the stomach the cavity is closed off at either end by bands of sterilised india-rubber tubing, tied tightly round the organ. The first incision at the outset is carried only through serous and muscular coats. It is important that its two limbs—one on the anterior, the other on the posterior wall—should be symmetrical to the attachment of the great omentum, otherwise a good pouch cannot be formed. At the bottom of

* *Sitzungsberichte der Wiener Akademie.* 1875.
† Heidenhain : Pflüger's *Archiv.* Bd. xviii. ‡ *Ib.* Bd. xix.

the incision is seen the outside of the mucous membrane, with the blood-vessels running transversely in the submucosa. These are to be double-ligatured and divided, to avoid subsequent bleeding. At first only a minute aperture is to be made in the mucous membrane to allow of disinfection of the interior, which is best done by injecting sterilised 0·5 per cent. hydrochloric acid. When thoroughly cleansed the mucous membrane is divided along both sides of the flap. An apparently difficult part of the operation, the division of the mucous membrane at the base of the flap, is in reality easily carried out. In the first place, with quick light strokes of a sharp knife a superficial incision is made across the whole base of the flap. While making this the assistant precedes the operator, lifting up the mucous membrane with a pair of forceps on either side and holding it tense. A gauze tampon is now laid along the track for two to three minutes, to arrest bleeding. Then the operator goes over the incision with the knife once more, dividing the submucosa down to the muscular coat. In doing this the assistant keeps the tissue tense as before, by holding the edges of the wound apart with the forceps. By this latter procedure a sufficient margin of mucous membrane is freed on either side of the line of incision to allow both flaps to be formed into cup-shaped depressions, as shown in Fig. 3, and applied back to back, so as to make a double septum of mucous membrane which separates the cavity of the pouch from that of the main stomach. When the submucosa is divided as described, a gauze tampon is once more laid along the incision to arrest bleeding, and, after a little, raised gradually to allow the larger bleeding vessels to be ligatured. To convert the flaps of mucous membrane into dome-shaped recesses, sutures are inserted, as shown in the illustration. These must never pierce the mucous membrane. On the one side they pass through the margin of serous and muscular coats, on the other through submucous tissue only. It is desirable to mark the apex and middle of the base of the flap on either side by a Péan's forceps. Beginning at both bases, the mucous membrane is then united along each margin by four or five sutures to its own adjacent piece of muscular coat. After this the incision in the stomach wall is closed in its whole extent, along both large and small cavities, by a line of Lembert sutures. The orifice of the pouch is to be reduced to the diameter of an ordinary lead pencil, otherwise prolapse of the mucous membrane inevitably occurs. After some practice the whole can be completed in one and a half to two hours.

Soon after the operation symptoms are frequently observed which may give rise to unnecessary anxiety, namely, quickness of the pulse, refusal of food, attempts at vomiting, sometimes paresis. They appear most markedly after the first feeding, and may be distinguished from similar symptoms due to peritonitis by their inconstant character. These symptoms may be best avoided by fixing the small stomach to the large by a pair of sutures, or even the large to the abdominal wall.

In spite of every precaution a prolapse of mucous membrane sometimes occurs, in which case it will be necessary to resect the mouth of the pouch and reduce its size by removing a narrow triangular flap of membrane. In obstinate cases it may be necessary to fix the small to the large stomach, or even provide it with a new opening in the abdominal wall.

It was only by forming the mucous membrane of the flap into a cupola, or, still better, that on the stomach side also, that we were able

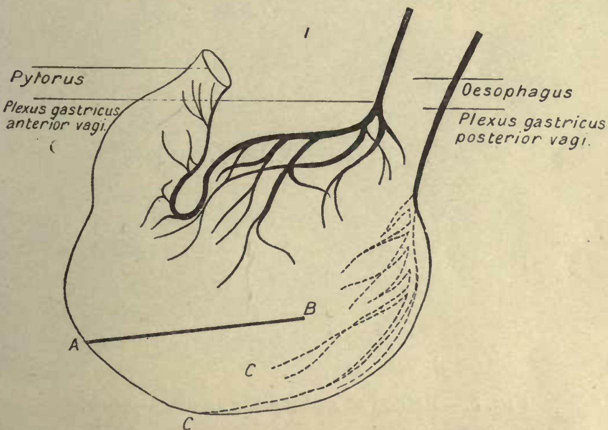


FIG. 2.—*A.-B.* Line of incision. *C.* Flap for forming stomach pouch of Pavlov.

to retain a dog with a permanent and closed pouch for any length of time. If the two layers of mucous membrane were sewn in the middle line a communication formed after a shorter or longer time between the stomach and the *cul-de-sac.* The animal was then useless for our purposes. 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. To make the description clearer, I give here illustrations of the operation borrowed from the work of Dr. Khizhin (Figs. 2 and 4), also one (Fig. 3) from my article on the physiological surgery of the alimentary canal (*Ergeb. d. Physiologie*, I. i. p. 259).

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 for 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 uninjured, since they course between the serous and muscular layers of the flap. 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

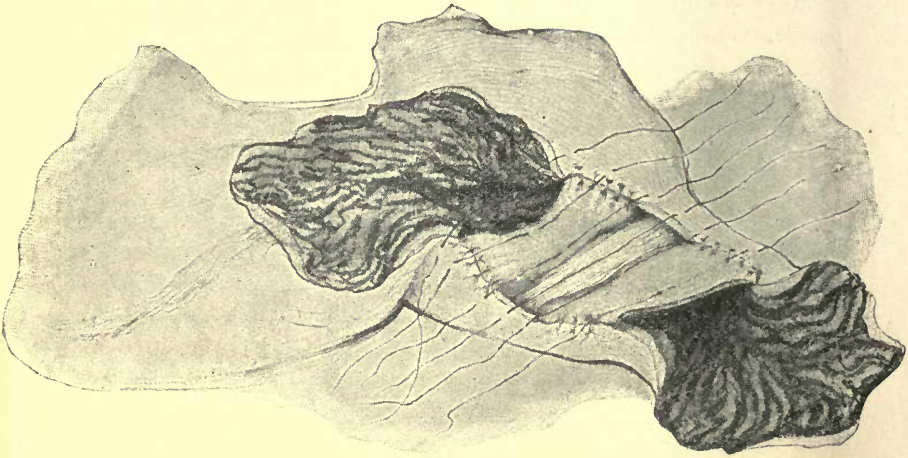


FIG. 3.—Method of making the stomach-pouch.

the former remains empty. A full answer to this question I shall reserve for a later lecture, when we shall be in possession of more material. At present I 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 have been compared both as regards conditions of work and properties of secretions, which leave no room for doubt that we may with perfect safety rely upon the stomach-pouch as a means of studying the functions of the normal organ. In our next lecture the miniature stomach will prove itself to be an instructive object worthy of earnest attention.

As has already been related, Dr. Fremont 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 such dogs we can hardly reckon upon normal conditions of secretion during ordinary digestion, 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 me that our combination of the ordinary fistula with œsophagotomy possesses important advantages over Dr. Fremont's procedure. Our method is incomparably simpler,

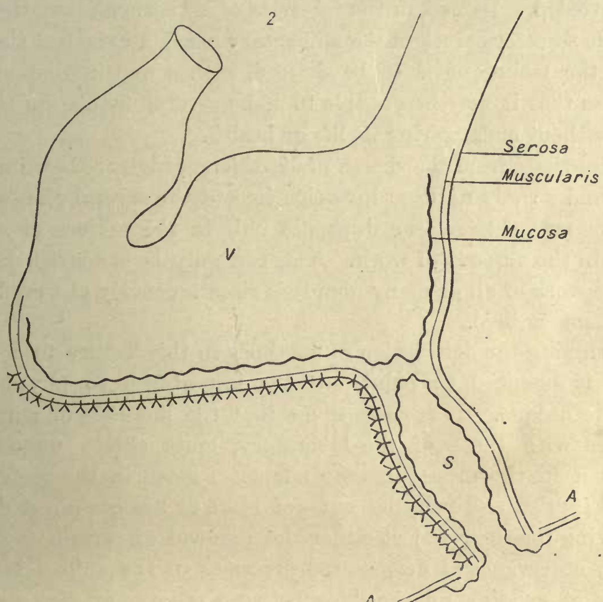


FIG. 4.—*V*. Cavity of stomach. *S*. Pavlov's pouch.
A.-*A*. Abdominal wall.

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 india-rubber tube, freely perforated at its deeper end and provided with a flange of thick rubber at its outer end, is led into the pouch. The tube either remains in of itself or is fixed by means of an elastic band brought round the animal's body, which also holds in position a small graduated cylinder for receiving the juice. A short piece of glass tubing of suitable size is inserted into the outer end of the rubber tubing and dips a little way into the graduated cylinder. During the collection of the juice the animal is supported in the standing posture in a suitable frame.

This method of forming a miniature stomach, so far as I can for the moment imagine, must be regarded as the only one possible and at the same time correct in principle. It possesses a few minor 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 parallel and strictly uniform investigations of the several glands should be, having regard to relationships not only in the periods of activity, but also in the amount of work. This can only be achieved, however, when the work of all or many glands is simultaneously observed in 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 the laboratory, must obtain unquestioned recognition in the procedures we adopt. I mean in the performance —the conception and carrying out—of more or less complicated operations having for their object either the removal of certain organs, or the ready observance of deep-seated processes in the animal body, the severance of existing relationships between organs, or *vice versâ*, the establishment of new ones, &c. With these must go hand in hand measures to secure healing of the injury inseparable from such operations, 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 performance of the ordinary 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 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 union for the performance of a common and purposive work, cannot in the nature of things remain indifferent to forces calculated to destroy any part of it. It is obliged, in its own interests, to restrain some functions to reinforce others, and, by thus economising its energies, to preserve everything that can possibly be saved. This interdependence formerly was, 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 a particular process on the uninjured and normal organism, it continues to be an unavoidable obstacle.

The discovery of new operations for the purpose of physiological research has by no means been exhausted. On the contrary, it is only 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 Minkovski; 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 qnestions been thus settled, and are there not innumerable others arising from the results obtained? It may be objected that I am warmly contending for what is already granted. Yes, but such operations are altogether rare, and only carried out by the few. If the number of physical instruments 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 allow the animal to survive, the paucity of the latter stands out in marked contrast to the plenitude of the former. Again, it is remarkable that many of these operations are introduced by surgeons and not by physiologists. Physiologists do not regard such problems as essential, or perhaps are not in possession of the ways and 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, while in the buildings for a physiological laboratory of the present day, provision is made for chemical, physical, microscopic, and other departments, none is made for an efficient, well-equipped set of surgical rooms. The general rooms of a laboratory cannot with safety to the life of the animal be used for carrying out frequent and complicated operations. Invaluable time and labour will be sacrificed if the surgical precepts of the age be neglected. There can be little doubt that even simple operations performed in the general rooms of the laboratory, even with the aid of antiseptic or aseptic precautions, do not succeed, or perhaps are not attempted, because in the absence of a large surgical department expressly fitted out for the purpose, it is almost impossible to maintain a sufficient degree of cleanliness during and immediately after the operation. 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 our 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. Stolnikov, who repeated the operation with the assistance of Dr. Eck, sparing neither trouble nor animals. It was only in the operation rooms of the physiological section of the Imperial Institute for Experimental Medicine, then just founded, and consequently in the surgical sense clean, that any considerable proportion of successful cases survived. 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 unclean 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 of the operators, till a new physiological department, with better accommodation in the operating rooms, was added to the buildings.

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

The surgical rooms, of which a plan is given in Fig. 5, occupy half the upper storey—that is a quarter of the whole laboratory buildings. They consist of a series of rooms placed along one side of the building, in which preparations, as well as the operation itself, are carried out. In the first room the animal is washed in a bath and dried in a special drying place. In the next it is narcotised, and the site of the operation prepared by shaving and cleansing with an antiseptic solution. The third is used for the sterilisation of the instruments and dressings, 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 thick wall from these rooms is a row 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, has a floor space of about four and a half square metres, 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

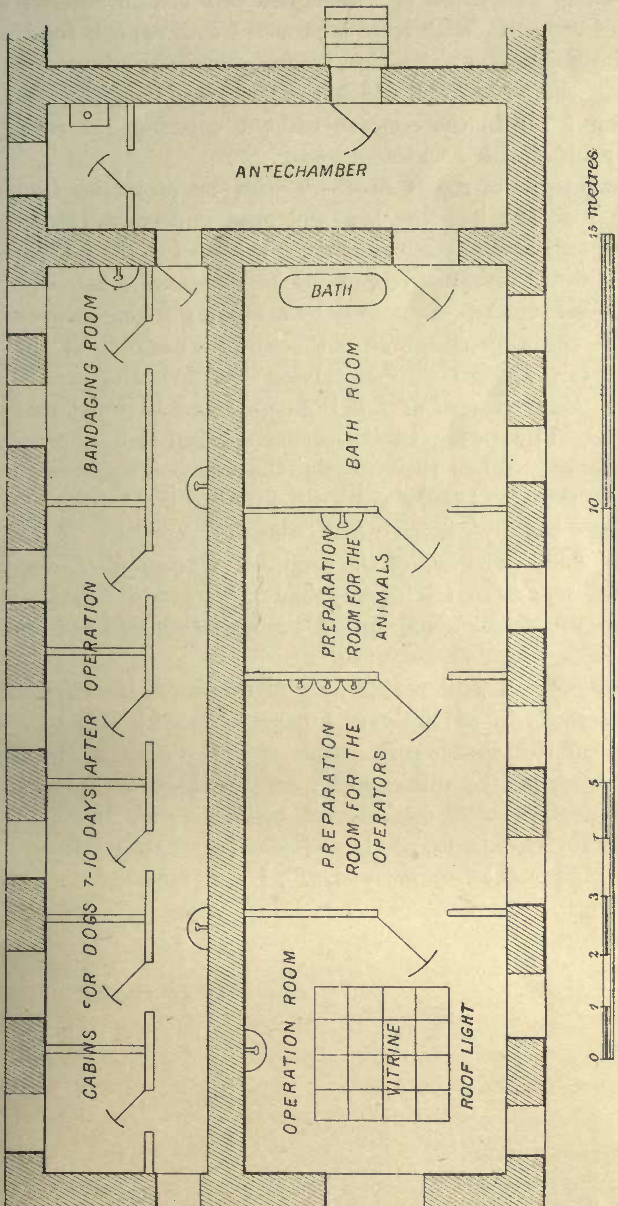


FIG. 5.—Plan of the Operating Rooms in the Physiological Laboratory of the St. Petersburg Institute for Experimental Medicine.

these dog cubicles, shut off from the operating-rooms by massive tightly-fitting doors. The floors of the department are all covered with a waterproof cement. Each room is provided with runnels for drainage. In the dog cabinets a water-pipe, having numerous minute apertures, runs along the wall, from which the floor can be copiously flushed by turning a tap in the corridor without entering the room. The whole is painted with a white oil colour.

The long series of rooms constitutes the best protection against the penetration of dirt into the last and most important, the operating room; for, although physiology is much indebted to the intelligence of the dog, it would be vain to count on its assistance when striving to attain surgical success. It is only by arranging a long series of dirt-catchers, in the ordinary as well as the surgical meaning of the word, that one can succeed in maintaining the operating room at its optimum. Many 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 triumph of 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 on the importance of surgical methods in physiology. I believe that it is only by devoting ingenuity and skill to the performance of operations that the exquisite chemical work of the alimentary canal, the bare outlines of which we can but trace with our present methods, will, in the end, be completely revealed to us. I beg of you to reflect on these closing words of my present lecture; you will, I am persuaded, be convinced of their truth.

LECTURE II.

THE WORK OF THE GLANDS DURING DIGESTION.

The beginning of secretion is related to 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 power 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. The first and most elementary facts concerning the activity of these glands were established with trouble and difficulty, in the light of the older methods (the ordinary gastric fistula and the earlier forms of pancreatic fistula). Thus, it was recognised by all authors that the glands only began to secrete when the food entered the alimentary canal, and, thanks to the methods now at our command, hardly any physiologists doubt that their activity is strictly dependent upon the taking of food. Every one of our experiments on dogs gives on this point 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 during fasting is only two to three cubic centimetres per hour, is increased to many times that amount after the entry of food. This fact, long suspected, has only now been fully established. It is, moreover, consistent with requirements. The juice is only poured into the alimentary canal when the material to be acted upon makes its appearance therein. The fact is apparently simple, 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 a question such 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 bear a different relationship to each other? As a matter of fact, it was scarcely possible to solve this question, so far as the stomach is 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 have perfectly accurate data upon these points. The problem is easily solved on the dog with the isolated stomach. We simply give 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. Khizhin 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.

We are justified in concluding from these figures that the gastric glands work with great precision. The rate of secretion is determined in the first instance by the quality of the food, but for varying quantities of diet they pour out an exactly proportional amount of juice. I regard this result as extremely instructive; it points, without doubt, to the great accuracy 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 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 rise to a multitude of investigations from which it appeared 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 uniformity. The cause is to be sought partly in the defects of the methods, partly in the investigators themselves, who did not always endeavour to secure the requisite degree of exactness in their researches.

Thus, food was often administered in unknown quantities, of indefinite composition, and under varying conditions of appetite or the reverse.

In our endeavours to accurately observe the work of secretion under different conditions we have bestowed from the first a degree of minute care upon the experimental arrangements. As a matter of fact, the curve of secretion under the same conditions, has now become an absolutely constant one. This almost physical exactness in complex physiological processes gives a feeling of satisfaction to the experimenter which rewards him for many hours of perseverance in watching the secretion of the glands during activity. As a guarantee for what I have said, I give here two experiments on the gastric glands, taken from the work of Dr. Khizhin, 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. 6 and 7.)

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 such deviations as exist are to be ascribed to differences in the conditions of experiment not yet discovered ; 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 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 in each case 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 all of these will be given later. Since such curves repeat themselves under similar conditions with stereotyped exactitude, we must admit that a given rate of secretion is not determined by mere blind chance, but in every case follows a necessary rule, requisite for the due elaboration of the food and therefore beneficial to the organism. The curves, however, in all of their separate features,

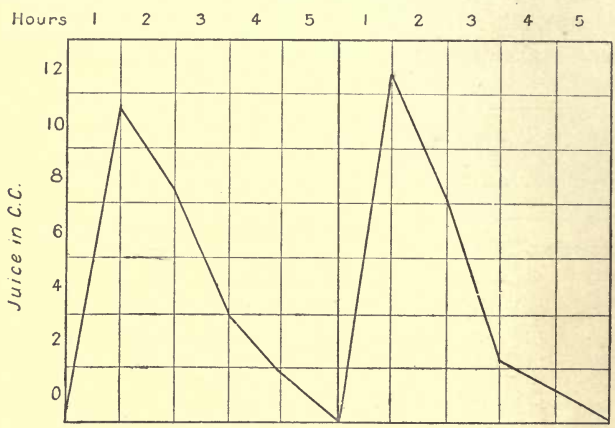


FIG. 6.—Curve of secretion of gastric juice, after a meal of flesh. (Two experiments.)

are not easy of interpretation; 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 in the curve of pancreatic juice during the third hour after a meal? A scientific exposition, that is, one which fully and accurately corresponds with the actual facts, can only be furnished by physiology when the changes, both quantitative and qualitative, in the food and its admixed secretions, 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 able to vary their work so remarkably in respect to the quantity of juice they produce, are they not likewise able to vary the properties of the secretion? Judging from a theoretical standpoint, one would expect that a juice of varying properties would be desirable in different stages of the digestion of the same food. The total mass of food can be 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 fluid of different composition. Thus, more or less water, or a varying

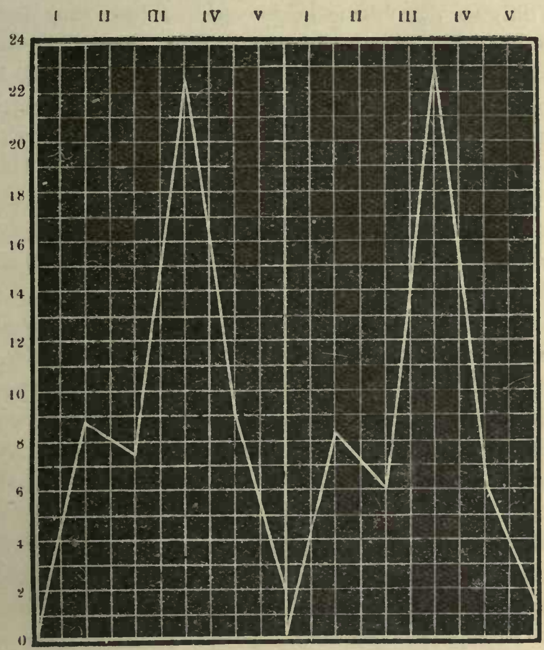


FIG. 7.—Curve of secretion of pancreatic juice. Food, 600 cc. milk. (Two experiments.)

degree of acidity or alkalinity, or a different content of ferment, may be required. All these separate conditions of juice-activity are naturally of importance. But so long as physiologists dealt only with digestion experiments *in vitro*, they could render no account of these matters. It is true that our question has long since been answered 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 a source of unremitting inquiry as to why and how these variations came to pass. Later I shall adduce instances from our store of observations which illustrate these highly interesting qualitative variations of the juice during the different periods of digestion. Naturally, the greatest importance is to be attached to variations in the ferment content, although, strictly speaking, the other properties of the digestive juices demand equally careful investigation to arrive at satisfactory explanations.

The available material, especially as regards gastric juice, could not be considered sufficient. Experiments with the ordinary gastric fistula permit of only very problematic 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 of the stomach be taken as furnishing a reliable index of normal digestive work, since the activity of the isolated part, cut off from its secretory nerves, obviously differed greatly from the normal. His investigations on the pancreatic secretion in dogs must, however, be recognised as scientifically accurate, though, unfortunately, the food was not of definite composition; nor were all the details published. They merely appeared in condensed form in Hermann's encyclopædic Handbook.

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 by us. It is as follows: 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° to 38° C., and requires no further watching. Solution of the proteid occurs at the ends of the small glass tubes. After a certain period, the length of the pieces of tube, and 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 accuracy of results are concerned. Test experiments specially carried out (Dr. Samoïlov) have convinced us that the digestion of the proteid columns, at least within the first ten hours, and employing the fluids we have to deal with, is directly proportional to the length of the period. These experiments removed a very natural mistrust that the solution of the proteid might proceed with varying rates at different depths in the tubes, due to retention of the digestive products within the lumen. It may, however, be accepted that the length in mms. of egg-white dissolved by the several juices in a given time, supplies an exact relative measure of the digestive power of the fluid. In the researches of Borisov, carried out upon this question in the laboratory of Professor Tarkanov, the relationship which exists between the length of the digested column of egg-white and the *pepsin* content of the fluid investigated, came out with perfect clearness. The following is the rule which expresses it, viz., *the quantity of pepsin in the prepared 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 given 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 been deduced from comparisons made with numerous artificial solutions of pepsin exactly prepared. Moreover, the result which Dr. Borisov 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 rule applies only to juices of certain strengths and is unreliable if they are very concentrated. When dealing with samples of the latter kind the fluids must be diluted from four to ten times with dilute hydrochloric acid of appropriate strength. I must, however, express my regret that the method of Mett, which was published so long ago as the year 1889, has not been so 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 enzymes might be comparable with each other? No one will deny that this is highly desirable, for then all observations on the juices of different animals and men could be represented on a uniform scale, making possible important deductions concerning variations of ferment in the individual, the species, and the genus. 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 Borisov applies also in its full extent to the action of trypsin.

The methods of comparing the activities of other ferments are less perfect, and in our experiments have been frequently modified. The activity of the amylolytic ferment of the pancreas was for a long time determined in the laboratory by titrimetric estimation of the sugar, formed by exposing, under certain conditions, a given quantity of starch paste to its influence. The number of milligrammes of sugar produced, served as a measure of the amylolytic power. 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 an attempt was made in the laboratory (Drs. Glinski and Walther) to estimate the activity of the proteolytic and amylolytic ferments of the pancreas by similar methods. Thin glass tubes were filled with coloured starch paste and then exposed in the thermostat to the influence of the ferment for a certain period, usually for half an hour. The paste was dissolved from the ends inwards, the extent of the 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 Borisov proved valid here also—*i.e.*, the quantity 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 be expressed in both ways in the experiments given below, viz., in terms of the milligrammes of sugar formed, and also as millimetres of starch-column dissolved.

Unfortunately all attempts to estimate the work of the fat-splitting ferment upon the same system have, up to the present, remained fruitless. We have consequently had to determine by titration with baryta solution, the acidity of the mixture of fat and pancreatic juice, after it 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 has not prevented us from endeavouring to obtain a method uniform with those applied to the other ferments. The procedure we are compelled to use demands the continuous attention of the experimenter, and is therefore very troublesome 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 Borisov has, however, been confirmed here also. Naturally our experiments dealt in general with *comparisons* of ferment *activity* only, and our deductions concerning *quantities* and *total amounts* of ferment must therefore be accepted conditionally. In many instances, perhaps with gastric juice in all, it may be correct to 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 our method of estimating the alkalinity of pancreatic juice. The solid residue of a measured quantity of juice

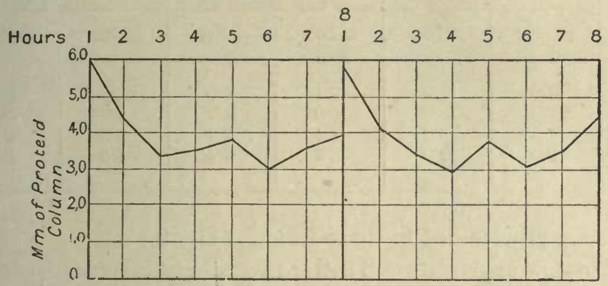


FIG. 8.—Digestive power of hourly portions of gastric juice after administration of 400 grms. of flesh. (Experiments of 15th and 16th May 1895.)

was incinerated over a weak flame, 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.

We may now return to the description of the experiments from which I broke off in order to give these necessary explanations of methods. The results of two pairs are given below, 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 hold good for variations in the 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. Lobasov).

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. 8.)

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

These are represented in curve form. (Fig. 9.)

We can now appreciate still better the astonishing exactitude of the work of the glands: that which is demanded of them 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 very characteristic of gland activity. They are capable of producing secretions of varying composition, with more or less ferment, or with different proportions of the individual ferments, when, as in the case of the pancreatic juice, several such are present. Moreover, other properties of the juices, not alone their contents 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 show variations running courses independently of each other, a fact which undoubtedly proves 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. What has been said of the ferments may also be applied to the quantities of *salts* present in the juices.

All the more astonishing, therefore, in the light of the above results, appears the fact, as it seems to be, that *the gastric juice as it flows from the glands possesses a constant acidity*. It is true that in clinical investigations into the secretory activity of the human stomach variations of acidity are almost daily demonstrated, 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 forcibly to the 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 over alkaline mucous membrane and inevitably becomes more or less 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 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 the actual. In order to test this explanation, experiments of various kinds were instituted by Dr. Ketscher. The wall of the stomach is usually covered with a considerable layer of mucus, and it is quite natural that the first portions of juice secreted, for example under the influence of sham feeding, will have the lowest acidity. The more freely and rapidly the juice flows, the more acid will it be. During the decline of the secretion we find an absence of the low acidity corresponding to a similar 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

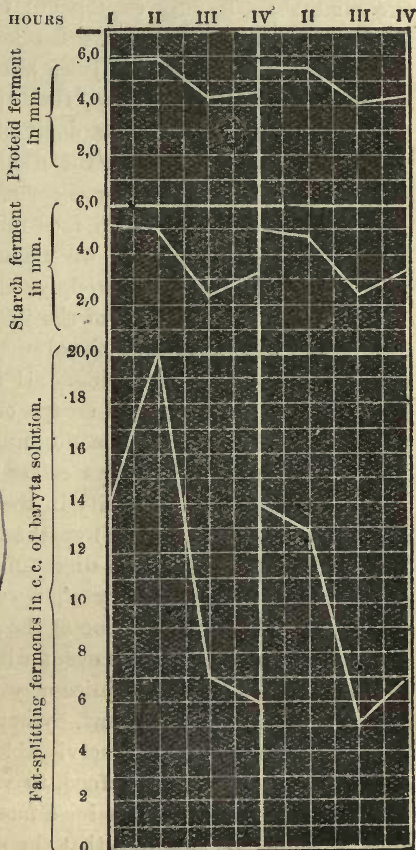


FIG. 9.—Ferment content in hourly portions of pancreatic juice after a meal of 600 c.c. milk.

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 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 appeared, 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, they will still more easily arise in a stomach to which food mixed with saliva can gain access. Further, a short time ago we made observations in the laboratory upon a dog suffering from strongly marked hyperacidity of pathological origin. In no single sample of the juice did the degree of acidity exceed the normal. (*Pavlov.*) Additional support is given to the theory of constant acidity by the following. If a fasting dog be daily given a fictitious meal the continued escape of hydrochloric acid in the gastric juice secreted leads to such a diminution of chlorides in the body that sham feeding after some days ceases to produce an effect. Nevertheless, the fluctuations of acidity in the samples of juice last secreted lie within normal limits. If the hypothesis be correct, the varying necessity for acid during the course of digestion is supplied by alterations 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. It may be that 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 fluctuates remains a fact, however it is brought about. It must, however, be admitted that the possibility is not wholly excluded, of some relation existing in the case of gastric juice between the rate of secretion and the degree of acidity such as we shall find in the case of saliva between the rate of secretion and the content of inorganic salts.

You have now seen striking instances of the fact that the juices furnished by the pancreas and by the gastric glands during the course of the same act of digestion do not remain uniform, but are 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 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 later 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 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 the factory, where 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 implies that the conditions under which gastric digestion has been accomplished must be radically changed, since they are injurious to the action of the pancreatic juice. 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 different and successively occurring phases in the elaboration of the food. We may justifiably suppose that this adaptability only appears in its full extent when we compare the variations in the rates of secretion on different dietaries with each other. The food is made up of several constituents, and various juices are poured into the alimentary canal. The supposition might therefore appear natural that each fluid is furnished in the main for a particular kind of food.

Is this in reality the case? It is obvious that an answer was impossible by the aid of the older methods. Now, however, the fact that we are able to take the question into consideration is of itself a brilliant testimony to the service rendered by the newer methods. At present we can show by actual experiment what *a priori* only appeared probable, viz., that each kind of food calls forth a particular activity of the digestive glands, with varying properties in the digestive juices supplied.

We may commence with the stomach. Researches carried out by Dr. Khizhin on dogs with stomach pouches have shown that feeding with mixed diets, as well as the separate administration of milk, bread or meat, &c., call forth each time special modifications in the activity of the gastric glands. The peculiarities in the secretion are not limited to the properties of the juice, but extend to the rate and duration of its flow, and also to its total 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. Khizhin, 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 compare the ferment content of these juices with one another we find, according to the law of Schütz and Borisov, that "bread juice" is represented by 44 ($6{\cdot}64^2$), "flesh juice" by 16 ($3{\cdot}99^2$), and "milk juice" by 11 ($3{\cdot}26^2$).

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

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

At eight o'clock in the morning a 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
The dog was now given 200 grms. raw meat.		
12 noon	8·0	5·37
1 P.M.	8·8	3·50
2 „	8·6	3·75
The dog now received 200 c.c. milk.		
3 P.M.	9·2	3·75
4 „	8·4	3·30
An additional quantity of 400 c.c. milk was 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 show that the order of administration could not have influenced the result I append another experiment.

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

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

200 c.c. of milk were again given.

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

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

If the quantity of juice secreted during a given period be divided by the number of hours in the period, the mean hourly rate of secretion is obtained. Even this number, which represents the mean degree of gland activity, 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 gland work per hour is almost the same with 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 flow of juice is correspondingly prolonged.

The special features of gland work, dependent on the nature of the food, are not limited to the distinctions given. They likewise prominently appear as qualitative variations in the juice secreted hour by hour. This time I furnish only one example for each kind of food, and beg you to believe that it repeats itself with the same beautiful precision we have already seen.

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

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

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

The above is represented in the following curves. (Figs. 10 and 11.)

These facts are highly interesting and of the greatest importance. Each separate kind of food determines a definite hourly rate of secretion, and produces characteristic alterations in the properties of

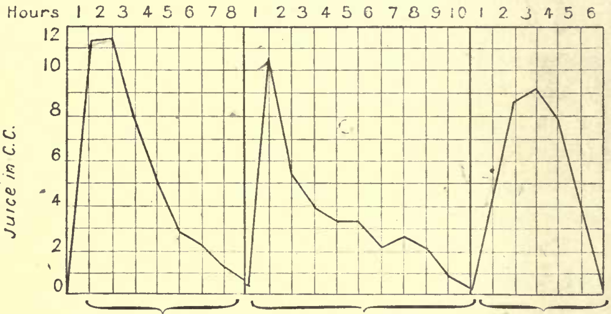


FIG. 10.—Curves representing the rate of secretion of gastric juice with diets of flesh, bread, and milk.

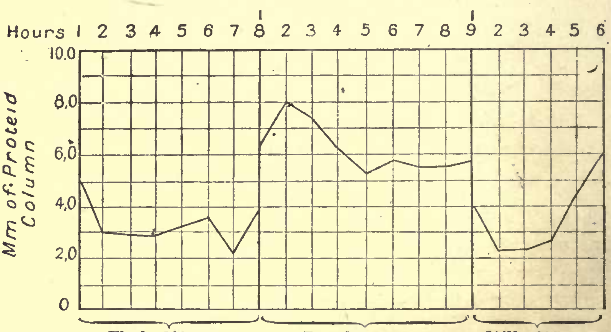


FIG. 11.—Curves representing the digestive power of gastric juice, hour by hour, with diets of flesh, bread, and milk.

the juice. Thus, with flesh diet *the maximum rate of secretion* occurs during the first or second hour, the quantity of juice furnished in each being approximately the same. With bread diet we have invariably a pronounced 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 and the third, and with milk in the last hour of secretion. Thus the period of maximum outflow, as well as the whole curve of secretion, is characteristic for each diet.

It appears to me that the facts here given lend strong support to our previous conclusion, that the variations seen in gland activity during the course of a digestion period have some essential meaning. When, for example, a special curve of secretion is determined by every single kind of food, surely this must argue a definite purpose and be assigned a special significance.

We have now learned something of the many fluctuations in the work of secretion under different conditions. Their conformity to laws is a guarantee that they are important. I do not, however, propose that we shall at this stage endeavour to discover the meaning of all these variations. I wish merely to convince you that the work of the digestive glands is, if I may say so, elastic to a high degree, while at the same time it is specific, precise and purposive. It is to be regretted that till now the *rationale* underlying the latter feature of gland activity has been so little investigated. The belief that gland work conforms to laws is based chiefly on general inferences, and only in part upon facts, by no means clear in themselves and not wholly free from objection. Take, for example, the quantities of ferment poured out by the stomach on nitrogen equivalents of the different kinds of food, namely, 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. Khizhin

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

and

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

For 250 grms. bread we find no corresponding data, since he experi mented with different quantities. The quantities may, however, be easily constructed from the data at hand, assuming a proportionate relationship between the amount of food ingested and the quantity of juice secreted. If this be done it appears that

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

The squares of the digestive strengths (in millimetres) yield 38 for bread, 16 for flesh, and 10 for milk. These figures enable us to compare the ferment concentration in similar volumes of the different juices. Since, however, different quantities are called forth by the different varieties of food, we must take this also into consideration when calculating the total quantities of ferment. Multiplying, therefore, the squares of the numbers representing digestive strengths by the number of c.c. poured out on each food, we obtain the above-mentioned numbers, 1600, 430 and 340. These indicate that, on protein contained in bread, five times more pepsin is poured out than on the same quantity of protein as it exists in milk, and that flesh protein requires 25 per cent. more pepsin than that of milk. Thus these different kinds of protein receive quantities of ferment corresponding to differences in their digestibility as already known from experiments in physiological chemistry.

The work of the gastric glands in providing juice for the different food-stuffs, must be recognised to be also purposive in another sense. The vegetable protein 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 infer from this that it is only the ferment of the gastric juice that is here in great requisition and that large quantities of hydrochloric acid would be useless or possibly injurious. We see, from the following, that during gastric digestion of bread an excess of hydrochloric acid is actually 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 a 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 period of secretion. This harmonises well with the facts of physiological chemistry, namely, 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.

As an aid towards the digestion of starch, or at all events in relation thereto, another phenomenon plays a part which has already been several times mentioned but not yet explained. I mean the long pause of at least five minutes which always intervenes between the taking of food and the beginning of secretion. This interval invariably occurs, whether the observation be made on the large stomach of a sham-fed animal, or on the miniature pouch 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 assuming that it depends on conditions, such as the time 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. Further, it would be singular if the gastric glands, *per se*, were incapable of responding to a stimulus before the lapse of five minutes after its application. Nothing, therefore, remains but to recognise in the occurrence, a definite aim. Perhaps these five to ten minutes are provided 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 investigated.

I now gladly proceed to consider the work of the pancreas, where we shall find that the adaptation of the secretion to the nature of the requirements is also to be seen. The following table selected from the experiments of Dr. Walther, 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 of the column of dissolved proteid or starch, or of the number of cubic centimetres of standard alkaline solution employed for neutralisation. By total quantity of ferment units, we mean the product of the strength multiplied by the quantity of the juice in cubic centimetres.

In the next table the amounts of food given, also represent equivalents of nitrogen.

Diet.	Proteid ferment in mm.	Starch ferment in mm.	Fat ferment in c.c of standard alkali.
Milk .	4·54	6·75	9·02
Bread .	3·81	6.16	2·7
Flesh .	3·56	4·29	5·7

In view, however, of the discovery that the proteid ferment in normal pancreatic juice occurs mainly, if not wholly, in an inactive form, the foregoing observations of Walther in some respects require confirmation. As we shall see later, the inactive zymogen is converted into the active ferment by admixture with succus entericus (*Schepovalnikov*). The activating constituent of the intestinal juice is itself of the nature of a ferment, and has been given the name of *enterokinase*. It is maintained by Delezenne and his co-workers that in natural pancreatic juice the proteid ferment occurs only in the inactive form. Slight degrees of activity observed by other investigators are ascribed to the presence of an activating substance clinging to the fibrin used. But even if this proves an extreme view, the facts adduced make it necessary to repeat Walther's experiments.

There is reason for believing that the fat-splitting ferment also occurs, on occasions at all events, in the form of a zymogen. Nencki * long ago pointed out the favouring influence of bile on the fat-splitting action of the pancreatic juice and Babkin † quite recently obtained specimens of the juice which were wholly inactive on monobutyrin, but became so when admixed with bile. In future determinations of the fat-cleaving action of pancreatic juice, bile must be added.

As regards the condition of the starch ferment there is still much doubt. Both bile and succus entericus often strikingly increase its action, but we have no infallible test wherewith to ascertain whether this result is due to the activation of a zymogen or merely to the provision of more suitable media.

Apart from the quantities of ferments the results of Walther are, however, in other respects reliable. It is of interest, therefore, to compare certain other variations in the juices secreted by the glands on different diets, as shown in the following table, also taken from his publication.

Diet,	Quantity of juice in c.c,	Duration of secretion,	Mean rate of secretion in c.c. for 5 mins.	Per cent. of dry solids.	Per cent. of ash.	Per cent. of organic subs.	Per cent. of N.	Alkalinity of ash.
		h. m.						
Milk, 600 cc.	47·7	4 30	0·85	5·268	0·869	4·399	0·68	0·348
Bread, 250 grm.	162·4	7 35	1·75	3·223	0·925	2·298	0·39	0·564
Flesh, 100 grm.	131·6	4 12	2·61	2·465	0·907	1·558	0·24	0·588

From the above it will be seen that, as regards the *total quantity* of juice, the *duration* of its outflow, the percentage of *total solids*, and, in particular, the percentage of *organic solids*, there are striking differences manifested in the secretion poured out for the different foods. The quantity of juice corresponds neither to the total weight of the food not to the amount of solids which it contains, nor to the quantity of protein in the different varieties given. It is related to the physical and chemical properties of the food as a whole. The percentage of organic solids which runs parallel with the quantity of ferment is seen in "milk juice" to be nearly double as high as that in "bread juice" and nearly three times as great as that in "flesh juice." The

* *Archiv. f. Exp. Pathol. u. Pharmak.*, 20. † *Archiv. d. Sciences Biolog.*

percentage of ash and the degree of alkalinity are also very different in the three cases.

If the total quantities of organic solids be calculated for the foregoing diets, it will be seen that milk and flesh receive almost equal amounts, while bread receives double that of either. This latter agrees

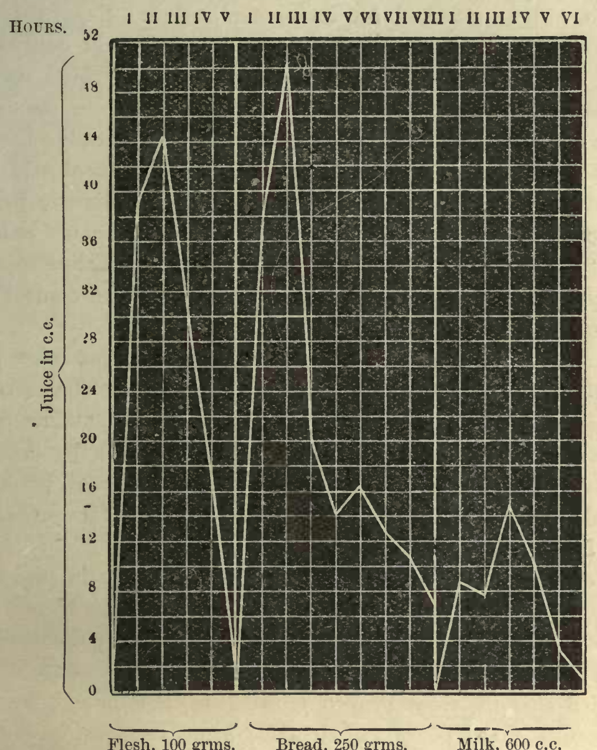


FIG. 12.—Curves of secretion of pancreatic juice with different diets.

with what we know of the difficulty with which bread proteid is digested, and also with the need for much amylolytic ferment required by the large mass of carbohydrate contained in the ration.

The work of the pancreas, like that of the gastric glands, is also specialised in regard to the hourly rate with which the secretion is poured out on the different classes of food. This is represented in the accompanying tables and curves (Fig. 12) 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.

In considering the physiological significance of the foregoing facts we shall limit ourselves to that of the quantity of juice—that is of alkaline solution of sodium carbonate—poured into the duodenum. The first duty of intestinal digestion is to convert the acid medium of the stomach into an alkaline or neutral one in the bowel. Consequently the more acid secreted in the stomach on a given food, the more pancreatic juice will be required for its neutralisation. Regarded from this standpoint the different quantities of pancreatic fluid poured out on the foregoing diets receive a satisfactory explanation. Milk receives very little pancreatic juice of itself: it neutralises a certain amount of gastric juice and considerably dilutes the remainder. Bread in the proportion contained in the compared diets receives more total acid than the ration of flesh. In consonance therewith more pancreatic juice is poured out on the bread than on the flesh. This is all the more remarkable, since it is by no means necessary to provide an alkaline medium for the amylolytic ferment of pancreatic juice. On the contrary its action is best in a weakly acid one.

In feeding with flesh and bread, the most active secretion takes place during the first two hours, after which in the former case the secretion rapidly declines to *nil*, while in the case of bread the fall, at first rapid, is interrupted by a second rise, after which it gradually declines. With milk, the secretion in the first two hours is very small (even less in the second than the first), then it rises to a maximum at the end of the third hour, from which it quickly falls to *nil*.

In view of the tendency of all organised tissues (under the prolonged influence of forced work or its converse) to enter into conditions of a more or less stable nature, it was to be anticipated that similar effects might arise in the case of the glands. An investigation of the pancreas with this in view proved fruitful in our hands, but the following results must be taken with the same reservation as those of Walther, and for the same reason.

If, in the feeding of animals, the kind of food be 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. For example, if a dog be fed for weeks on milk and bread, and be then given an exclusively flesh diet, containing more proteid but scarcely any carbohydrate, a continuous increase in the proteid ferment of the juice is observed. The ability to digest proteid waxes from day to day, while, on the contrary, the amylolytic power of the juice continuously wanes. The following is an experiment taken from the work of Dr. Vasiliev. 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, 16·8, 15.

Afterwards the dog was fed daily on a pound and a half of flesh. Within 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 it must be added, that in the latter case the starch ferment was allowed to act for twice as long as the first.

Although the results of the foregoing experiment are apparently indubitable, it is possible the objection may be raised that the quantity of each ferment produced in the two cases was the same, but that the distribution over the several hours was different. We resolved, therefore, in order to make our results more certain, to compare the ferment properties of the juice secreted over the whole period of 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 proteolytic 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's method 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 made after the lapse of a further twelve days, gave a digestive power of 1·25 mm. The starch ferment at the beginning steadily increased; later, however, it showed irregular fluctuations, with a slight tendency to fall.

Moreover, when, under the influence of a given diet, a particular condition of the pancreatic activity had been established in our experiment animals, we were able, by altering the feeding, to reverse it several times in one and the same animal. This excludes all suspicion that we were dealing with spontaneous and unavoidable alterations of the glands, such as might arise from the effects of the operation or other pathological condition.

But if the food affects the nature of the work of the glands, is it not possible that a permanent type of pancreatic activity may be produced under the influence of long-continued natural conditions, or from the effects of a diet maintained perhaps throughout the whole of life, such, for example, as happens 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 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 another may often produce serious illness.

As regards the gastric glands, the question of lasting alterations in ferment production must still 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 sham feeding, but have never seen any striking or constant differences in the digestive power of the juice. To endeavour to solve this problem Dr. Samoïlov made observations on three gastro- and œsophagotomised dogs. The animals were tested beforehand by oft-repeated sham-feeding experiments and then placed on different diets. After a considerable time they were again tested, but the gastric juice showed no essential divergence from that previously obtained. How are these results to be interpreted? Are the gastric glands different in this important respect from the pancreas? It is, of course, possible that the pancreas plays the *rôle* of a supplementary, or reserve gland, the duty of which is now augmented, now diminished, in accordance with the total work of the digestive canal, while the gastric glands, being the first important digestive agents, must always work at maximum pitch. A fact not easy to interpret, has, however, been recently observed in the laboratory by Dr. Lobasov, which possibly indicates that lasting alterations of the gastric glands may appear under the influence of prolonged dietetic conditions. In one of our dogs a portion of the fundus of the stomach had been 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 fed freely on flesh every day for a considerable period, a given test meal always yielded a much greater secretion than when the animal had been fed upon other foods, such as oatmeal porridge, &c. But in a dog thus operated upon, the gastric glands exist and work under altered conditions, and too great stress cannot be laid upon this instance.

All these facts accord sufficiently with our previous conclusion, namely, that the work of the digestive glands which we have so far investigated is extremely complex and elastic, but at the same time surprisingly 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 concerning 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 vagus conveys secretory fibres to the gastric glands—This is proved by excitation of the nerve in two different forms of experiment—The vagus is also the secretory nerve of the pancreas (experiment)—It likewise conveys inhibitory influences to the foregoing glands—These depend upon actual inhibitory secretory nerves.

GENTLEMEN,—On the last occasion we were occupied with somewhat trying figures and curves, which, however, taught us an extremely interesting lesson. They showed that the gastric and pancreatic glands have what at first sight appears to be a form of instinct. They possess to a high degree the power of adaptation. Their juices are poured out in correspondence, both qualitatively and quantitatively, to the amount and kind of food partaken of. Moreover, they secrete precisely that quality of fluid which is most serviceable for the digestion of the meal. We naturally ask ourselves, how is this made possible? On what does this apparent instinct of the glands depend and in what does it consist? A probable answer is easily given, and naturally an explanation of the adaptability of the glands is first of all to be sought in their innervation. It is only when such supposition proves itself untenable that we must seek for another. We shall therefore concern ourselves, in the present lecture, with a study of the influences exerted by the nervous system upon the activity of the gastric glands and the pancreas.

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

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

call into play the chemical activity of the gland cells, and thereby bring about the secretion of saliva. These nerves receive the name of "secretory" or "katabolic" nerves. Heidenhain* carried the matter farther, and produced undoubted proof that the secretion of saliva in the glands resolves itself into two processes; namely, 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 processes, Heidenhain, and with him the majority of physiologists, recognise two special kinds of nerve-fibres governing the activity of the salivary glands. The one kind influences the secretion of water and of the inorganic salts in solution, the other leads to an accumulation of the organic body, the specific agent of the secretion. For the former nerves, Heidenhain retained the old name "secretory," to the latter he gave the name "trophic." They have also been termed "anabolic" nerves.

The question as to whether the gastric glands have a similar secretory innervation is now a very old one and has had an interesting history. In this matter physiology stood for a long time in sharp conflict with practical medicine. Physicians from clinical observation had long decided in the affirmative, and looked upon the existence of secretory nerves to the stomach as undoubted. Different morbid conditions of the innervation apparatus had even been spoken of. Physiologists, on the other hand, had for decades fruitlessly endeavoured to arrive at definite results upon this subject. It is a striking, but by no means isolated, instance where the physician arrives at a correct verdict upon physiological processes earlier than the physiologist himself; nor is it indeed strange. Pathological phenomena constitute an endless series of the most varied and unusual combinations of physiological occurrences which do not make their appearance in the normal course of life—a series of physiological experiments instituted by nature, often with such complex dovetailing of events as could never be conceived by the physiologist, or reproduced by the technical resources at his command. Clinical observation will consequently always remain a rich mine of physiological facts. It is therefore only quite natural that the physiologist should endeavour to maintain a close connection between his science and that of medicine.

Notwithstanding the wide range and perplexity of the literature of the nerve-supply of the gastric glands, we can now pick out, with clearness and precision, the fundamental truths of the earlier researches. We can see why these experiments were unfruitful, and from their

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

teaching draw up rules for the performance of ideal experiments which shall definitely suit our purpose.

There are three commonly employed methods for determining whether a nervous control over a given organ exists or not. First, we may cut through, or in some other way paralyse particular nerves connected with the part in question, and then submit the organ to accurate observation in order to ascertain whether its activity has been suspended or increased, or in any other way altered from the normal state, either quantitatively or qualitatively. Naturally our conclusions regarding the relations between the nerve and the organ will be the more accurate, and come nearer the truth, the more carefully and successfully we compare the two conditions. A second and striking proof of the existence of nervous influence over an organ may be furnished by the results of excitation of its associated nerve. When 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 the nerve as governing the organ. Even here, however, the possibility of two adverse contingencies must not be disregarded. It may happen that the function of the organ suffers no alteration because the nerve or the tissue is placed under abnormal conditions, and considering the defects which still, unfortunately, cling to many of our physiological methods, this is very possible. For this reason, experiments yielding negative results have only a very qualified significance, and by many authors are never published. On the other hand, alterations of function which appear in an organ on stimulation of a particular nerve may have been brought about indirectly through the intervention of one, or several other organs. Only a careful and complete physiological analysis, and where necessary anatomical isolation of the organ, can guard us from these sources of error.

There is still a third mode of proof which, perhaps, it would have been better to have given in the first instance. It often furnishes evidence of a nervous influence where the direct method remains fruitless. This depends upon wide general evidence of a relationship between the organ in question and the nervous system. It is nothing more than accurate observation in the clinique and in everyday life. The well-known fact of salivation at the sight of appetising food has on this ground been always accepted as valid proof of nervous influence over the salivary glands.

This line of observation has also been followed when investigating the innervation of the gastric glands. Several workers had noticed alterations in the quantity and properties of the gastric secretion, when the vagi, the chief anatomical nerves of the organ, were divided in the neck. But only few were convinced that the vagus had an intimate relationship with the secretory activity of the stomach glands. As is well known, division of both nerves in the neck is an operation producing the severest consequences to the animal, and usually followed by death after two or three days. If in the course of such a short time the operation brings the whole body functions to a standstill, it is not to be wondered at, that, amongst other things, the activity of the gastric glands is disturbed. It was therefore unsafe to conclude from such an experiment that the vagus had any special relationship to the gastric glands. (This is a good illustration of the second rule given above, concerning the experiment of nerve-division.) Such a cautious attitude towards the experiment seemed all the more justified because Schiff* succeeded without difficulty in keeping his dogs healthy and well-nourished 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.

Relying on these experiments of Schiff; many investigators have in the past refused to recognise any secretory nerves to the gastric glands, and unfortunately the view is still extant. But there are two important objections to Schiff's experiments. In the first place, the survival of the animals cannot be taken as proof that no deviation from the normal activity of the gastric glands had occurred. We are more and more convinced every day that the several organs of the animal body work on the principle of mutual help and defence. In this case it should have been remembered that the sympathetic nerve also sends fibres to the stomach. Further, Schiff had made no precise or 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 experiment takes no cognisance of the possibility that the secretory fibres of the vagus may have left the trunk of the nerve and entered the wall of the digestive tube above the diaphragm and coursed down to the stomach along its deeper layers.

The results of excitation of the vagus proved also to be uncertain. Hardly any of the authors, no matter where or how they stimulated the nerve, could claim a distinct secretory effect. The meagre and not very convincing records of positive results received no attention in the loud chorus of confident denial, and this all the more because the conditions were similar in all these contradictory experiments.

Quite alone, amongst the records, stands the result of two French authors,† who on stimulating the vagus of a decapitated criminal saw

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

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

drops of gastric juice forming on the inner surface of the stomach forty-five minutes after the execution. It must be added, however, that this may possibly have been due to a squeezing of gastric juice out of the glands, such as might arise from the contractions of the stomach-wall set up by the excitation of the vagus nerve. Later we shall come upon facts which make it but little likely that true secretory activity could have occurred under the experimental conditions of these authors.

It is interesting, however, to note how differently the question of secretory innervation of the stomach has been viewed by German and French physiologists. The former, demanding precise and constant results, have maintained till recently, a rigid unbelief in the existence of secretory nerves to the organ. With French authors, on the other hand, one always finds related some apparently convincing experiment, or at least comes upon forms of expression which assume the probable existence of such an innervation.

Experiments with the sympathetic turned out to be also negative; consequently, the first two modes of investigation which I have named —the division, and the excitation of nerves—yielded no results when applied to the gastric glands, or at least none that convinced the majority of physiologists. The third method of procedure was, however, strikingly effective.

In the year 1852 Bidder and Schmidt * observed that, under certain circumstances, the mere sight of food calls forth a secretion of gastric juice in the dog. Although every investigator has not been able to verify this statement, the majority have been able to convince themselves of its truth. More recently the French physiologist Richet † has made observations on a patient on whom the operation of gastrotomy had been performed for an incurable stricture of the œsophagus. Soon after anything sweet or acid was taken into the mouth, Richet observed a secretion of pure gastric juice. Bidder and Schmidt's experiments and Richet's observations prove, therefore, that the nervous system exerts an influence on gastric secretion, be this direct or indirect. This fact must henceforth constitute the point of departure of new researches on the subject. The observation proves undeniably that the gastric glands are influenced through nerves by "distant effect," since the phenomenon occurs 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 explanation.

* F. Bidder u. C. Schmidt, *Die Verdauungssafte*, &c., 1852.
† *Journal de l'Anatomie et de la Physiologie*, 1878.

In point of fact, I am now able to show you experiments which yield absolutely constant and unequivocal results. We have here before us a dog operated upon in the manner already 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 interior of the stomach. The latter has been washed out before the beginning of the lecture, and, as you see, 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 for five minutes (which for shortness we shall henceforth call "sham feeding" or "fictitious feeding"),* perfectly pure gastric juice makes its appearance at the fistula, the stream steadily increases, and now, five minutes after its commencement, we have 20 c.c. of juice. We may feed the dog as long as we wish, the secretion will flow at the same rate for one, two, or more hours. We have had dogs so greedy that they continued eating in this fashion for five or six hours, secreting a total quantity of 700 c.c. of the purest gastric juice. The meaning of the experiment is clear. It is obvious that the effect of the feeding is transmitted by nervous channels to the gastric glands.

We shall return later to consider what constitutes the actual stimulus in this case. At present we may carry our experiment a step further by dividing the vagi nerves. If, before the division, we take away the animal's food, the secretion does not cease immediately; it continues for a long time—three to four hours—gradually dying out. Without waiting, however, till it completely stops, we may proceed to other experiments. In this dog, at the time of making the gastric fistula, the right vagus nerve was divided below its recurrent laryngeal and cardiac branches. Thus only the pulmonary and abdominal branches on the side in question were thrown out of action, the laryngeal and cardiac fibres remained intact. About three hours ago I prepared the left vagus in the neck, passing a loop of thread round the nerve, but not dividing it. By gently pulling on the thread I now draw the nerve out 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 discomfort or pathological condition. There are no symptoms of cardiac or laryngeal distress, the usual

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

causes of danger after complete division of the cervical vagi on the two sides. We again offer the dog food, 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 fictitious feeding. The experiment may be repeated at will, and always with the same result.*

These investigations were first carried out by me in conjunction with Madam Schumova-Simanovskaia, and our results were confirmed by Dr. Jürgens with dogs having both vagi severed below the diaphragm. Finally a like effect was obtained by Professor Sanotskii in a dog the fundus of whose stomach was resected after the manner of Heidenhain, an operation which involves, as is well known, the division of the fibres of the vagus.

Basing my conclusions on these results, I take the liberty of asserting that the proof of the question at issue has been placed beyond the possibility of all doubt or chance. You see, then, gentlemen, that it is only necessary to divide 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, on the one hand, the fibres of the cervical vagus going to the larynx and heart are not completely divided, while on the other the abdominal fibres are totally severed, there can be no question of any general feeling of discomfort producing a harmful influence on the secretion of gastric juice. There is, indeed, no feeling of ill-health whatever ; the dog eats immediately after the operation quite as eagerly as before. (This is an essential advantage of our procedure over the former method, of double vagotomy.) Lastly—and this is the most essential characteristic of our experiments—we employ in the fictitious feeding, an immediate, uniform, and adequate test. This is an important improvement as compared with the experiments of Schiff.

The negative effect of sham feeding after vagotomy does not, however, prove 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 may act on the gastric glands

* The dog which served for the above experiment remained alive for several months. The right vagus was later divided *in the neck*, nevertheless the animal continued in perfect health. Oft-repeated sham-feeding experiments gave no trace of secretion. The same result was obtained with another dog, which likewise survived a double division of the cervical vagi for many months.

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 running in the vagi.

But what kind of fibres are these? Are they special secretory fibres or do they influence the glands indirectly—for example, through the medium of the blood-supply? Accepting 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 as a rule eats flesh much more greedily than bread. If we give it bread we obtain less juice, and of a much more watery kind; that is to say, less rich in ferment. Likewise, when we give flesh in pieces with long intervals between, we obtain not only less juice than when the dog is fed rapidly, but the juice possesses a much lower digestive power. It follows, therefore, that the stronger we stimulate, the more and the richer is the juice we receive. This fact is, however, the best proof of the specific activity of the nerve-fibres supplying the glands. If only vaso-motor (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 be carried 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.
$6\frac{1}{4}$ mm.	$8\frac{1}{2}$ mm.
$4\frac{1}{2}$,,	7 ,,
$4\frac{3}{4}$,,	8 ,,
$5\frac{1}{2}$,,	$7\frac{1}{4}$,,

In all cases 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 it follows, first, that specific secretory fibres, and not merely vaso-motor, run in the vagi to the gastric glands; and, secondly, that these fibres must be divided into true secretory and trophic, as was done by Heidenhain for the nerves to the salivary glands. This is shown by the fact that the extraction of the water and 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 containing wholly different amounts of ferment, determined by different working conditions of the glands.

But although the experiment of nerve-section speaks eloquently in favour of the existence of secretory nerves to the stomach, it is desirable, for many reasons, to consider the excitation method also. It is only by artificial excitation that we can study accurately, and in all its features, the working of a given nerve and the process which it controls. In some cases, however, great difficulties are encountered. This explains the failure of the many investigators who have previously endeavoured to solve our question by this method. 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 results obtained by the ordinary so-called "acute" experiment, performed at one sitting on an unprepared animal, can be accepted as a true interpretation of normal conditions in this case. In such an experiment 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 upon the activity of the most important digestive glands, had already been recorded. It was shown by Bernstein,* in Ludwig's laboratory, and later by myself, in conjunction with Professor Afanasiev, that sensory stimuli frequently and unquestionably inhibit the work of the pancreatic gland for long periods of time. Dr. Netschaiev † has found also that an excitation of the sciatic nerve for two or three minutes is able to stop gastric digestion for several hours. This suggested the attempt to excite the nerves supplying the stomach in such a way that no sensory or other reflex impulses could precede or accompany the experimental stimulation.

Madam Schumova-Simanovskaia and I achieved this result with dogs prepared in a manner similar to that which has been now demonstrated to you. Gastrotomy and œsophagotomy had previously been performed, 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, surrounded by 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

* Pflüger's *Archiv.* Bd. xvi.

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

before us. In this way we avoided appreciable discomfort to the animal before exciting the nerve. Observing such precautions, we invariably succeeded in obtaining a secretion of juice from the empty stomach when the nerve was excited by slow induction shocks at intervals varying from one to two seconds (the so-called "rhythmic excitation").

And now that we had the matter under perfect control we attempted to obtain the same in the "acute" experiment, that is to say, with a dog prepared at the time, naturally observing certain precautions. Dr. Ushakov, 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). This was done to prevent all reflex effects on the gastric glands from further operative procedures. The vagi nerves were then 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 placed in a standing position in a suitable frame. In later experiments Dr. Ushakov 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 œsophago-tomised) 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 always 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 secretion began, the stimulus were removed, the secretory effect disappeared gradually, to return however with greater rapidity, if the stimulus were reapplied a few minutes later. The administration of a drug such as atropin, which restrains secretion, destroyed the irritability of the nerves.

The existence of so lengthened a period during which stimulation of the nerves gave no result might be explained, on the supposition that the shock of the operation depresses the excitability of the gastric glands. It can, however, be accounted for in another and more likely way. We have already seen that sham feeding, very soon after the anæsthetic, excites a perfectly normal secretion of juice, and yet in the experiments with narcosis, the period of latency is quite as long as in those without it. It is hardly conceivable that the operation, in spite of the narcosis and the division of the spinal cord, exerted any appreciable reflex inhibitory influence on the gastric glands. We are forced to conclude, therefore, that in artificial stimulation of the vagus, both exciting as well as restraining impulses are transmitted to the glands. This would be most simply explained by assuming the existence of inhibitory nerves acting in antagonism to the secretory, that is to say, in a manner similar to those innervating the heart, the vessels and other organs. This hypothesis will be more fully discussed in connection with the pancreas; we shall then be able to make use of a series of apposite 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 conveys secretory fibres to the gastric glands. It is necessary to repeat, however, that one must not infer the integrity of the vagus to be 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 juice 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. Professor Sanotskii 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 it still remains for future investigations into the work of the sympathetic nervous system —now that we know the relationship between the vagus nerve and the gastric glands—to fully elucidate the problem.

We cannot leave this subject without expressing regret that physiologists have grown accustomed to regard the gastric glands as being independent of nervous influences, and, in consequence, continue to neglect the results just given, although they have been published for many years, not only in Russian but also in foreign literature. Some authors speak of the continuance of gastric secretion after severance of the vagi, but pay no regard to the peculiar alterations of the juice, which is the special point in question. In the case of many other organs we are able to divide their nerves without arresting 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 repetition of our experiment, if only the conditions we have given be observed, will yield the selfsame results in the hands of any investigator, and will leave no room for doubt in the existence of secretory nerves 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 been occupied for any length of time 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 subtract from the total number of his investigations; for not even the greatest care, nor the ripest experience in the making of pancreatic fistulæ, will overcome the incomprehensible sensitiveness of the organ, which only too often annuls its function for a length of time after 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 frequent repetition of the experiments. I must openly confess that I have never undertaken a series of experiments which entailed the sacrifice of so many dogs and with such poor results." *

At the present moment, however, the investigation of the nerve supply of these glands has greatly advanced. We have already stated that Bernstein, in Ludwig's laboratory, and myself with Professor Afanasiev, have shown that sensory stimuli exert an inhibitory influence on the pancreatic gland. Later Heidenhain, with his pupil Landau,† obtained, in a few experiments out of many fruitless ones, an undoubted effect upon the gland, from excitation of the medulla oblongata. On the whole, however, the innervation of the pancreas remained very unsettled. Why could Heidenhain obtain an effect in

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

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

exceptional cases only? 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 were as yet no answers to all these questions.

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

It is definitely settled that the vagus is the secretory nerve of the pancreas. For this discovery we have to thank a special experimental procedure, which 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 appreciable discomfort to the dog. Observe that not a drop of juice flows from the metallic funnel, the wide end of which includes the part of the abdominal wall where the orifice of the pancreatic duct is situated. Now I begin to excite the nerve with an induction current. As you see, the dog remains perfectly still without exhibiting the least sign 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, 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 or five minutes from the cessation of the stimulus. I again apply the current, and obtain the same effect. This is the invariable result upon every dog. It must be added that the vagus nerve was stimulated by other workers with the same purpose in view, and yet what I can now publicly demonstrate was never seen. The reason of success lies in the nature of the preparations for the experiment. These are in particular two: The animal is subjected to no painful sensations, not even narcotised, as is the usual custom elsewhere. On the other hand, owing to the time which has elasped (four days) since the vagus was divided, all circulatory disturbances which would otherwise follow excitation of this nerve are excluded. On the fourth day after its section, the cardio-inhibitory fibres, for example, have lost so much of their irritability that the strongest excitation is scarcely able to produce even a momentary trace of slowing of the heart-beats. To understand this it is necessary to remember that the excitability of different nerve-fibres disappears after section, with different degrees of rapidity. Thus, the cardio-inhibitory fibres lose their irritability earlier than the secretory fibres of the pancreas. In our experiment, therefore, the *glands* have neither suffered by the operation nor by the conditions accompanying the excitation.

But a positive result can also be obtained with the acute experiment if it be only carried out on suitable lines. Our procedure is as follows: Tracheotomy is performed as quickly and painlessly as possible; then the cervical cord is severed from the medulla. This occupies only a couple of seconds, after which artificial respiration is set up. And now we may quietly proceed further. The chest is opened to seek out the vagi below the heart, and then 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 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 remaining operations are prevented, while, by exciting the vagus in the thorax, its influence on the heart's beats is avoided.

Investigations carried out in this manner have shown us 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 observers, the pancreas has proved to be extraordinarily sensitive to circulatory disturbances. It is only necessary to excite its vaso-constrictors or to compress the aorta for two or three minutes, in order to prevent it for a length of 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, the gland of an animal taken even at the height of digestion, often does not yield a single drop of juice.

Great importance must likewise be attached to another circumstance which 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 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 ceased. Moreover, the following phenomenon can often be observed (*Mett*). Suppose the right vagus be excited for a considerable length of time, and a steady flow of juice set up. If now, without interrupting the stimulus, the other vagus be excited in like manner, the secretion is brought to a standstill after a definite, but often considerable length of time. All these phenomena have led to the belief 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 suppose that the inhibitory influences 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 belong to two opposing groups, the same may be rightly assumed, for the glands. It is quite possible that an antagonism of this nature belongs to the general principles of innervation. In the physiological literature of the last few years one may find references here and there to inhibitory nerves of 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 most prominently seen.

Before considering this question more fully, I shall 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 results are from the work of Professor Kudrevetski:

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 in the cannula is observed, but only during the first few seconds; during the later stages of the excitation, and after its stoppage, the onflow is completely arrested. If, instead of the electric current, mechanical stimulation (for example, with Heidenhain's tetanometer) be employed, a different result is observed: soon after the beginning of the excitation a tolerably strong secretion sets in. The same may be obtained by 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 recalls 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 nerve divided some days previously) can the secretory fibres manifest their effects.

In the case of the sympathetic nerve we can now clearly recognise the relationship which exists between the vaso-motor and secretory fibres going to the pancreas. The view expressed regarding the effect of the vagus upon the gland has not been altered by the results of these special modes of stimulation. Its inhibitory effect upon the secretion remains to the full. This gives us good reason for believing that the inhibitory influence of the vagus does not depend upon a contraction of the vessels. The matter has recently received an important advance from the work of Dr. Popelskii. He has, in the first instance, devised 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 set up. If the vagus nerve be now strongly stimulated, a slowing of the secretion—often to complete standstill—is obtained every time without exception. Excitation of the sympathetic, on the other hand, slows, but does not arrest, the secretion, and this only after the lapse of some time. A compression of the aorta only arrests the secretion after two to three minutes. To this it must be added that, according to the latest experiments of François Frank, the vagus nerve dilates rather than constricts the vessels of the pancreas. The possibility of simultaneous excitation 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. Absolutely no inhibition, but rather an augmentation of the secretion made its appearance. Further, by a careful preparation of the nerves, some branches were discovered, the excitation of which 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. Popelskii 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. The possibility is not 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 meet. Why, for example, Heidenhain only obtained 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 proved to be; the innervation of the one is in every respect a copy of the other. It is therefore permissible to fill up gaps in our knowledge of the scheme in one case 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 may be said concerning the experiment of the two French authors on the gastric secretion 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 you will agree, after all that has been said and shown to you, that the existence of secretory nerves to the stomach and pancreas is just as real and indisputable as the classic and universally known fibres for the salivary glands in the chorda tympani nerve. It need hardly be said that, in addition to these special nerves, vaso-motor nerves—constrictor and dilator—also pass to the gland.

LECTURE IV.

GENERAL SCHEME OF INNERVATION OF AN ORGAN—THE NERVOUS MECHANISM OF THE SALIVARY GLANDS—ARTIFICIAL EXCITATION OF THE EFFERENT SALIVARY NERVES.

Constituent parts of a complete innervation apparatus—The special duty of the peripheral terminations of afferent nerves—The specific qualities of nerve-cells—Analogy between the innervation of the salivary glands and that of the deeper-lying digestive glands—The exciting agencies of the nervous mechanism of the salivary glands; their particular properties—Differences between the exciting agencies of the several salivary glands—Variations in the quantity and composition of saliva secreted in response to different natural stimuli—The specific function of saliva and adaptation of the secretion thereto—The mechanism of response, exclusively nervous—The effects of artificial excitation of the efferent salivary nerves—Alterations in the quantity and composition of the saliva under different conditions of artificial stimulation—Discussion of the results.

Gentlemen,—As you have learned in the last lecture, and have in part seen by direct experiment, the nervous system can influence the work of our glands in the most diverse ways. We have seen that the vagus nerve, already laden with other duties, is employed to transmit impulses to the gastric glands and the pancreas. We must also assign to the sympathetic nerve a similar *rôle*. This cannot be questioned as regards the pancreas, and is highly probable as regards the stomach. Moreover we saw good reason for believing that these two nerves contain two different classes of fibres, secretory and trophic, a condition which had already been proved by Heidenhain to exist for the nerves of the salivary glands. We might almost have proceeded a step farther and have divided Heidenhain's trophic nerves into fibres controlling the secretion of the individual ferments. Lastly, we advanced important experimental evidence to show the existence of special inhibitory fibres to the glands, and also that these run in the vagus, the list of whose functions seems almost interminable.

We obtained these results by division and artificial excitation of the nerves to the glands. But when, how and why these nerves are thrown into activity during the normal course of physiological events, has yet to be answered.

In order to avoid repetition, and at the same time give greater clearness to our subject, it may be useful to present to you the general plan of innervation of an organ, since the scheme is seldom completely considered or adequately described in physiological text-books. Consequently, it is not remembered with sufficient precision by the majority of medical men.

A complete nervous 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 an established fact, that nerve-fibres serve only as *conductors* of 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 receivers of the nervous system. Whether the peripheral ends of centrifugal (efferent) nerves are likewise able to serve as receivers of external stimuli has still to be answered. Consequently, when any external agency excites the peripheral terminations of afferent nerves —the receiving stations—in one or other organ, the effect of the stimulus will be conveyed through the centripetal nerves, as though receiving wires, to the central station—the nerve-cells. Here it becomes changed into a specific impulse and then comes back along the centrifugal nerves—the outgoing wires.

The utmost importance is 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 functions of the end-organs with which they are connected are therefore of a purposive nature; in other words, these organs are only called into play by certain definite conditions, suggesting 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 possess a high degree of specific excitability, and cannot therefore have any doubt regarding the specific purpose of the end-organs of other centripetal nerves. But, notwith-

* By the term "external stimulus" I mean here without distinction every outward natural agency, 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.

standing our knowledge of the separate parts of the animal body, we can only form a true conception of the agencies which move the whole complicated machine, when we have examined the specific excitability of the end apparatus of every centripetal nerve, and have discovered all the mechanical, chemical, and other factors which throw each of them into active condition. I always look upon it as indicating a defect in our science when the results of most diverse external agencies acting on a normal physiological process are confessed to be indistinguishable. The description of the work of the digestive canal, as given formerly in the majority of text-books, bore the impress of this inadequacy. To impart to the physician a more correct conception of its different processes is my chief object in giving these lectures, I hope to furnish convincing evidence to show that the alimentary canal is endowed with no mere general excitability, that is to say does not respond indifferently to every conceivable agency, but on the contrary responds only to special conditions which vary in its different parts. Just as men and animals in the outer world are able to maintain their existence and adapt themselves to changing circumstances by the aid of the peripheral endings of their sensory nerves, so every organ, indeed every cell of every organ, is capable of fulfilling its *rôle* in the animal microcosm, and of adapting itself to the activity of innumerable associates, as well as the general life of the whole, solely by virtue of the fact that the peripheral end-organs of its centripetal nerves possess specific excitability.

The same applies to the *nerve-cells* themselves : 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 only from a number of physiological facts but also from various pharmacological data. Thus we learn that different 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 is as necessary to the purposive action of end-organs as the same property of peripheral end-organs themselves.

Hence, our first duty is to endeavour to discover the normal excitants of the centripetal nerves of the glands we considered in our last lecture, or, more correctly, to find out the conditions which excite the *centres*, as well as the peripheral endings of the *afferent nerves*, belonging to those glands. We have, therefore, for each phase of each secretion, to find out what portion of the nervous mechanism is then and there under excitation, and to discover the primary agency by which the excitation is set up. This requires an exact analysis of the stimulating influence exerted by mastication and food upon the nervous mechanism of these glands. When this is done we shall be better able to comprehend the inner meaning of the facts which formed the subject of the second lecture. This, of course, is an ideal programme which we can only follow as far as the present state of physiology permits.

It will be instructive, and, for our further conclusions, advantageous, to glance shortly at the nervous control of the salivary glands. The salivary glands have generally been accepted as types of the deeper lying digestive glands, and when it became necessary to form a conception of the mechanism of activity of the latter, medical science boldly resorted to the analogy of the nervous apparatus of the salivary glands. But attempts to adhere rigidly, in the case of other glands, to the type of innervation which holds good for the salivary, have done considerable harm to the value of the analogy and have retarded a correct knowledge of the working of the abdominal glands. Authors naturally expected to see simple and prompt stimulation-effects under the same conditions which sufficed for the salivary glands, and when these failed they thought themselves justified in denying the existence of any extrinsic nervous control of the abdominal glands. The error is now obvious; the abdominal glands behave in some ways differently from the salivary glands, and to investigate the former successfully, other conditions of experiment are necessary than those which hold good for the latter.

The experiences of daily life teach us at the outset, that the activity of the salivary glands often begins 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 into activity; indeed, the well-known expression, " to make one's mouth water," is based upon this fact. Hence a psychic event, the observation and contemplation of food, must be accepted as an undoubted excitant of the nervous centre for the salivary glands. On the other hand, numerous experiments upon animals as well as everyday experience, teach us that a host of subtances, when brought into contact with the mucous membrane of the mouth, are also able to set up a secretion of saliva. One almost gets the impression that anything or everything brought into the mouth reflexly influences these glands, the only variation being a gradation in the effects, determined by the amount of the stimulation which the substance is able to exert. It appears to me that it is precisely this impression which has retarded the development of the true concept, that the peripheral end-apparatus of the centripetal nerves of the digestive canal are specifically excitable. The facts were more or less correctly observed; their indications were erroneously interpreted.

The great multiplicity of excitants of salivary secretion has, without doubt, some connection with the comprehensive physiological functions of the saliva. This fluid is the first which everything encounters on entering 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 with mucus the bulky and hard so as to facilitate its passage down the narrow œsophagus, and finally submit certain food materials, such as starch, to a process of chemical elaboration. Nor is its duty by any means ended there. The saliva is secreted in the first compartment of the alimentary canal, which at the same time is 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 counteract injurious effects in this way; thus, for example, a strong acid is to a certain degree neutralised, while other corroding substances may be simply diluted, and by mere lessening of concentration have their harmfulness diminished.

Further, when injurious substances have to be wholly removed, the saliva plays the *rôle* of a rinsing fluid; otherwise the material adhering to the mucous membrane of the mouth, might sooner or later enter the blood and there produce noxious effects. This last function is hardly taken into account in physiology, and yet it is evident that the fluid must be of great importance as a cleansing agency. If one only remembers how often it is necessary to expectorate after tasting anything unpleasant (that is to wash out the mouth with saliva), this will be clear. This view finds additional support when we reflect, that a feeling of disgust produces almost as great a flow of saliva as the sight of a tasty meal. In each case the secretion performs the office of forerunner: in the one it prepares for the washing out of the mouth, in the other for the requisite elaboration of the food.

Hence I hold that substances entering the mouth start a secretion of saliva solely because they excite definite physiological sensitivities, and not because the peripheral terminations of the buccal nerves are devoid of specific excitability, and liable to be thrown into action by every conceivable form of stimulus. In other words, the specific excitability of the peripheral endings of the salivary nerves is very susceptible and comprehensive. This is no picture of the imagination; it can be supported by facts. To say nothing of the testimony of earlier authors (which shows that the salivary glands have each particular exciting agencies), we can demonstrate the following facts from material collected in the laboratory.

Dr. Glinski isolated the mouths of the salivary glands in dogs together with portions of the adjoining mucous membrane; carefully prepared short lengths of the subjacent ducts, and transplanted the natural orifices to the cutaneous surface, where the mucous membrane was sutured to the edges of the skin wound. The ducts of the submaxillary and sublingual glands which lie close to each other are, as a rule, transplanted outwards together. The latter gland furnishes relatively little saliva, and of a nature similar to that of the submaxillary. Moreover, the rates of secretion in both run parallel, so that the saliva from both ducts may be conveniently collected together. If the secretion from one gland alone is desired, the duct of the other must be severed in the *frenum linguae*. By means of Mendeliev's cement, the wide end of a small conical glass funnel is attached to the skin surrounding the orifice. To its narrow end, a small test-tube, which serves to collect the saliva, is suspended by wire loops. I now offer a piece of flesh to an animal thus prepared, and, as you see, the tube fills up at once with saliva. I remove the food, 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 third tube is now attached to the funnel, the dog's mouth is opened and some 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 a strong flow of saliva is obtained. A large number of substances may be employed in this way with a similar effect. The excitability of the nervous apparatus of the salivary glands seems so general that one might readily attribute to it the power of response to every form of stimulus. We proceed, however, to another dog, whose *parotid duct*, in a similar manner, has been diverted outwards. The saliva is collected in the same way. We offer the dog a piece of flesh, but to our astonishment no saliva flows, and yet the animal is most eager for the savoury food. We now give it some raw flesh to eat; again the secretion of saliva is as good as absent; only on close observation can one or two drops of saliva be detected 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 think that the variation in the result is not dependent on the specific excitability of the two 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 of the glands to that which we have just seen in two different animals. An analogous experiment with bread was also carried out by Dr. Glinski. The chewing 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 these experiments enable us provisionally 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 is, so to speak, very select in its choice 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 its dryness. Our example illustrates how "purposiveness" is introduced into the working of our glands and also how erroneous is the opinion that the mechanical stimulus is in itself adequate. Indeed, previous authors have already pointed out that dry substances cause a particularly copious secretion of saliva, and yet, notwithstanding, physiological opinion as expressed in text-books recognises a *universal* instead of a *specific* excitability.

A fuller study of the working of the salivary glands has been made in recent years by several investigators, namely, Wulfson, Snarski, Henri and Malloizel,* Heymann, Sellheim, and others. The animals employed were for the most part dogs prepared as above mentioned. Foods of different kinds were either given them to eat, or various substances, such as acids, alkalies or solutions of salts, were introduced into the buccal cavity. In each case the stimulus was kept up for a definite length of time, usually for one minute. The saliva secreted during that period was collected and measured. Determinations were also made of its content of total solids, of organic solids, of ash, and in some cases of its ferment and mucin. The viscosity of the saliva was also measured by noting the time required by a given quantity to flow through a narrow glass tube of definite bore. The following (*see* p. 72) table of mean values obtained in this way is taken chiefly from the work of Sellheim.†

The results shown in this table permit us to make the following deductions: (1) The work of the salivary glands varies widely both in quantity and quality according to the degree and nature of the stimulation; (2) the variations in the quantity and composition of the saliva secreted, do not always run parallel, indeed they often markedly diverge; (3) the differences, nevertheless, admit to a certain degree, of systematic arrangement. Thus, if eatable substances be given to the animal the drier and harder the food, the more the secretion poured out by the mucous glands. Milk constitutes a striking exception to this rule, which particularly applies to the same glands. Much more saliva is

* *Compt. Rend. de la Soc. Biol.*, 1902.

† *Dissert.*, St. Petersburg, 1904.

TABLE SHOWING VARIATIONS IN SALIVA SECRETED IN RESPONSE TO DIFFERENT SUBSTANCES INTRODUCED INTO THE MOUTH.

(FROM OBSERVATIONS BY SELLHEIM, EXCEPT WHERE OTHERWISE STATED).

Substance.	Quantity in c.c.		Viscosity in minutes and seconds.	Total solids per cent.		Ash per cent.		Organic solids per cent.		Quantity of amylase (Malloizel).	Quantity of mucin in 1 c.c. (Malloizel.)	Remarks.
	Sm. & Sl.	P.	M. S.	Sm. & Sl.	P.	Sm. & Sl.	P.	Sm. & Sl.	P.			
White bread	2·2	1·0	1 35	0·969	—	0·377	—	0·592	—	—	—	Sm. and Sl. refer to secretion collected from the ducts of the submaxillary and sublingual glands. P. refers to parotid saliva. Viscosity was determined by noting the time a given volume required to flow through a narrow glass tube of definite bore. The quantity of amylase is expressed in mgms. of sugar produced.
White bread (rolls)	3·0	1·6	1 16	1·433	1·183	0·466	0·399	0·967	0·784	—	—	
Milk	2·4	0·5	3 51	1·416	—	0·429	—	0·987	—	—	—	
Raw flesh	1·1	0·5	2 53	1·277	—	0·321	—	0·956	—	3·8	0·01–0·02	
Quassia extract (1 per cent solution)	1·9	0·7	0 11	0·544	—	0·323	—	0·221	—	—	—	
Formalin (0·5 per cent. solution)	2·8	1·0	0 8	0·666	—	0·499	—	0·116	—	—	—	
Saccharine (10 per cent. solution)	2·8	1·3	0 8	0·621	—	0·400	—	0·221	—	—	—	
Sodium chloride (20 per cent. solution)	4·0	2·0	0 9	0·717	0·883	0·480	0·433	0·237	0·450	0·2	0·0016	
Sodium carbonate (10 per cent. solution)	4·5	2·0	0 13	0·920	1·433	0·620	0·483	0·300	0·950	—	—	
Oil of mustard (emulsion of 1 drop in 100 c.c. water)	4·5	2·1	0 12	—	—	—	—	—	—	—	—	
Hydrochloric acid (0·5 per cent. solution)	4·3	2·0	0 10	0·781	1·200	0·504	0·433	0·187	0·767	—	—	
Sulphuric acid (0·671 per cent. solution)	4·3	2·2	0 11	0·832	1·400	0·601	0·463	0·231	0·937	—	—	
Glycerine	4·0	2·0	—	—	—	—	—	—	—	—	—	
Sand	1·9	0·8	0 13	0·483	—	0·350	—	0·133	—	0·36	—	

N.B.—The stimulus in each case was kept up for one minute and the quantity of saliva secreted during that time observed.

poured out by them for milk than for flesh. The meaning of this will afterwards be referred to. The mucous glands also secrete for eatable substances generally, as contrasted with substances refused by the animal, a more slimy tenacious saliva, richer in solids, particularly in organic solids, including mucin and ferment.

In the case of the parotid glands the influence of the hardness and dryness of the material on the properties of the saliva, is still more marked. On food-stuffs a very concentrated saliva, rich in organic substances, is poured out from these glands. A similar secretion is also evoked by acids and alkalies (sodium carbonate) amongst substances refused by the animal. Other substances of this latter class receive a saliva markedly poorer in organic constituents. Neither water nor physiological salt solution excite any secretion of saliva, whether they be poured into the mouth or taken as drink. Quartz pebbles also, if clean, excite no secretion.

The specific nature of the work of the salivary glands is plainly obvious in these results. The *rôle* played by saliva is above everything that of a watery secretion. When dry hard foods are eaten the fluid is particularly required in order to dissolve their soluble constituents and render them perceptible by the nerves of taste. By so doing, provision can be further made for the removal of physical properties unfavourable to their advance along the alimentary canal. This was shown long ago by Claude Bernard in the case of a horse with parotid fistulæ. It was with the greatest difficulty that the animal could swallow dry food, such as hay or oats, although only deprived of its parotid saliva.

The exception with regard to milk is of interest in view of the fact that when mucus saliva is mixed with it, a looser, more easily digested coagulum is afterwards obtained when it meets with the gastric juice. "Milk saliva" is very concentrated, the richest of all in organic solids; its volume is large, and in particular the ordinary proportionate relationship between the quantities of submaxillary and of parotid saliva is distinctly altered owing to a relatively great increase of the former.

The general function of mucus, however, is to lubricate substances prior to swallowing. Hence all eatable substances receive from the mucous glands a slimy mucin-holding secretion. The uses of saliva for diluting concentrated solutions and for washing away harmful or disagreeable substances are also illustrated in the table. When such are introduced into the mouth the submaxillary glands always pour out a thin watery secretion.

Amongst substances resisted by the animal, some require very special measures and these are apparently provided by the parotid glands. Thus acids and alkalies, in marked distinction to all other chemical irritants, receive a saliva very rich in protein material. Their harmful effects on the buccal mucous membrane are thereby greatly reduced. That these measures are of use is shown by the fact that large quantities of 0·5 per cent. hydrochloric acid can be repeatedly poured into a dog's mouth without causing the least injury, whereas if its tongue be dipped in the same solution for a few minutes the epithelium peels off in a layer as if scalded.

The link of connection by which agencies acting on the mucous membrane of the mouth produce effects on the salivary glands is exclusively a nervous one. If the nerves be divided no influences are transmitted from the one to the other; consequently, it is of importanee to consider the nervous mechanism of these glands. This in its general features has long been worked out. To each gland, efferent (centrifugal or commanding) nerves proceed from the central nervous system by two channels, one by way of the cranial nerves, the other by way of the spinal cord and sympathetic chain. The cranial efferent nerves, at all events, arise from special groups of nerve-cells situated in the medulla oblongata and known as nerve-centres. Those to the submaxillary and sublingual glands emerge by the facial trunk, run in the chorda tympani branch to join the lingual, which they finally leave in the submaxillary region to be distributed to the glands. Those to the parotid leave the brain by the *N. glosso-pharyngeus*, run in its tympanic branch (N. of Jacobson) to enter the small superficial petrosal, from which they pass through the otic ganglion to the fifth cranial nerve and thence by a branch of the latter, the *N. auriculotemporalis*, to the gland.

Besides these, there are nerves which convey impulses from the receiving surfaces, the buccal and lingual mucous membranes, towards the nerve-centres, where they intercommunicate with the efferent nerves. These are known as afferent (centripetal or signalising) nerves. Their peripheral terminations, and probably those of the efferent nerves also, constitute very special portions of the nervous mechanism of the salivary glands.

In the study of these paths most attention has been given to the efferent side. We shall therefore deal with it first and chiefly with facts which bear upon the results of the investigations already related.

By artificial excitation with the induced current, of the chorda tympani nerve as it leaves the lingual, a free secretion of saliva is obtained corresponding within limits to the strength of the stimulus. In a few minutes a quantity of saliva several times the weight of the gland is poured out. After removal of the stimulus, the secretion gradually diminishes to cessation.

By variations in the strength and duration of the excitation not only is the quantity of the saliva altered, but also its composition both in regard to inorganic and organic constituents. The proportion of *inorganic* salts runs parallel with the effect of the stimulus, that is to say, rises and falls with the rate of secretion. This is shown in the following table :

Quantity of saliva in 1 minute.		Percentage content of inorganic salts.
0·400	...	0·472
0·500	...	0·515
0·700	...	0·599
0·900	...	0·616
1·333	...	0·628

The secretion of *organic* constituents is less simple. If the gland has been previously resting, the output of organic substances increases with each increase of the stimulus up to a certain point. But as soon as the gland becomes exhausted, an augmentation of the stimulus brings no addition to the organic constituents. They remain as before, or are even reduced in quantity. The following table (*Heidenhain*) illustrates these effects:

Experiment.	Distance of coils apart in mm.	Quantity of saliva per min. in c.c.	Per cent. of organic solids.	Per cent. of salts.
1	325–265	0·18	1·15	0·29
2	220–210	2·20	1·84	0·44
3	315–295	0·22	1·59	0·32
4	100–80	2·00	2·09	0·58
5	320–290	0·15	1·85	0·34
6	200–180	3·20	1·29	0·58
7	315–295	0·19	0·98	0·25
8	240–200	1·60	0·86	0·37
9	100–50	2·50	1·30	0·57

In the first four of these experiments the quantity of saliva and also its content of organic material increased with the strength of the stimulus. In experiments 6 and 8 the volume increased, but the percentage of organic substance diminished. Example 9 is exceptional ; the stimulus in this case was probably excessive. The percentage of inorganic salts in every case increased with increase of the rate of flow.

The augmenting effect of a strong stimulus on the output of organic constituents is not limited to the period of excitation. It extends to the secretion subsequently produced by a weaker stimulus. This rule does not apply to the inorganic salts. Both effects are seen in the following table (*Heidenhain*) : *

Strength of stimulus.	Quantity of saliva secreted in 1 min. in c.c.	Per cent. of organic solids.	Per cent. of inorganic salts.
Weak	0·17	0·84	0·20
Strong	0·72	2·06	0·46
Weak	0·17	1·67	0·26

* Pflüger's *Archiv*, xvii. 1878.

When the stimulus is prolonged, if other conditions remain the same, the percentage of organic material decreases the longer the excitation is kept up. The quantity of inorganic salts remains practically constant. The following table illustrates these points (*Becher* and *Ludwig*): *

Experiment.	Per cent. of organic solids.	Per cent. of inorganic salts.
1	1·12	0·61
2	1·07	0·61
3	0·93	0·67
4	0·58	0·64

Thus, under artificial excitation of the efferent cranial nerves, important variations in the amount of organic material in the saliva can be produced similar to those occurring during normal activity of the salivary glands.

Under artificial excitation of the sympathetic nerve a secretion of submaxillary saliva also arises, but the effects are very different from those obtained by stimulation of the chorda. The flow is much less, although it begins pretty freely. Soon, however, it declines, and in a short time ceases altogether, notwithstanding continued excitation of the nerve. If a pause be made in the excitation, the flow will begin again on resumption of the stimulus and continue for a time. Thus by intermittent excitation, a quantity of sympathetic saliva sufficient for analysis can be obtained. In the dog the saliva is thick and slimy, containing two to three times more organic constituents than chorda saliva. This does not, however, hold good for all animals. In the cat, the sympathetic is less concentrated than the chorda saliva (*Langley*). Further, when the flow of sympathetic saliva is long maintained the percentage of organic material is much reduced. The saliva in other respects also comes to resemble chorda saliva. Heidenhain collected sympathetic saliva for a period of four and a half hours. The portion first collected contained 3·734 per cent. of organic solids, the final portion 1·488 per cent.

Interesting effects are obtained by simultaneous and alternate excitations of the cranial and sympathetic nerves. Thus, if excitation of the sympathetic nerve be preceded by stimulation of the chorda, a brief, rapid flow of sympathetic saliva results, lasting for some seconds, called by Langley "augmented secretion." By alternate excitation of the two nerves a considerable amount of saliva may be collected, in which the percentage of organic substances steadily declines. The viscidity is also much reduced. In the following table taken from Heidenhain the first experiment shows the effect of a chorda stimulation on the composition of sympathetic saliva subsequently obtained.

* *Zeitschr. f. rat. Med.*, N. F., i. 1851.

EXPERIMENT I.

Nerve excited.		Duration of excitation.		Per cent. of organic solids.
Sympathetic	...	1hr. 57m.	...	5·92
Chorda	...	2hr. 9m.	...	2·02 to 0·82
Sympathetic	...	2hr. 39m.	...	2·38

A stimulation of the sympathetic interposed between two excitations of the chorda likewise reduces the percentage of organic solids in the second chorda saliva. This is shown as follows:

EXPERIMENT II.

Nerve excited.		Duration of excitation.		Per cent. of organic solids.
Chorda	...	0hr. 2m.	...	2·39
Sympathetic	...	6h. 8m.	...	——
Chorda	...	0hr. 2m.	...	1·01

Simultaneous excitation of both chorda and sympathetic nerves gives, when of medium strength, a summation of the effects of both; but, if strong, less saliva is obtained than by stimulation of the chorda nerve alone.

In view of the fact that secretory fibres to the submaxillary and sublingual glands are mixed with vascular nerves in both the chorda and sympathetic nerves,—in the former with vaso-dilator, in the latter with vaso-constrictor,—it is worthy of note that progressive reduction of the blood-supply to the gland by compression of the blood-vessels from which it is supplied, reduces the amount of saliva obtained by chorda stimulation, ultimately to *nil*. This reduction in volume is accompanied by an increase in the content of inorganic salts but not of organic constituents.

A similar diminution is seen, if the chorda stimulation be accompanied by section of the cervical spinal cord and consequent slowing of the circulation through the gland. In this case, however, the organic constituents are increased. Again, when a flow of the saliva is obtained by injection of pilocarpin, interference with the blood-supply by bleeding to the extent of 150 to 200 c.c. causes a reduction in the volume produced with increase of its organic constituents, as compared with the saliva secreted under the influence of the drugs alone.

Finally it is of interest to bear in mind that atropin, which annuls the secretory influence of the chorda, has no paralysing effect on the sympathetic fibres unless employed in very large doses.

The effect on the *parotid gland* of stimulation of its cranial nerve is similar to that of the chorda stimulation on the mucous glands. The result of sympathetic stimulation is somewhat different. As a rule no secretion is excited by the latter. Marked changes are, however, produced in the microscopic appearance of the glands if the stimulation be long continued. Moreover, excitation of the sympathetic, either before or in conjunction with the auriculotemporal, causes a decided increase in the organic solids of the saliva, as compared with that secreted by stimulation of the cranial nerve alone. The following table from Heidenhain * illustrates these effects:

Experiment.	Nerve or nerves excited.	Duration of excitation in minutes.	Position of coil.	Weight of saliva in grammes.	Per cent. of total solids.	Per cent. of salts.	Per cent. of organic solids.
1	Jacobson's	11	110	2·6875	0·56	0·31	0·24
2	Both	34	110–108	3·0148	2·42	0·36	2·06
3	Jacobson's	12	100–90	3·1068	1·03	0·26	0·76
4	Both	20	90–80	2·6251	1·74	0·32	1·41
5	Jacobson's	21	70	2·9278	0·57	0·36	0·21
6	Both	28	70–75	2·9883	0·64	0·25	0·38
7	Jacobson's	19	75	3·0918	0·49	0·32	0·16

"Both" here refers to the two nerves, Jacobson's and the cervical sympathetic.

In seeking an explanation of the foregoing results of artificial excitation, it may unhesitatingly be accepted that the efferent nerves to the salivary glands convey fibres which directly influence the production of their secretions apart from those which act on the blood-vessels. Heidenhain, as stated in the last lecture, believes, and his view has been widely accepted, that two kinds of secretory fibres exist, namely, on the one hand, those which control the escape of water and dissolved salts (secretory proper); on the other, those which regulate the production of organic constituents (trophic). In the chorda tympani nerve, together with vaso-dilator fibres, there is a large supply of secretory and a small number of trophic fibres: in the sympathetic together with vaso-constrictor fibres there is a small number of secretory but a rich supply of trophic fibres. According to other investigators, however, secretory fibres of only one kind exist, these being associated with vascular nerves having two opposite effects on the blood-vessels.

Variations in the quantity of saliva, arising under different conditions, and to a certain extent in its quality, can be readily explained by this theory; not so easily the divergence in content of the inorganic and organic constituents under like conditions of stimulation, nor the occurrence of histological changes in the cells of the parotid gland when the sympathetic is stimulated, although no flow of saliva is excited. It is not possible to decide with certainty between the two theories without further knowledge.

The results obtained from natural stimulation, as shown in a previous table, are explainable on either hypothesis. The secretion of

* *Op. cit.*

a concentrated saliva, for instance, could arise from a definite, proportionate relationship between the degrees of excitation of secretory and trophic fibres, or between the degrees of excitation of secretory and vascular nerves. In the same way, a secretion of dilute saliva may be accounted for by either theory. But that different qualities of secretion can occur with equal rates of flow speaks rather for Heidenhain's hypothesis. Malloizel* has, however, shown that after section of the cervical sympathetic and removal of the influence of its trophic fibres, the natural stimulus of an eatable substance calls forth even a more concentrated saliva than before. A fact which is difficult to explain by either theory has, however, been recorded by the same observer, namely, that after atropin is given to a dog with permanent salivary fistula, a thick saliva is poured out in small quantity by the mucous glands, not only for eatable substances, such as flesh, but also for substances refused, for example, salt, and in the latter case the quantity of saliva is less than in the first, the reverse of what happens under normal conditions. A similar response was shown by a dog with the chorda tympani nerve regenerating after section. These observations strengthen our claim that neither theory is to be regarded as final.

This result, though apparently opposed to Heidenhain's theory, is not necessarily so. We have seen that a similar effect, obtained by stimulation of the chorda after section of the cervical spinal cord, is probably to be accounted for by the disturbance of the circulation which the latter operation entails.

* *Op. cit.*

LECTURE V.

THE AFFERENT SIDE OF THE SALIVARY NERVOUS MECHANISM—THE FUNCTION OF THE PERIPHERAL END-ORGANS OF THE BUCCAL NERVES—THE PSYCHIC SECRETION OF SALIVA—FICTITIOUS FEEDING AND THE PSYCHIC SECRETION OF GASTRIC JUICE.

Reflex secretion of saliva from stimulation of various sensory nerves—Reflex inhibition of the secretion—The functions of the end-organs of the buccal nerves—The psychic secretion of saliva—The result is due to a conditional reflex—Conditions which modify it—Theory of its causation—The experiment of fictitious feeding—Mechanical or chemical stimulation of the buccal mucous membrane has no effect on the gastric glands—The experiment of Bidder and Schmidt on psychic secretion of gastric juice—Conditions for success in the experiment.

The afferent or centripetal side of the salivary nervous mechanism is relatively simple although the channels of influence are numerous. A profuse secretion of saliva can be obtained by stimulation of the proximal ends, not only of the lingual and glosso-pharyngeal nerves, but also of many others, as for example, the vagus, the splanchnic, the auricular, the crural and the sciatic nerves. These reflex effects do not occur if the cranial efferent nerves to the glands have been divided. As a rule no reflex influence is transmitted through the sympathetic channel. The reflex secretion of saliva is often, but not always, limited to the gland on the side of the nerve excited. Not only variations in *quantity*, but also in the composition of the saliva may be elicited by stimulation of these afferent nerves. Thus by excitation of the sciatic, the flow of saliva is hastened, its concentration raised and the amount of organic substance increased. These effects are obtainable even after division of the cervical sympathetic and hence can be produced through the chorda alone. According to Heidenhain, however, the effect on the composition of the saliva may also be transmitted in part through the sympathetic nerves. If on stimulation of the sciatic, after unilateral division of the cervical sympathetic, the saliva be collected from both glands it is found to be less concentrated from the gland on the side of the divided nerve than the saliva collected on the normal side.

In some cases, evidence of reflex inhibition has also been elicited. Further, the following somewhat remarkable results of Ostrogorski * point to the existence of an inhibitory mechanism. Ostragorski divided the *chorda*, mostly in cats, sometimes in dogs, and gave pilocarpin, after which he found that excitation of various sensory nerves during the phase of declining secretion, caused an augmentation of the flow of saliva. The effect, whatever it may have been, must in this case have reached the gland by way of the sympathetic nerve. By modifications of the experiments (such as the use of strychnine to heighten the irritability of the nerve centres, and maintenance of the secretion by periodic excitation of the chorda), Ostrogorski satisfied himself at the outset that the result could not be ascribed to increased excitement of the nerve-centres, nor of the secreting cells, nor was it related to variations in the blood flow through, or blood pressure in, the vessels supplying the gland. Further, and quite unexpectedly, the same effects were obtained, though in less degree, after section of the cervical sympathetic. The animals were in all cases fully curarised and no influence on the salivary secretion could be traced to collateral sensory excitation. Ostrogorski therefore concluded that the pilocarpin must have paralysed the restraining action of certain inhibitory nervous influences, conveyed to the glands by other channels than those already known. The experiments, however, require repetition.

Of particular interest is the *rôle* played by the receiving or peripheral ends of the afferent nerves from the buccal mucous membrane, which take part in the salivary reflex. In normal life it is by their aid that the secretion of saliva, its rate, and particular curve of flow are determined. They officiate in deciding the most minute, exact and highly specialised adaptation of the salivary glands to the nature of objects on which their secretions are poured out. We all know the various properties, physical, chemical, &c., of external objects, which we recognise in the buccal cavity. It is by means of these peripheral end-organs that we are made cognisant of them. Whether all the end-organs of the sense of taste take part in each and every variety of the simple salivary reflex is difficult to definitely determine. Experiments carried out by Heymann † bearing particularly upon this question support the affirmative. The investigations were carried out on dogs after the cerebral hemispheres had either been removed or their activities annulled by large doses of curare, the results being in both cases identical. Observations were made on the three pairs of salivary glands

* *Dissert.*, St. Petersburg, 1894. † *Dissert.*, St. Petersburg, 1904.

and also the orbital. It is not surprising that the defects of the acute experiment should have made themselves particularly obvious. In many of the experiments the activity of the glands was wholly destroyed for a considerable time. In most, however, it returned again, though often very slowly and incompletely. Nevertheless a sufficient number of positive results were obtained to make it clear that all stimuli which are subjectively perceived in the mouth by the end-organs of taste or otherwise, find their use in the ordinary reflex control of salivary gland activity.

The mechanical stimuli were sharply differentiated from the chemical. Under the same conditions the one was effective, the other not; or again, the one elicited a secretion when applied to a definite region of the buccal mucous membrane, the other from a different region.

Diverse forms of the mechanical stimulus, as in the normal animal, gave dissimilar results. Sprinkling an indifferent powder on the tongue excited one gland to activity, not the other. Scratching the tongue with the finger-nail likewise gave converse effects on the glands.

The response of the different glands to different chemical stimuli (acids, alkalies, salts, bitters) was also characteristic as regards the quantity of saliva, the seat of action, and the influence of local conditions on the results. Dry foods, such as meat powder or biscuit powder, produced a much stronger flow of saliva than if moist. The normal specific variations in the *composition* of the saliva were less satisfactorily preserved. The results were also more constant from the submaxillary than from the other salivary glands.

The topographical distribution of the positive response to chemical stimuli, such as bitters, &c., and the alterations produced by drugs, such as *Gymnema sylvestre* and cocaine, corresponded to their effects on the nerves of taste. We have therefore in the salivary reflex an objective means of studying the distribution of the end-organs of taste. The normal activity of the salivary glands is determined by a series of specific influences to which these organs respond. An example from the publication of Sellheim illustrates this fact. As already stated, when acids or alkalies are poured into the mouth of a dog with permanent salivary fistulæ, they excite a free secretion of parotid saliva, which contains double as much organic substance as of inorganic. After section of the lingual and glosso-pharyngeal nerves the specific effect on the composition of saliva is no longer observed, although the quantity obtained is almost as great as before. The general reflex from the buccal mucous membrane is preserved, the specific response to acids and alkalies is lost. It is remarkable, however, that for eatable substances, the saliva secreted is almost as rich in organic material as before the division of the nerves. The following table shows these effects :

Stimulus applied to the mouth.	Per cent. of solids.	Per cent. of salts.	Per cent. of organic material.
Before section of the glosso-pharyngeal & lingual nerves:			
Meat powder . . .	1·500	0·400	1·100
Sulphuric acid solution .	1·425	0·475	0·950
Sodium carb. solution .	1·433	0·466	0·967
Sodium chloride solution	0·900	0·466	0·437
After section of the nerves :			
Meat powder . . .	1·500	0·475	1·025
Sulphuric acid solution .	0·760	0·400	0·360
Sodium carb. solution .	0·700	0·425	0·275
Sodium chloride solution	0·725	0·400	0·325

We now come to view the work of the salivary glands from a new aspect. In the course of our experiments, we found that all the phenomena of adaptation which we saw in the salivary glands under *physiological* conditions, such as the introduction of stimulating substances into the buccal cavity, appeared in exactly the same manner under what we may call *psychological* conditions. That is to say, when we merely drew the animal's attention to given substances agreeable or disagreeable, or, when we offered it particular foods, a secretion either immediately appeared, or did not appear, in accordance with the previously ascertained effects of the substances when directly brought into the buccal cavity.

You have already seen that the mere sight of food was sufficient, in the case of a hungry dog, to elicit a flow of saliva from the ducts of the submaxillary and sublingual glands. I repeat the experiment to-day, and present to the same animal, a piece of flesh. Again a secretion of stringy saliva begins to drop from the funnel attached around the orifices of the ducts, into the cylinder below.

After a little is collected I take away the flesh, change the tube and make pretence of throwing pebbles into the dog's mouth. As you see, no saliva flows. Instead of the pebbles I use sand. A free secretion of thinner, less tenacious saliva at once sets in. When enough is collected to compare the viscidity of the two samples, I pour them both into small thistle-head funnels, the stems of which are drawn out to fine tubes of about two millimetres diameter. As you see, the drops fall much more slowly from the funnel filled with the first sample.

I now change the tubes again, and present to the animal the bottle containing the acid solution used for exciting a flow of saliva by application to the buccal mucous membrane. The dog is familiar with the appearance of the bottle and I proceed, as it were, to pour some of the contents into its mouth. A free secretion of saliva, thinner, more watery, and less viscid than that poured out at sight of flesh, begins to fall from the funnel.

I now take a dog with parotid fistula prepared in a similar way. You have previously seen that the exhibition of a piece of flesh meat produced no secretion from this gland, but if I use dry meat powder, as I do now, a rapid secretion of clear limpid saliva at once begins to flow. Similar effects are produced by the sight of dry bread, and of the acid bottle.

The response of the salivary glands in this way to "psychic excitation" has formed the subject of extended investigations in the laboratory since we first drew attention to it. It has been abundantly shown that the "specific adaptation" of the secretion elicited by direct application of the substances to the buccal mucous membrane applies, at all events qualitatively, to the same substances acting from a distance.

The peculiar feature of this *psychic excitation* at first sight seemed to be that the stimulus acts without coming into direct contact with the receiving end-organs of the nervous apparatus. But when more closely considered it will be seen that this constitutes no real basis of distinction. In the psychic form of the experiment the substances act by specific excitation of other end-organs, namely, those of the nose, eyes, and ears, which we know are receptors for many influences originating reflexes from a distance.

In the *physiological* form of the experiment, however, the response of the glands directly corresponds to the intrinsic properties of the object on which the saliva has to operate. These properties constitute the immediate stimulus. The secretion elicited is not dependent on conditions or surroundings accessory to those qualities. The PHYSIOLOGICAL REFLEX may therefore be said to be UNCONDITIONAL. Relatively speaking, it is so. In the *psychic* form, on the other hand, qualities unessential or merely incidental play an important *rôle*. The optic and olfactory properties influence the result, although, dissociated from the particular object, these qualities have no secretory influence of themselves. Even conditions altogether collateral to the stimulus, such as the room and furniture of the room in which the animal is placed, the vessel containing the food, the presence of the attendant who ordinarily feeds the animal, the sound of his approach, produce an effect. It is not surprising that the marked feature of a result dependent upon so many factors is a considerable degree of fickleness and inconstancy. The psychological effect in comparison with the physiological is dependent on a far greater number of conditions. The PSYCHIC REFLEX is a CONDITIONAL one, but it never occurs without perceptible stimulation of some sense-organ from without.

A psychic response is only obtained when the animal is hungry. To explain this, it may be supposed that the salivary secretory centre is influenced by the state of the blood in hunger, much as the respiratory centre is affected by an overcharge of carbon dioxide in asphyxia Further, the pyschic response very rapidly diminishes on repetition of the stimulus, the rapidity of disappearance being dependent on the frequency of repetition. The stoppage cannot be due to fatigue, since the stimulus is very weak ; and, moreover, the response may be at once restored by applying the excitant directly to the buccal mucous membrane—for example, by giving the animal dry food to eat, or by pouring dilute acid into its mouth. The production of a direct reflex restores the response of the secretory centre, the restoration being all the surer and more effective the greater the flow of secretion. Further, if a secretion is not established, all other stimuli, no matter how strong or complex, or how much they excite the dog's attention, are ineffective.

The arrest of one conditional reflex does not prevent the occurrence of another from the same gland. Thus, when the sight of bread ceases to evoke a flow, the exhibition of the acid is no less effective than at the outset. Once lost, however, to a given substance the "psychic reflex" does not return for at least two hours.

All the properties of the exciting object apparently combine to produce the distant effect, but each acts singly, though less powerfully, than the combination of the whole. Thus the mere smell of dry meat-powder on the hands of the attendant is sufficient to excite a flow. Even the artificial or extraneous properties superadded to those of the stimulant, become after repetition, effective by themselves. Instances of this nature are as follows: If the acid fluid used to excite a direct reflex be coloured dark, the subsequent presentation under otherwise similar conditions of a non-acidified fluid of the like colour sets up a secretion. If a definite musical note be repeatedly sounded in conjunction with the exhibition of dry meat-powder; after a time the sound of the note alone is effective. Similarly with the exhibition of a brilliant colour. These facts are being made use of to ascertain the acuteness of the dog's senses for musical sounds and for colour perception respectively. It is surprising what small differences in the pitch of the note prevent it from being effective. In this way the psychology of the dog is being made a subject of objective study and an immeasurably wide field for new investigation is opened up before us.

Interesting results have also been obtained from another variation of the experiment—namely, the combination of a non-effective stimulus with an effective one. Moist flesh alone produces no secretion, but if acid be poured over it, a secretion is set up. Further, and very curiously, the distant effect of a feeble excitant is strengthened by combination with a non-excitant. Again, the result of combining substances like dry bread and moist flesh is not always what one would expect, and seems to depend on which of the two the dog most keenly desires—that is, judging from its efforts to obtain it. In the instance given no secretion flows; the usual bread effect is here restrained in some way by the negative influence of the more eagerly desired flesh. The same result may be obtained by merely imparting the smell of flesh to the bread. Inhibition of the conditional reflex is also produced in other ways. Thus, the strong excitement produced by seeing a second dog fed with the same bread is sufficient to arrest the flow previously elicited in the first animal.

In framing a hypothesis to account for the psychic flow of salivary secretion, it is important to bear in mind that it is intimately connected with the essential unconditional response. The former only comes into existence and can only continue by virtue of its association with the latter. It is permissible to suppose, therefore, that when the salivary reflex is excited by the contact of a stimulus with the buccal mucous membrane, the influence aroused by the essential salivary-secreting properties of the object as it proceeds to the "nerve centre" is reinforced by effects arising from qualities unessential to the main result. These latter find their way to the salivary centre by circuitous routes, through other gateways and along other paths. It would appear as if the salivary centre, when thrown into action by the simple reflex, becomes a point of attraction for influences from all organs and regions of the body specifically excited by other qualities of the object. The connection, however, of these incidental centripetal paths with the centre is a loose one, easily interrupted, and needs constant repetition of the associated stimuli to preserve it. But nevertheless, the establishment in this way of temporary relationship between external objects and important life processes, as well as the ease with which they are lost, are matters of very considerable value to the organism. By such means functional activity is better adapted to surrounding conditions, while, on the other hand, readjustment is readily permitted when the conditions alter.

On these lines an explanation may also be offered for the fact that the sight of flesh arrests a salivary secretion set up by the sight of bread. The vigorous efforts of the animal to obtain the flesh indicate that a motor centre is strongly excited at the same time. This, therefore, becomes as it were a more potent centre of attraction, to which the collateral paths of influence are for the time being shunted and upon which the unessential qualities of the object play. This explanation is supported by the fact that the secretion set up at sight of bread is quickly annulled if another dog is seen eating the same food: the motor reaction is much increased, the salivary reaction as it were inhibited. That many other definite specific reflexes are also hindered or arrested by too great eagerness, as well as by concomitant motor effects, is well known.

These experiments have also taught us that eager desire, as manifested by the efforts of an animal to obtain a particular food, is not the essential factor underlying the psychic response. Presentation of dry meat-powder or dry bread, for which the animal has no particular inclination, produces a copious flow of saliva; moist flesh, for which it actively strives, produces little or none. Given favourable conditions all that is required for a positive effect is to awaken the animal's attention. We must, therefore, in future, distinguish between gland secretion and muscular reaction. For eager desire we must substitute attention. It is important to state that the conditional reflexes disappear on removal of the cerebral hemispheres.

It may be added that the specific adaptation of secretion to the qualities of the stimulus does not require the assumption of anything in the nature of so-called vital action. It signifies nothing more than the existence of an exact and close interdependence between the elements of a complex system, with a continuous adjustment of the whole to variations in the surroundings. The same applies to every non-living body. A complex chemical substance, for instance, can only preserve its state so long as the equilibrium of its atoms and atomic groups is undisturbed by alterations in the external forces which play upon it.

The second reagent which is poured out on the raw material in the digestive canal is the gastric juice. We have, therefore, to ask, how, in the normal course of events, the work of the gastric glands, which prepare this juice, is called into play? With the first, and manifestly important factor, related thereto, you are already acquainted. I refer to the production of gastric juice by the empty stomach, as a result of the chewing and swallowing of food in the so-called sham feeding of an œsophagotomised dog. When one remembers the absolute certainty and the intensity with which this effect makes itself evident, by the secretion of a large quantity of juice of high digestive power, the exciting agency which brings it about 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 appeared (and when I previously drew your attention to the fact I expressed the opinion) that we had here a simple reflex effect from the cavity of the mouth playing upon the secretory nerves of the stomach. Now, however, I assert quite emphatically that this cannot be the case. We have, indeed, in the activity of the salivary glands an analogous phenomenon—that of which we have just spoken. We might, for instance, apply to the mouth 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 a divided œsophagus, I try such an experiment, using one of the most effective chemical stimuli to the buccal mucous membrane, viz., the 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 can experiment in the same way with a number of other substances: salines, 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. For example, we may wipe out the dog's mouth with a sponge soaked in the solution used in the experiment, but always with the same negative result. We may finally give pieces of the sponge, or even smooth stones of considerable size, to the dog to swallow, passing the objects back behind the anterior pillars of the fauces and receiving them again as they fall from the upper portion of the œsophagus. It may be added that a well-taught dog puts up with all these procedures without the slightest difficulty. 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 if they are placed in the fore 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 fore 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 can collect 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 execute their work in normal manner. At one time we even had a dog which voluntarily took the stones out of one's hand and swallowed them; seeing our object in early experiments the animal soon 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 concomitant stimulation of nerve-centres; 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 intrinsic influence of the sham feeding consist, an influence we have not been able to reproduce in our analytical investigation? There is only one thing to think of, namely, the interest aroused by the sight of food, and the feeling of satisfaction and contentment derived from having it.

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, is sufficient to cause a flow of gastric juice from the empty stomach. We shall presently have occasion to observe this result. Here I bring before you another dog, having, like the previous one, 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 begin to excite the animal's attention 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 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 observation of 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, as a rule, the

* *Op. cit.*

greater the desire on the part of the dog for the food, the more certain and intense is the secretory effect. In many cases it corresponds exactly with the effect of the sham feeding.

Here is an experiment of Professor Sanotskii, in which the secretory effect of 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 below:

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 contemplation of food, instead of being less effective than the sham feeding, actually excelled it.

Considerable variations are seen in the psychic effects of different foods, in regard not alone to the quantity, but also to the composition of the juice secreted. At sight of milk, less juice is secreted than at sight of flesh or bread; further the milk juice contains less pepsin than either of the others, even if the rate of flow be similar. These results are not dependent on the keenness of the animal's desire for food, so far as can be judged from its efforts to obtain it (*Sokolov*).

Psychic excitation of the gastric glands has also been observed in man, though most clinicians have failed to obtain it, through lack of sufficient care and detail in their arrangements. Bulavinzev,* who has taken great pains and used much ingenuity to arouse a desire for eating in the subjects of his operations, has constantly obtained results which agree with those seen in animals.

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 even mentioned. We shall therefore

* *Dissert.*, St. Petersburg, 1903.

consider how the matter must be dealt with by those who wish to observe the effect. It is only under certain conditions that it can be seen. First, 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. Second, the success of the experiment is dependent upon how freely and how long beforehand the dog has eaten, and also upon what it is offered, whether food that excites its desire or leaves its interest unawakened. It is known that dogs have very different tastes, just as men have. Third, one may find among the dogs, positively indifferent ones, incapable of being roused in this way by anything not actually within their mouths, and patiently waiting till the food is given them. Hence for success in the experiment, impressionable and excitable animals are necessary. Fourth, one has to reckon with the understanding and cunning of the dog, a factor which is not lightly to be disregarded. Often the animal perceives at once that it is not intended to receive the food, becomes annoyed thereat, and turns away offended at the farce enacted before it. We must, therefore, so arrange matters that the animal does not get the impression that it is going to be disappointed, but on the contrary that it is to be fed in reality. If attention be paid to these conditions the experiment of "psychic excitation of the gastric secretion" will be found to be as reliable as the experiment of sham feeding. Indeed, long study of the gastric secretion under different conditions convinces one of how dangerous a source of error this psychic excitability may be in various experiments. We must constantly keep the possibility in view and guard against it. If the dog has not eaten for some time, every movement, the going out of the room, or reappearance of the attendant who ordinarily feeds it—in a word, every little triviality—may give rise to excitation of the gastric glands. The minutest attention is necessary to avoid sources of error, and we should not be far wrong if we said that in former investigations much of what has been ascribed to the effect of this or that agency, was in reality a result of unobserved psychic influence. Consequently, to verify our own conclusions concerning the effects of different procedures, 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 chief secretory effect is due to the psychic stimulus, that is to say, to the desire of the animal for food and the pleasure of having it.

The value of the act of eating as a factor in the secretion of gastric juice was indicated by Blondlot about the middle of the last century. Richet also observed in a patient with gastric fistula (performed on account of impassable stricture of the œsophagus) that the presence of condiments in the mouth elicited a secretion of gastric juice. In animals the subject was first systematically investigated by myself and Madam Schumova-Simanovskaia.

In view of the importance of the effect of eating on the secretion of gastric juice, a matter which will become more apparent when the succeeding stages of digestion are investigated, we spared neither time nor trouble to arrive at a correct explanation of the results. We performed numerous modifications of the sham-feeding experiment, and these have confirmed the opinion now set forth. If the dog is prepared by a fast of two to three days, a very copious secretion of gastric juice is always obtained by the fictitious feeding, no matter what may be given it to eat, whether boiled or raw flesh, bread or coagulated egg-white, &c. If the dog has not fasted, that is to say, has been fed fifteen to twenty hours before, it picks and chooses amongst the different foods, eating one with great greed, tolerating another, and refusing altogether a third, and the juice either does not flow at all or manifests great variations in quality and quantity. The more eagerly the dog eats, the more juice will be secreted and the greater its digestive power. 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 devour bread with greater appetite than flesh. In these cases more and stronger juice is obtained by sham feeding with bread than with flesh. Here is an instance: a dog is given boiled meat cut into pieces of definite size, and the pieces follow each other at regular intervals. The animal eats, but soon, from its behaviour, you see that it has no particular relish for the meal, and this is confirmed by the fact that after fifteen or twenty minutes it ceases eating. 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, either at once or next day, give the same dog raw flesh in pieces of the same size and at the same rate as before. The taste of the raw meat is much relished, the dog eats for hours, and the secretion of gastric juice, which begins precisely after five minutes, is very active. With another dog, which prefers boiled to raw meat, exactly the reverse occurs. Thus the influence of fictitious feeding on the peptic glands varies with the food. Milk is much less effective than either bread or flesh. With sham feeding it frequently produces no secretion, and when it appears the juice has a low digestive power. It is worth remembering that the juice secreted *at sight* of these foods shows similar variations in quantity and quality.

In sham feeding, when the food is relished by the dog, the rate of secretion is as a rule maximal, the concentration of the juice being above the average. Further, no matter how long the secretion is maintained by a given fictitious meal, the output of ferment is undiminished. Indeed the later portions of the fluid are more concentrated, and have a stronger digestive power than the earlier, owing probably to a reduction in volume, as the result of a large escape of water from the body.

If sham feeding be carried out daily in a fasting animal, the secretion stops about the fourth day. Enemata of water then restore it, and by using these the flow may be maintained till about the tenth day, when it again stops. If saline enemata be now given, instead of water, the secretion once more returns and continues at least till the fourteenth day. The most suitable strength is 10 per cent. sodium chloride. Even to the end there is no observable diminution in the proportion of pepsin.

It is not surprising that in fictitious feeding the psychic influence may readily become a dominant and independent factor. All the conditions enumerated above, which are necessary for success in obtaining gland secretion at sight of food, hold good collectively for the sham-feeding experiment. The dog eats with greed, the food received is pleasant, it not only imagines food but actually eats it, and has no reason to feel disappointed, for naturally the idea does not occur to any of the dogs that all their trouble is in vain.

Consequently, in fictitious feeding, the excitation of the nerves of the gastric glands by the process of chewing and swallowing depends largely on a psychic 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 these 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 lies in this, that the ultimate object is attained by the co-operation 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 exertion, 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 (much as in the case of the salivary glands) the first and strongest impulse which arouses the activity of the gastric glands. This especially applies to the two latter senses, since they are only excited when the food has arrived very near to or has already entered the organism. Through the medium of this response, nature, resourceful and unerring, has linked the seeking and finding of food, with the commencement of digestion. That this initiation of secretion should stand in closest connection with an everyday phenomenon of human life, namely appetite, might easily have been surmised. Thus appetite, so important to life and so full of mystery to science, here at length assumes a tangible existence and becomes transformed from a subjective sensation into a concrete factor within reach of physiological investigation.

We are therefore justified in saying that appetite is the first and most potent exciter of the secretory nerves of the stomach, a factor which embodies in itself something able to compel the empty stomach of the dog during the fictitious meal to secrete large quantities of the strongest juice. A good appetite in eating gives origin at the outset to a vigorous secretion of the most active juice; where there is no appetite this juice is absent. To restore appetite to a man, means to provide him with a large stock of gastric juice wherewith to begin the digestion of a meal.

LECTURE VI.

PLACE AND IMPORTANCE OF THE PSYCHIC OR APPETITE JUICE IN THE SECRETORY WORK OF THE STOMACH—THE INEFFICIENCY OF MECHANICAL STIMULATION OF THE MUCOUS MEMBRANE.

The psychic secretion is the normal commencement, in the majority of cases, of the secretory activity 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 when psychic juice is 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 of food with the stomach-wall may indirectly set up activity of the glands by awakening or increasing the desire for food.

GENTLEMEN,—On the last occasion we learned something of 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: it consists in the desire for food, 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 say explicitly, APPETITE SPELLS GASTRIC 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, therefore, desirable that we should 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

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

definite *rôle* to be assigned to it? What course does gastric digestion take when it is absent? Fortunately experiment furnishes satisfactory answers to all these important questions. We have only to regret that these answers have been so long delayed.

Let us recall how the secretion of gastric juice proceeds after feeding with flesh or bread in the case of the dog with the isolated miniature stomach. The following are the quantities and digestive capabilities of the first and second hourly portions of juice after the administration of 200 grms. of flesh and bread respectively (experiments by Dr. Khizhin);

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 that the secretion of the first hour is virtually identical in the two cases both as regards quantity and digestive power, and only in the second, is the secretory work altered by the nature of the food. How are we to explain the secretion which takes place at the commencement? Is it not the same we have already seen in the sham-feeding experiments? Is not this first onset of the stream, 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, it is clear that what occurs in fictitious feeding cannot wholly be absent from normal feeding, since the former is nothing else than the isolated commencement of normal digestion. This natural inference is fully confirmed, if the secretion of the first hours after eating flesh and bread be compared with that after simple sham feeding. In normal feeding with both flesh and bread, the identically similar digestive power of the first hourly portions is strikingly high, and this power coincides with what is observed in sham feeding. Further, if from the quantity of juice secreted by the miniature stomach during the first hour after normal feeding, we calculate 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—we again find that the calculated quantity approximately corresponds to the mean amount obtained by sham feeding. Finally, the fall in digestive power or quantity of juice (with flesh, decrease of digestive power; with bread, decline in the quantity of juice) which sets in soon after eating the food, indicates that the conditions preceding the fall are connected with the ingestion of food—*i.e.*, with a transitory factor which soon disappears and gives place to other influences. Our explanation becomes still more convincing when we consider the effects of other foods. If we give the dog, for example, something else to eat which it does not relish to the same degree as flesh or bread, we find the initial increase in quantity and strength of juice does not appear. Thus after normal feeding with milk, which in sham feeding, especially of short duration, calls forth, as a rule, no secretion, or at all events very little, the rapid flow of the commencement—the already-mentioned initial rise—absolutely fails to appear. You have already seen figures which deal with this matter; I think it necessary, however, to bring them forward again in order that you may compare them with those just given for flesh and bread.

The dog received 600 c.c. of milk (experiment by Dr. Khizhin):

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

In the above way we began an analysis of the variations of our secretory curve. But owing to the importance of the matter, we could not be satisfied with conclusions drawn from the earlier investigations. It was necessary to turn 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 Privatdocent Kotliar and Dr. Lobasov.) Each time after the dog received its 100 grms. of flesh we saw a rise both in the quantity and in the digestive power of the juice. The following table gives 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, the variations of digestive power only are represented.

It is clear that the increase, not alone in digestive power but also in volume of juice, is connected with the act of taking food.

It nevertheless appeared of interest to determine directly the volume and properties of the secretion from the main stomach set up by the act of eating in the case of the dog with the isolated pouch. We endeavoured, therefore, at the beginning, to imitate the conditions of sham feeding as they occurred in the dog with divided œsophagus. In addition to the fistular orifice leading into the miniature stomach, another was opened into the main portion of the organ. We now fed the dog in the ordinary way with small pieces of flesh, which 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 from both the large and small stomachs simultaneously. The secretion ran a corresponding course in the two cavities and simultaneously ceased in both after the administration of food was stopped. Here is an instance taken from an experiment performed by Dr. Lobasov.

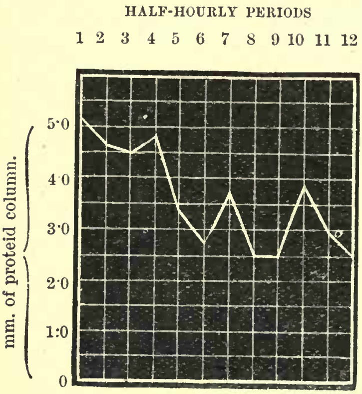


FIG. 13.—Curve of digestive power constructed from the foregoing table.

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. It also came to an end in both at the same time.

Hours.	Miniature stomach.		Main stomach.	
	Quantity of juice.	Digestive power.	Quantity of juice.	Digestive power.
1	7·7 c.c.		83·2 c.c.	5·35 mm.
2	4·5 „	6·25 mm.	58·1 „	In consequence of a mixture with bile (10–15 c.c.) the digestive power was greatly reduced.
2½	0·6 „		8·5 „	

This experiment proved to us, first, that the large and small stomachs work in perfectly parallel manner. The beginning, the end, and the intermediate variations of the secretion correspond in both. Secondly, the digestive power of the secretion coincides in both, and is the same as was observed in the sham feeding. In this case it 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 feeding with flesh.

This was also confirmed later, when we performed an œsophagotomy on the dog, and gave a fictitious meal in the usual way. Here are the data of one of these experiments taken from Dr. Lobasov's article.

The first drop of juice appeared from both cavities during the sixth minute of 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 stopped in both stomachs at the same time.

The above are represented in curves in Figs. 14 and 15, 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 fistula leading into the large stomach makes it possible to perform an experiment upon our dog which is exactly the converse of the sham-feeding experiment, and which constitutes a real *experimentum crucis*. In sham feeding, we had only the beginning of digestion before us. We are now able, under the new conditions, to start where this beginning stopped. For this purpose it is only necessary to introduce food into the stomach through the fistula, without attracting the dog's attention. In this experiment it is above everything necessary to avoid exciting the desire for food, and therefore 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, if its attention be diverted from thoughts of food.

The results of the experiment are striking, and do not in any way resemble the secretion after normal feeding. Some foods, for instance bread and coagulated egg-white, when thus directly introduced into the stomach, do not yield a drop of juice during the first hour or more afterwards. This applies both to the small and the large stomach. A glass rod passed into the food contained in the organ, comes out dry. Flesh, if introduced at this stage, is able to excite a secretion, but the appearance of the juice is considerably retarded. It begins from fifteen

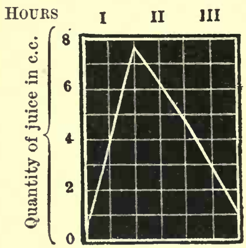


FIG. 14.—Curve of secretion from the miniature stomach.

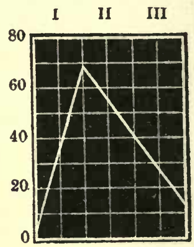


FIG. 15.—The same from the main stomach reduced ten times.

to forty-five minutes after the feeding (instead of from six to ten), is extremely scanty as a rule during the first hour (3 c.c. to 5 c.c. instead of 12 c.c. to 15 c.c.), and possesses very weak digestive action.

Here is an experiment made by Dr. Lobasov:

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 (Khizhin).		Flesh (150 grms.) brought into stomach (Lobasov)		Fictitious feeding (Lobasov).		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 curves of juice secretion in the above are also represented in the following figures:

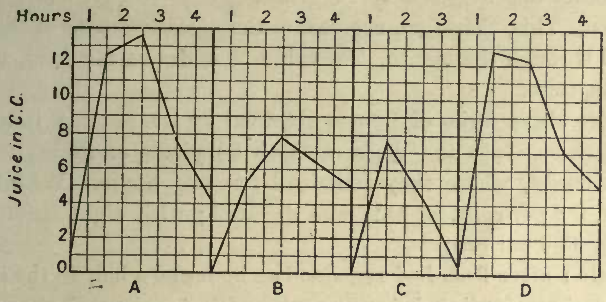


FIG. 16–19.—A. Ordinary curve of gastric secretion (200 grms. flesh). B. Curve from direct introduction of food (150 grms. flesh). C. Sham feeding with same. D. Summation of B and C.

As you see, the curve showing the results of 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 the direct introduction of flesh be added to those of sham feeding the resulting curve is almost identical with the normal.

The *digestive power* of the secretion in the foregoing experiments can be treated in the same way, and with the same result. It is a good instance of how a secretion curve can be synthetically constructed from its constituent factors.

I am also able to demonstrate to you the following instructive experiment. In the presence of some of my hearers, who were 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, a definite number of pieces of flesh were introduced through the fistula, the animal's attention being distracted by patting and speaking so as to avoid arousing any thoughts of feeding. The morsels were threaded on a string, the free end of which was fastened into the mouth of the fistular cannula by a cork. The dog was then brought into a separate room and left by itself. A like number of pieces were introduced into the stomach of the other dog in the same way, but during the process, a fictitious meal was given, the animal being afterwards left alone. Each dog received 100 grms. of flesh. An hour and a half has elapsed since then, 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 a desire for food, the value of an appetite.

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

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

Once more: of flesh which remained five hours in the stomach; without sham feeding 58 per cent. was digested, with sham feeding 85 per cent., 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 its nature, this experiment is not well adapted for class demonstration, and may often fail. On the one hand, it is not at all easy to conceal from the dog the introduction of the flesh; on the other, the distracting and unusual surroundings often cause a short fictitious meal to have less effect than it would otherwise have. To avoid these failures in the lecture theatre, it is better to carry out this experiment only on dogs accustomed to appear before an audience, of whose temperament the experimenter is well assured.

I hope you have been convinced of the great importance of the passage of food through the mouth and œsophagus, or, in other words —and this, according to our former experiences, means much the same thing—of the desire for food. Without this interest, without the assistance of appetite, many foods which enter the stomach remain wholly unsupplied with gastric juice. Others may excite a secretion, but the juice poured out is scanty and weak.

Later, when we more fully comprehend the conditions upon which the secretory work of the gastric glands depends, we shall be better able to grasp the meaning of these facts. For instance, why is it that bread if brought unnoticed into the stomach of the dog causes no secretion for hours, while flesh soon after (within twenty to forty minutes) provokes a flow? This will be explained in the next lecture; now 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? How long does appetite juice flow after the normal act of eating, which, especially in the case of animals, is not of long duration? We have determined many times, not only on dogs with the stomach isolated, but also on other animals, how long the after-effect of sham feeding continues.

Here is an example from an experiment of Professor Sanotskii which deals with the question. The dog had a gastric fistula and also a divided œsophagus. After a fictitious meal of five minutes the secretion began, and 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 long time. Naturally the same must hold good when food is taken in the normal way. One must, however, bear in mind that in sham feeding, with all the force and reality of a hunger sensation unsatisfied; the desire for food, the effective agency, probably becomes more and more accentuated, and therefore the secretory influence is prolonged and more powerful. In normal feeding, however, the quelling of desire, the feeling of satisfaction which, as is well known, sets in long before the termination of the digestive period, must diminish the psychic effect of food, and, consequently, this stimulus to the secretory process comes to an end.

It is improbable, therefore, 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 we have up to the present investigated. This is all the more obvious since a fictitious meal of five minutes, even under the most favourable circumstances, does not produce a secretion lasting for longer than three to four hours. We must, therefore, seek for other excitants of the nerve apparatus of the gastric glands.

Why and how is the secretion, started by psychic influence, maintained? What would first occur to all your minds is probably the immediate influence exerted by the food upon the walls of the stomach. And this is true, but it does not happen in the simple, direct way commonly supposed by many physiologists and physicians. When I said that bread or boiled white of egg, introduced directly into the stomach, may not produce a trace of secretion for hours, probably many of you may have asked yourselves with some astonishment, "How, then, is the result of the forced feeding of phthisical and insane patients to be explained, and also of the artificial feeding of patients through gastric fistulæ established on account of stricture of the œsophagus?" I will preface my answer with a very unexpected pronouncement concerning mechanical stimulation of the wall of the stomach as a means of exciting the secretory work of the glands. This assertion, so categorically made in text-books of physiology, and consequently fixed in the mind of the physician, is nothing else than an unfortunate misconception, which has degenerated into stubborn prejudice. My own statement, repeated in many published articles, and at meetings of various medical societies, that it 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 stubborn unbelievers are not here, so that we might together bring the matter before the tribunal of fact, to which I now make my appeal. It is a matter to which I attach very great importance. On this ground, in my opinion, the whole battle must be fought 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 select stimuli. If once the defenders of the old opinion are driven from their position, and obliged to admit the inefficacy of mechanical stimulation, there will be nothing further left for them than to construct new theories out of old facts concerning gland activity which have hitherto been kept in the shade. We may take it that it was because people were so determined to believe in the direct and simple mechanical stimulus, that Bidder and Schmidt's experiment, of exciting gastric secretion by mental effect, received so little notice, although it appeared thoroughly reliable and convincing.

I now repeat the experiment of mechanical excitation of the gastric mucous membrane before you in the well-known and traditional manner. Here is a dog with a gastric fistula on which a cervical œsophagotomy has in addition been performed. I open the cannula: as you see, nothing flows from the stomach; it was washed out clean with water an hour ago. We take the renowned feather and also a stout glass rod. Folds of blotting-paper saturated with red and blue litmus are placed at hand. I now ask my assistant to continuously move the feather and glass rod, alternately, in all possible directions within the stomach, changing from one to the other every five minutes. On removal from the cavity each is carefully dried with red and blue litmus paper. You have now all seen, gentlemen, that this procedure has been kept up for half an hour. From the fistular orifice not a single drop of juice has escaped, and, moreover, the damp patches on all the pieces of red litmus paper I have handed to you have a distinct blue tinge, caused by the moisture of the alkaline mucous membrane. The blue litmus paper, however, has merely been made wet without altering its 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 having a decided 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 give the same animal a fictitious meal. The dog takes the food offered to it with keen appetite, and you see that exactly after five minutes from the beginning of 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. After thirty minutes' sham feeding we have collected 150 c.c. of juice, which, even without filtering, looks as clear and transparent as water.

We cannot possibly doubt that, when the proper stimulus is used, the gastric glands react to it in perfectly normal fashion, yielding healthy juice. From this it irrefutably follows that there is only one explanation 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 will soon quit the field, and give place to the one I have now 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 efficacy of the mechanical stimulus. The rules are two. First, it is necessary that the stomach should be clean, and that nothing gain entry to it from above. 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 entered and quickly became acid in the incompletely emptied and imperfectly washed-out organ. It is not surprising, therefore, that the glass tube, by setting up contractions of the stomach, was the means of expressing small quantities of acid through the cannula. (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 before has obtained in any quantity pure and genuine gastric juice of an acidity equal to 0·5 or 0·6 per cent. It is only necessary to call to mind that Heidenhain, when estimating the acidity of the juice first obtained from the resected stomach, was in no little doubt as to whether his results (0·5 to 0·6) were correct or not, and his assistant at the time (Gscheidlen) was set to verify the reliability 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 mentioned 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 if we wish to perform the experiment 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 while it lasts that no impulse come into play, which, apart from mechanical excitation, could of itself excite the glands to secretion. We have no proof that observers formerly waited for hours before commencing the experiment, and convinced themselves that the gastric glands had ceased working. On the contrary, there is not the slightest evidence that they attempted to guard against accidental psychic stimulation of the glands —a matter which we have seen is of considerable difficulty. 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 devote his whole attention to keeping his observation free from objection. If any food be near the dog, or if the hands of the attendant smell of it, or if some other similar circumstance comes into play, the glass tube, quite undeservedly, will be made answerable for the excitation of the gastric glands. As you have just seen, both of the conditions have been fulfilled with the dog before you, and the result irreconcilably contradicts that 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 concerning mechanical stimulation, that to obtain results, the agency must come into simultaneous contact with numerous points of the inner surface of the stomach. But in order to meet this possible objection I now show you two new modifications. 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 now in a state of complete rest. Into the fistula I bring a wide 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 fine 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, sand is injected 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 cannula and the glass tube, either dry or scarcely moist, 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 jet of sand rushes out. If you hold your hand against it, you feel that the grains of sand strike with considerable force. And now, when our experiment is ended, we may convince ourselves by sham feeding, in simple and unquestionable manner, 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, maintained in this condition for a little time, and then 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 a subsequent fictitious meal 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 beforehand, otherwise a psychic excitation of the secretion can readily be induced.

If one dispassionately pursues this question in the laboratory, by any reliable method for the study of gastric secretion, the uselessness of mechanical stimulation becomes evident step by step. In the case of dogs with ordinary gastric fistulæ, 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 if the mechanical stimulus were effective, since the inner rim of the fistula-tube is continuously in contact with the mucous membrane? The same holds good for the dog with resected stomach. During the experiment a glass or india-rubber tube is brought far enough into the *cul-de-sac* to collect the juice, and yet not a drop flows through the tube, nor does its mucous membrane ever become acid, so long as true secretory conditions are absent. Moreover, the tube has frequently to be taken out and set right.

In the ordinary gastric fistula in dogs, after 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 sets up a secretion. Further, it is of 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 when digestion has ceased. Such a result would have been particularly obvious in the dog with the isolated stomach, after bedding with sawdust to guard against maceration of the wound by juice trickling out. Very often enormous quantities of sawdust were found in the stomach, as much as half a pound weight; obviously the dog had licked the adherent sawdust from the wound, and swallowed it, likewise that adhering to its nose. And yet these particles of sawdust of themselves, though they certainly acted as mechanical stimuli, never caused secretion. It appears to me that this long series of facts ought to suffice to carry to its grave, the superstition that direct mechanical stimulation is able to excite the neuro-secretory apparatus of the stomach to activity.

Before concluding this lecture, we may consider a question connected with the matter just discussed. The mechanical contact of food with the gastric mucous membrane has no direct influence on the secretion of juice, but is its entry into the stomach devoid of all effect on the secretory process?

It can hardly be doubted that, under normal conditions, the stomach is the seat of 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 disregard it in the normal course of digestion. They enjoy their sensations of general well-being, and especially of satisfaction from the partaking of food, without taking cognisance of the factors contributing to them. The feeling of 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 mouthful of favourite wine, the whole way through the œsophagus down to the stomach, especially when the latter happened to be empty. Naturally the gourmand, by continuously devoting attention to the act of eating, can ultimately perceive sensations distinctly, and even recall them to consciousness, which in most people are normally masked by other feelings 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 lower 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, less appetite, than the food which passes the whole way into the stomach. The appetite, the eager craving for food, is indeed, a very complex sensation, and for its excitement, not merely the need of the organism for food is necessary, but also a feeling of thorough well-being, together with a normal healthy condition of all parts of the digestive tract. It is easy, therefore, to understand how patients who have had disordered sensations in these organs, and in consequence have lost the feeling of appetite, do not recover the desire for food owing to remembrance of the abnormal sensations, whether consciously or unconsciously, although they are no longer generated. Cases are known to neuro-pathologists where people with gastric anæsthesia suffered from 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, as it were, into an empty sack. In this way one can also conceive it possible for the appetite to become 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 I had otherwise fully recovered, no desire for food returned. 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 break down, 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 my stomach, and literally at that moment perceived the onset of a keen appetite. This observation teaches that the sensation of the stomach at the moment of entry of food, is capable of awakening or increasing the appetite. It is well known that withholding food, or, in other words, the creation of a necessity for it, does not immediately or in all cases lead to the production of an appetite; to a desire for food. How often does it happen that the ordinary meal hour has struck, and yet, owing to some intensely 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 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 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 distinct 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 appetite; and when the appetite is awakened the juice flows. This may possibly have been a third reason why, in the old experiment, the mechanical stimulus came to be considered effective, and may, to a certain degree, reconcile my assertion concerning the inefficacy of the mechanical stimulus with the formerly prevalent belief. I also admit that mechanical excitation may 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 impressed the idea of food on the dog's consciousness, and thereby set up the desire for it. 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 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 exercised by sham feeding in an œsophagotomised dog with that in one having a simple gastric fistula.

LECTURE VII.

THE CHEMICAL STIMULI OF THE NERVES 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 directly excite a gastric secretion—Chemical excitants are also produced in the peptic digestion of proteins—Starch influences the quality of the juice by augmenting its content of pepsin. Fat inhibits the work of the gastric glands, both quantitatively and qualitatively—The miniature stomach 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 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. But to answer the question as to what circumstances acting within the stomach may stimulate its glands 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 provided with miniature stomachs. The fluid substances to be tested were at first passed through the œsophagus into the large stomach by means of the sound. Later, we opened a second fistula into the large stomach, and they were henceforth introduced directly. Obviously the second 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, for instance, be set up which, it cannot be denied, may affect the working of the glands. Further, in spite of every precaution, during the withdrawal of the sound, a few drops of the liquid injected, frequently fall on the mucous membrane of the mouth, and may awaken the idea of food in the dog's mind. All this is avoided by using the fistula leading directly into the large stomach. The substances may even be introduced when the animal is asleep, without waking it. Moreover, not only fluids, but also semi-solid 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 a 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 from the small one (*Dr. Khizhin*), though not a large secretion. The constancy of the result, and especially the regularity in 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 regarding 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 Sanotskii. 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. Jurgens 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, although 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 appears. It is only a prolonged and extensive contact of the water with the gastric mucous membrane, which gives a constant and positive result.

Before passing on, I wish further to emphasise the fact that section of the vagi nerves, which excludes all psychic influence from 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. But why does water act as an excitant? The fluid needs no digestive juice. The chief reason, I believe, is 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 juice secreted finds no use if water alone be taken, is of no consequence, and cannot weigh as a serious objection against our explanation. In the first place, as we have already seen, the secretion caused by water is not of itself abundant; and secondly, the free flow of psychic juice may perhaps at times be secreted when we have no use for it—for example, when (with an empty stomach), we have a keen desire for eating, but are unable, for some reason or other, to gratify it. 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 substance with the effects of a like quantity of water alone.

Besides water, a number of different inorganic substances, either contained in food or employed in the practice of medicine, were also tested. Thus, the effects of the constituents of meat ash, of chloride and bicarbonate of sodium, and of hydrochloric acid were repeatedly investigated (*Dr. Khizhin*), till we were fully satisfied of the certainty and accuracy of the results. It appeared that only one of these substances, namely, bicarbonate of sodium, exercised any influence on the secretory work of the stomach—that is to say, the watery solutions of the others had precisely the same effect as water itself. To sodium bicarbonate an inhibitory influence must be ascribed. Not one of its 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 evoke 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 shall, however, return to them later.

Next it appeared of special interest to study the effects of the food constituents—viz., the carbohydrates, the fats, and the protein bodies.

It was natural to expect, from *a priori* reasons, seeing that the gastric juice is specially adapted to act on the proteins, that these substances would also act as chemical stimuli to the mucous membrane of the stomach. How astonished were we then to find that when fluid egg-white was introduced into the stomach of the dog, either pure or diluted with an equal volume of water, we obtained no greater secretion of juice than a similar volume of water had caused! This seemed 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 Riazantsev 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, without exciting digestive action. The fact was indeed wholly unexpected, and it would be difficult to find either a physiologist or a physician who, if asked what happens to raw egg-white 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." We shall return to this question later.

In pursuing this line of investigation further, and in order to settle definitely some new as well as old problems, we found it necessary to perform still more complicated operations upon our dogs than those described. Thus the following operations were successively carried out on one and the same animal. In the first place an ordinary gastric fistula was made, and then a miniature stomach formed. Next, 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 by mouth, the gastric and duodenal fistulæ were connected externally by means of glass and india-rubber tubing. On the other hand, this passage could be closed at will, and the contents of the stomach retained there as long as desired. Dogs thus operated upon are exceedingly convenient for experiment. (*Investigations of Dr. A. P. Sokolov.*) With such animals it can easily and conclusively be decided whether gastric secretion following a chemical stimulus is determined by an effect proceeding mainly from the inner surface of the stomach or from the bowel lower down.

The fact that the peptic glands can be excited at all from the bowel was first observed by myself, and later confirmed by Le Conte ("La Cellule," 1900). In our analysis of the effects of food-stuffs on the stomach it therefore became necessary not only to exclude influences arising in the mouth, but also to study the results independently of events occurring in the intestine. The experiments of Sokolov fulfil these requirements.

With the same dogs we also discovered 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 certain other acids, for example, phosphoric, &c , do not exert this inhibitory action. Butyric acid, indeed, strongly excites gastric secretion, and thus provides for the arrest of its own formation, for it is a fact that hydrochloric acid strongly inhibits butyric acid fermentation. What could be more striking as an instance of the specific excitability of the mucous membrane of the stomach?

The experiments on such dogs were characterised by an astonishing degree of accuracy and constancy in the results. It might seem that the arrest of the movements of the food, and removal of the effects of the different exciting substances, from lower parts of the digestive canal, would make it otherwise, but this was not so.

A positive result from chemical excitation of the gastric mucous membrane was obtained when considerable quantities of minced raw flesh were introduced unnoticed into the stomach of the dog with open passage into the duodenum. The secretion of juice began, at the earliest, from fifteen to thirty minutes afterwards. Here I must not overlook an arrangement which was used for bringing the flesh into the stomach (*Dr. Lobasov*). 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 disturbs it, and the feeding has then to be finished in the waking condition. To prevent this mishap, we filled a wide glass tube with meat-pulp from the mincing-machine, introduced the tube gently into the orifice of the fistula, and then pushed the flesh into the stomach with a suitable rod. If the dog should wake up, it does not guess what has happened, for the whole thing is finished, and it drops off to sleep again immediately. Flesh introduced in this way always set up a secretion. The flow, as compared with that following normal feeding, appears later, is somewhat more prolonged, and the juice has less digestive power.

When retained in the "obstructed" stomach (Sokolov's method), a considerable secretion of juice is also excited by flesh. But if long kept there, the flow gradually declines, owing to the inhibitory influence of the accumulated acid on the peptic glands.

The active constituent of flesh may be either (1) the water contained in it, or (2) its protein constituents, or (3) its extractive substances.

Water, as we have already seen in the earlier form of experiment, acts mildly as a direct excitant. The same applies to experiments in which the water was retained in the stomach (*Sokolov*). A secretion was observed from the pouch after from ten to fifteen minutes.

With regard to protein substances, fluid egg-white in Lobasov's hands showed, as we saw, no stimulating effect. If it be prevented, however, from escaping into the bowel a secretion begins after about seventy minutes. This is shown in the table below. The absence of effect in the earlier experiments is, no doubt, due to the rapid passage of the egg-white into the duodenum. The tardy flow of juice when it is retained is probably excited in the first instance by the water which it contains, and later by the products resulting from its own digestion by this earlier juice.

In support of this explanation we have some experimental data. If the fluid digestive products be obtained from the stomach of a dog which has eaten egg-white, and injected directly into the main stomach of a dog with an isolated miniature pouch, a much stronger and more constant secretory effect is produced than that yielded by a like quantity of water or fluid egg-white (*Dr. Lobasov*). The formation of this product cannot, however, be very active, because after two to three hours, when the psychic secretion comes to an end, the hourly quantity of juice poured out upon bread or egg-white is very small. The explanation is also, however, supported by the following experiment. When a secretion is already going on in the stomach, caused either by psychic effect or by continued influence of the last period of digestion, the unobserved introduction of fluid egg-white is always followed by a considerable augmentation of the secretion (*Dr. Khizhin*). How is this to be interpreted, unless by assuming that at the commencement of digestion, a body is formed from egg-albumen which stimulates the mucous membrane? The explanation which holds good for egg-white may be extended and applied to the protein of flesh. Its chemical exciting substance is partly formed during digestion, but the preformed extractives of flesh-meat constitute its chief direct excitant.

From numerous experiments carried out by Dr. Lobasov with solutions of meat extract, I give the following as an example. A solution of 10 grms. of Liebig's Extract in 150 c.c. of water was injected through the fistula into the large stomach of a dog. The first drop of juice appeared thirteen minutes after its introduction. 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 had naturally to be connected beforehand with the fistula. When retained in the "obstructed" stomach, a solution of Liebig's Extract (7 per cent.) also excites a flow of juice many times greater than the same volume of water. This is shown in the following table, side by side with the effect of raw egg-white under the same conditions. The quantities of juice in c.c. were recorded every fifteen minutes.

Liebig's Extract		Raw egg-white.
0·3	2·3	0·0
0·7		0·0
0·6		0·0
0·7		0·0
0·8	2·5	0·4 *
0·8		0·5
0·5		0·2
0·4		0·3

Further, if flesh be deprived of its extractives by prolonged boiling and freed from water by compression, it produces no exciting effect on the gastric glands. The residue merely exerts a mechanical influence. It is 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.

The individual extractives of meat, such as kreatin, kreatinin, &c., were found to be ineffective. We also know, from the experiments of Dr. Lobasov, that when Liebig's Extract is digested with absolute alcohol, the active bodies for the most part remain behind in the residue.

It may seem that the solution of Liebig's Extract of Meat, judging from the quantity of juice secreted in the foregoing experiments, is a stimulus of only moderate strength. Under natural conditions a larger quantity of juice is, however, excited by the constituents of the meat extract, owing to prolongation of their effects in the stomach. As a matter of fact, when we made a mixture of meat extract with starch solution, starch itself being inert, and divided the cooled jelly into pieces which were afterwards introduced into the stomach, we obtained 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 "
7th	0·7 "	
8th	0·2 "	
Total	12·3 "	...

* An acid reaction was first observed after 1 hr. 10 min.

The above experiment is also interesting because it apparently supports the assumption we have tacitly made, that all the substances hitherto employed excite the nervous machinery by reflex effect from the mucous membrane, and not by being absorbed into the blood, and then acting directly on the peripheral neuro-glandular apparatus, or even on the glands themselves. If the meat extract acted through the blood, it is fair to assume that it would be much more effective in solution than when mixed with starch-jelly, and, therefore, in a less absorbable form. It is still possible, however, that the meat extract may indirectly act through the blood channels by giving origin to a substance in the mucous membrane which is absorbed and serves as the immediate excitant of gland activity. Experiments of Dr. Edkins,* to which we shall later refer, have made this probable.

If the foregoing substances, namely, flesh, water, extractives of meat, digestive products of egg-white, be directly introduced into the duodenum of an animal with "obstructed" stomach, care being taken to exclude psychic effect, they exert either no influence on the gastric glands or a very unimportant one. In the following table the results of two experiments are compared, in which meat pulp was passed unobserved, in the one case into the duodenum, in the other into the stomach of an animal with obstructed pylorus. In each case the same quantities were used, namely, 100 grms. of minced meat mixed with 100 c.c. of water. The juice secreted by the pouch is given in c.c.

Hours.		Effect from bowel.		Effect from stomach.
1	...	1·0	...	2·7
2	...	0·4	...	2·0
3	...	0·1	...	1·5
4	...	—	...	1·4
5	...	—	...	1·2

Nor did any of the substances cause gastric secretion when injected into the rectum. This has also been confirmed clinically.

Under normal conditions, therefore, provision is made for the digestion of flesh in the stomach as follows. During the act of eating a flow of gastric juice is excited, which begins after a latent period of five minutes and continues for about a quarter of an hour. At this time the chemical influence produced in the stomach by the food and its digestive products comes into play. As a result of these two factors, the great flow of gastric juice lasting to the end of the second hour is produced. With the passage of the food into the duodenum the secretion gradually declines, and comes to an end when what is left of it passes to a portion of the bowel from which no influence is reflected back to the gastric glands.

* *Journ. of Physiol.* xxxiv.

When analogous experiments were undertaken with bread and boiled egg-white, that is to say, introducing the food-stuffs into the stomach in a way which wholly excluded psychic influence, a negative result was always obtained. The foods remained for 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 that these unexpected results are due to the unfavourable physico-chemical condition of the material (locking-up of the water), or that direct chemical excitants are really absent. As regards the latter, Dr. Lobasov found that mixtures of water and finely broken bread had no stronger stimulating influence on the gastric glands than equal quantities of water.

The mere moistening with water secures, however, for bread a certain amount of gastric juice, and it has been shown (*Sokolov*) that saliva is more effective than an equal quantity of water. In several experiments quantities of saliva varying from 100 to 200 c.c. were introduced into the stomach of a dog, with the constant result that considerably more gastric juice was secreted from the pouch than followed the injection of a like volume of water.

The further effect of bread is probably due to the digestive products of its proteins arising in the stomach itself. The quantity of these, however, cannot be large, for, in the first place, the amount of proteins in bread is small, and, moreover, vegetable proteins are very difficult of digestion by gastric juice.

The prolonged curve of secretion of gastric juice following the eating of bread may therefore be accounted for as follows: To begin with, the act of eating promotes a flow of "appetite" juice much the same as in the case of flesh. The chemical stimulus which follows is, however, comparatively weak, and, in consequence, two or three times less juice is secreted during the second hour than in the first. During this phase the secretion from the small pouch may altogether cease (to begin again later), especially in the case of some dogs in which the flow is normally small. The long duration of the flow is attributable to the indigestible character of the protein constituents.

Particular care was also devoted to the investigation of vegetable and animal fats. They were tested not only 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. No stimulating effect on the gastric glands was at any time obtained. But in the investigation of the fat influence a new fact, important to a knowledge of secretory processes, came to light, just as in the case of the mixture of starch and flesh we saw an interesting effect of the former on the properties of the juice secreted.

This is shown in the following experiments. One hundred cubic centimetres of olive oil were poured into the main stomach of a dog either through the cannula or by means of the sound. From half an hour to an hour later, the dog was given its ration of 400 grms. of flesh, but the curve of gastric secretion from the small pouch was totally different from that obtained if the same food, without oil, had been given (*Dr. Khizhin*). 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 two to three hours we collected only 3–5 c.c. per hour, instead of the normal 10–15 c.c., and it was very much later that the normal quantities appeared.

A corresponding result was obtained when the fat was introduced into the stomach immediately after the meal of flesh. The only difference consisted in this, that the flow began with normal energy at the usual time after feeding, the inhibitory influence making its appearance later. The same results were obtained by eating fat mixed with flesh. In these cases (*experiments of Dr. Lobasov*), not only a diminution of the juice, but a lowering of its digestive power was also observed. I give here an example from one of the experiments, and also by way of contrast 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 one and a half hours after 75 c.c. of olive oil had been introduced into the stomach :

Hour.	Quantity of juice.	Digestive power.
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 thus brought before us. Fat depresses—that is, inhibits—the normal energy of the secretory process. How is this effect to be interpreted? When one recalls the experimental arrangements and remembers that the secretion was collected from the gastric *cul-de-sac*, the result can only be explained in one of two ways. Either the fat hinders the secretion indirectly and in a mechanical way—for example, by covering over the mucous membrane of the stomach and preventing exciting substances from reaching its nerve-endings —or else directly, by reflex inhibition of the secretory process, the reflex not necessarily originating in the stomach, since the oil has free passage into the bowel. 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, that is inhibited by the fat, as may be clearly seen from the following experiment of sham feeding.

On a gastro- and œsophagotomised dog a sham feeding of short duration (one minute) was carried out. The time at which the flow commenced, as well as the quantity and properties of the juice, were accurately determined. Then 50 c.c. to 100 c.c. of oil were poured into the stomach, and after a quarter to half an hour, or in some cases still later, the sham feeding was repeated precisely as before, both as regards the duration of feeding and the quantity of food. Occasionally the oil was allowed to flow out of the stomach immediately before the fictitious meal. The secretion of juice was observed by means of a wide glass tube closed at its lower end, and fixed into the fistula cannula. The heavier juice thus collected at the bottom of the tube and was at once visible. In every case a marked diminution of the psychic secretion was observed. Often there was none, and, when present, it began much later, the quantity was much less, and the juice also much weaker. One experiment on the dog with isolated stomach and divided œsophagus was particularly convincing. The sham feeding in this case lasted six minutes, and the following were the results:

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 following, 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. If the effect of such a powerful excitant as the psychic impulse can be diminished by fat, how much more that of the weaker stimuli, which act directly on the mucous membrane of the stomach?

Whether the covering of the gastric mucous membrane with a layer of fat contributes in any way to the diminution of the secretion would seem to be doubtful. At all events, fat exerts its inhibitory influence on gastric secretion when poured directly into the duodenum. This was proved by Sokolov on a dog with obstructed pylorus. A meal of flesh was brought into the large stomach and retained there. Oil was then poured through a fistula into the duodenum. Even under these conditions a marked inhibition of the secretion from the stomach pouch was observed.

The inhibitory action of fat, which we have just discussed, assists in explaining the slow rate of gastric secretion after taking milk, and also the low digestive power of the juice. Milk poured directly into the stomach produces a flow of juice, and therefore acts as a chemical excitant. The secretory impulse is no doubt given in the first instance by the water it contains, and maintained later by the digestion products of its proteins. Possibly other constituents have stimulating effects.

The fat, however, acts as an inhibitor. This is shown by the results of administering cream—that is to say, milk with an increased amount of fat. If the fat is to be credited at all with the small amount and low digestive power of "milk juice," that secreted upon cream should be still less and still weaker. As a matter of fact this was the case. The following table gives a comparison of the secretions obtained with milk and with cream (*Dr. Lobasov*).

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 also compared the effects of milk from which the fat had been removed by filtration with those of normal milk (*experiments of Dr. Volkovitsch*). The results were that the former produced a greater quantity of juice in the earlier hours, with a more vigorous rate of flow for the whole period.

Thus we have discovered two reasons for the slow rate of secretion and poverty of "milk juice" in ferment, viz., the weak psychic effect and the inhibitory influence of the fat. Further support of the latter view is afforded by experiments of Sokolov, in which milk was retained in the closed stomach. The maximum rate of secretion then occurred in the first hour instead of later, owing, apparently, to the absence of the inhibitory effect of the fat from the duodenum.

The effect of fat on the secretion of gastric juice is not, however, limited to inhibition. Its preventive influence may last for one or perhaps two hours, but a secretion of gastric juice begins again in the third hour if the meal of fat be at all large. This late secretion lasts a long time and furnishes a considerable quantity of juice. The result has been so often confirmed that we must unquestionably accept it. But how is it caused? It is possible that it may be due to the return of duodenal contents into the stomach. Such a reflux not infrequently occurs, and, moreover, Sokolov observed on his dogs that both pancreatic juice and bile when brought into the stomach evoked a secretion from the small pouch. But the regurgitation of duodenal contents is of much less constant occurrence than the excitatory effect of fat. Consequently some other cause had to be sought. It was ultimately found to be due to one of the products arising from the cleavage of fats in the intestine—namely, soap. When directly introduced into the duodenum, soap evokes an energetic secretion of gastric juice (*Piontkovski*). Also, if fat mixed with bile and pancreatic juice be kept for a time at 40° C. in the oven a similar effect is produced when used in the same way. Further, neither oleic acid nor bile stimulates the gastric glands if poured into the duodenum singly, but constantly do so when mixed together. The glycerine constituent of the fat was found to have no influence. It has also been found that the stimulating effect of soap is very largely prevented or delayed by mixing it with fat.

We have still to explain the gradual increase in the rate of flow of gastric juice which sets in when milk is given as a food and lasts till the end of the third hour. It may be either due to a reduction of the inhibitory influence of the fat from cleavage and disappearance, or to an increase of the stimulating effect of its protein constituents from accumulation of their digestive products, or to both. These factors no doubt assist each other in producing the result. But an important *rôle* is also played in the process by soap formation, as shown by the following experiments. Animals were fed in one series with egg-yolk and flesh (*Soborov*), in another with meat naturally rich in fat, such as goose-flesh or pork, or with lean meat to which fat was freely added. In both series of experiments the flow of gastric juice was at first very scanty, but in the end a large secretion was evoked, reaching its maximum in four to five hours. The first phase is accounted for by the early inhibitory effect of the fat. That the later augmentation is due to the influence of soap appears from the following experiments. Dogs operated upon in the complicated way described by Sokolov were given egg-yolk, which was passed into the "obstructed" stomach and either retained there or allowed to enter the duodenum at will by the artificial passage. It was only in the latter case that the maximum effect was obtained, reaching its height in four to five hours. If the egg-yolk were kept in the stomach and saponification prevented, the flow was much less, and showed a maximum in the first hour.

It is of importance that this twofold effect of fat should be recognised clinically, especially since its inhibitory influence has already been usefully turned to account in the treatment of gastric hypersecretion.

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 we know from the second lecture that the *qualities* of the juice also vary with the food. How are these alterations produced?

The variations in *acidity* are often considerable, but we have no reliable proof to show that they occur in the juice as it flows from the gastric glands. On the contrary, we saw reason to believe that they are due to different degrees of neutralisation of the acid by contact with the alkaline mucous membrane or its secretion of alkaline mucus. This would account for the fact that the acidity of the juice is proportional to its rate of flow. The theory of constant acidity is also supported by the fictitious feeding of the dog from which food was withheld. As soon as the chlorides of the animal's body became distinctly reduced the flow of juice stopped, but even in the portions last secreted the degree of acidity was normal. Nevertheless the possibility of a more intimate relationship between acidity and rate of flow is not wholly excluded, such, for instance, as exists in the case of the salts of saliva.

The proportion of *ferment*, however, undoubtedly varies in relation to the degree of acidity. This can only be accounted for on the assumption that the secretion of ferment and production of acid solution vary independently. There is no sufficient reason for speaking of an active and an inactive condition of the peptic ferment.

Two facts bearing upon this matter are, however, already in part known to us. The first is that the admixture of starch with direct chemical excitants augments their influence on gastric secretion, although the starch itself is inert. The quantity of the juice is not only increased, but also the amount of ferment it contains. In experiments carried out by Dr. Lobasov we mixed flesh with pure starch paste in the same proportions in which the proteid and starch of bread are found, gave this to our dogs to eat, and obtained, as a matter of fact, a juice of like digestive power to that secreted on ordinary bread (*see* Table on p. 125).

The other fact is that fat reduces the proportion of ferment in the juice.

Bearing the above in mind, we can account for most of the fluctuations in the composition of the juice secreted on ordinary foods. The differences in the acidity of "meat," "bread," and "milk" juice are explained by the rate of flow in each case. The secretion of "meat" juice is the most rapid, of "milk" juice the slowest, while that of "bread" juice is intermediate. The low acidity of the latter is also to some extent accounted for by the fact that more mucus is secreted for bread than for the other foods.

Hour.	200 grms. bread. Expmt. May 25, 1894 (Dr. Khizhin).		Mixture of 100 grms. starch, 100 grms. flesh, and 150 c.c. water. Expmt. May 10, 1895 (Dr. Lobasov).	
	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.

The combination of starch with protein explains the high digestive power of "bread" juice, that of fat with protein the opposite condition in the case of "milk" juice. The content of ferment in "meat" juice is intermediate between the two, and is less than that of the juice evoked by the extractives of meat alone (Liebig's Extract). But even lean meat contains some fat, the depressing influence of which is sufficient to account for the difference.

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 initiates a rapid digestion, which is afterwards aided by the flow evoked by the pre-existing excitant, thus shortening the stay of the material in the digestive canal. With other foods—for example, with bread—the psychic juice is an *indispensable condition* to digestion. Bread or egg-white eaten without appetite, or introduced into the stomach unobserved, will lie there for a long time without the least appearance of change. In such cases the appetite juice is the sole initiator of the digestive process. When started by its assistance, the digestion of these foods spontaneously proceeds. The psychic juice here plays a similar *rôle* to that of the igniting material which sets the fuel in the stove ablaze, and for this reason it has been called "Igniting-juice" by Dr. Khizhin.

It is useful to know that when bread or egg-albumen is eaten without appetite, water, or still better, meat broth or meat extract, may be used to play the part of igniting material. I have had an opportunity of verifying all these facts in actual practice, and in this way have tested whether our analysis of the secretory processes is correct. For the delivery of these lectures I had to repeat the experiment which shows the influence of vagus division on the secretion caused by sham feeding. As I had anticipated from my own previous experience and also from the publications of other authors, especially Ludwig and Krehl, a greatly disordered condition of digestion was set up by the operation. I resolved, therefore, in the light of our new discoveries, to try and aid the animal's digestion. In dogs with divided vagi, the psychic juice is wholly and for ever done away with. I therefore endeavoured to supply its place by some other means. Before each feeding I washed out the 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 was solid food introduced. By this means the food, which otherwise began to decompose, was satisfactorily digested.

It is, I think, now 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 claim of the miniature stomach to be taken as representative of the large one in all secretory matters, or, as Dr. Khizhin has put it, to serve as a mirror of the activity of the large one. The second is, whether the different substances which excite a flow of gastric juice by action on the mucous membrane do so through the peripheral terminations of its centripetal nerves—that is to say, through the agency of the nervous system—or in some other way. These questions are intimately connected with each other: I begin with the former.

It must at once occur to every one who studies our results on the secretion of gastric juice, that while the main stomach during digestion is filled in the ordinary way with food, the miniature stomach remains all the time empty. It might be supposed that the presence of food in the one case, and its absence in the other, mean a very great difference in the working conditions of the two stomachs. After a careful investigation of the facts we can, however, state with every confidence that this apparently weighty consideration is of no moment. When juice flows at the beginning of the meal from the gastric *cul-de-sac*, the activity of the latter at the time must be taken as identical with that of the large stomach. This can hardly be doubted if all the preceding facts be taken into consideration. The secretion begins with the psychic excitation of the secretory nerve-centres, and this excitation naturally spreads in one and the same fashion to all points of the mucous membrane and its glands, whether in the large stomach or the small.

But these are not the only reasons on which we base the reliability of our method. A complete parallelism between the work of the large and small stomachs has been proved by direct observation. We have here only to recall the facts and arrange them in order. In the sixth lecture a sham-feeding experiment on a dog with isolated stomach pouch and divided œsophagus was described, 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 agrees with the fact that the sham feeding is also ineffective in animals with the vagi divided in the neck. The similarity in the working of the two stomachs is further seen when excitants which act directly upon the mucous membrane are employed. Water produces a secretion in the large as well as in the small organ. The same applies to Liebig's Extract, the solutions of which act more strongly on both 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 that many of the facts, which were obtained on the dog with isolated stomach, have 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 after our method, the most important of the facts observed on the first animal, were reproduced in stereotyped fashion.

There can be no doubt that the miniature stomach accurately reflects the activity of the large, provided its nervous connections are unimpaired. It must also be admitted that the mechanism by which the psychic influence is conveyed to the gastric glands is undoubtedly nervous. The effect of sham feeding is no longer seen after the vagi nerves have been divided, nor is it obtained in the glands of the gastric *cul-de-sac*, formed by the method of Heidenhain.

In seeking to explain the flow of juice when the psychic influence has come to an end it must be borne in mind that the functional connection between the two cavities can only be by means of one or other or both of two systems—the circulatory and the nervous. It is, for instance, conceivable that chemical substances which excite the secretion are themselves absorbed and carried by the blood either to the secretory centres which they excite or possibly to the glands. This hypothesis can be easily tested. If it be correct, we ought to obtain the same effect when the substances in question gain entry into the circulation in other ways than by means of the stomach. The results of experiments on this point speak most decidedly against the theory. 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. Lobasov administered to 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 also ascertained that the excitatory material of the extract had disappeared. Hence we are at first sight driven by a process of exclusion to the 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. This conclusion appears to be confirmed 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 shows an exactly similar course of secretion in the two cavities under the same conditions. But the secretion from the *cul-de-sac* formed by Heidenhain's method becomes in the course of time very greatly altered. At first the glands are very active; after a full meal their secretion is copious and lasts for several hours (*Heidenhain*, *Sanotskii*). If, however, the animals live for some time, a gradual decline of the secretion is noticeable, and within a month or six weeks from 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 glands do not show the characteristic alterations in their work, produced by differences in the food, of which we learned in the second lecture. In such animals the variations are occasioned by differences in the water contents of the food alone.

Experiments of my own show that the reflex secretion is obtainable also from the small intestine. In a dog which had an ordinary gastric fistula, and also a duodenal one, the stomach near the pylorus was separated from the intestine by a septum formed of mucous membrane in a way somewhat similar to that described in the operation for making the miniature stomach. In this dog a secretion could be set up when the exciting substance was introduced either into the stomach or into the intestine.

Again, it would also seem from the experiments of Dr. Lobasov that the flow produced by the contact of chemical excitants with the gastric mucous membrane in the second phase of secretion is also reflex and dependent on the nervous connections of the organ, since the same substances when absorbed from the rectum produced no effect. This explanation was formerly accepted without question, and the centre for the reflex effect was assumed to be in the cerebro-spinal nervous system. The experiments of Dr. Popelskii have shown the latter part of the hypothesis to be untenable, since chemical excitants, such as minced flesh, meat extract, broth, produce their effects after division of both vagi nerves. In his later experiments the same result was obtained when the stomach was completely isolated from all its extrinsic nervous connections. This was accomplished by division of the vagi and splanchnic nerves, followed by removal of the cœliac plexuses. The spinal cord below the eleventh dorsal vertebra was also removed, and all connection with its higher segments through the rami communicantes of the thoracic roots cut off.

From these experiments, and also from the fact that direct injection of meat extract into the blood stream produced no secretion, Popelskii drew the conclusion that the effect was a reflex one carried out through nerve centres in the peripheral ganglia of the stomach wall.

But another possible explanation of the chemical influence and of its transmission from one organ to the other has been overlooked by the investigators mentioned. Digestive products are known not to be absorbed from the stomach to any extent, but it may be that by their agency other substances with stimulating properties are formed in its lining cells, from whence they are taken into the blood stream and become distributed to the gastric glands.

An analogous effect on the secretion of pancreatic juice produced by the contents of the stomach acting on the mucous membrane of the duodenum and jejunum, which also at first sight seemed to be unquestionably of the nature of a reflex action, has been shown by Bayliss and Starling * to be accomplished in this latter way. A substance formed in the duodenal mucous membrane by the action of the acid of the gastric juice is at once taken up by the blood-vessels and carried to the cells of the pancreas, which are thereby excited to activity. A similar explanation has been offered by Edkins † to account for the secretion of gastric juice by our chemical excitants. Direct injection of these substances into the blood stream produces no effect on gastric secretion. But if a decoction of the pyloric mucous membrane be made with water or dilute acid, or with a solution of peptone, and then injected repeatedly in small quantities into the jugular vein, a flow of gastric juice is set up containing both pepsin and hydrochloric acid. Similar preparations made from the mucous membrane of the fundus of the stomach were ineffective. From this it would seem that the flow in the later phases of gastric digestion is excited, not through nervous

* *Proc. Roy. Soc. Lond.*, 1902; also *Zentralb. f. Physiol.*, xv. 1902.

† *Loc. cit.*

channels, but by means of a chemical substance produced in the pyloric mucous membrane and carried by the blood stream to the glands of the fundus of the stomach.

I have depicted the work of the gastric glands for the most part as we have seen it in our own experiments, and as it has developed in 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 outlined more than fifty years ago, a fact which I hope will furnish an additional reason to medical science for relinquishing its characteristic shyness of new things and accepting our interpretations of the phenomena here presented.

The 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 support 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 incomprehensibly strange that the researches of Blondlot and his account of the secretion of gastric juice had not been added to, for fifty years—indeed, on the contrary, had passed out of sight, and been supplanted by the faulty investigations and erroneous representations of later authors. Only in the works of a few writers—and these mostly French—had Blondlot's theory survived.

Of other investigators, we must mention Heidenhain, who, particularly by his study of the secretory work of the stomach, has enriched the physiology of secretion, established important facts, and originated many fruitful ideas. He suggested the subdivision of the secretory process into periods according to excitants, and hinted that it would be important to investigate the effects of the individual food-stuffs on 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 *Archiv*. The work of Blondlot and the additions of Heidenhain comprise almost everything of importance accomplished by physiology in fifty years on the mechanism and conditions required for the secretory work of the stomach. Fatal to the solution of this question was the obvious error that mechanical stimulation constituted an effective excitant of the gastric glands, and this error, in its turn, arose out of faulty methods.

LECTURE VIII.

THE NORMAL EXCITANTS OF PANCREATIC SECRETION: SUMMARY OF MATTERS DEALT WITH: PROBLEMS FOR FURTHER INVESTIGATION.

Acids strongly excite the pancreatic gland—The specific properties of these excitants—The stomach contents, on passing into the duodenum, excite the pancreas to action chiefly because of the acidity of the gastric juice—The acid excites the pancreas by acting on the duodenal mucous membrane—Probable significance of this relationship between the gastric and pancreatic secretions—Starch does not augment the total secretion of the pancreas, but increases 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 activity—Psychic excitation of the pancreas may possibly exist, but it plays an unimportant *rôle*—Water is an independent exciter of the pancreas—Solutions of neutral and alkaline salts of the alkalies inhibit pancreatic secretion—Group of problems still to be investigated in connection with the work of the digestive glands—The definite establishment of specific excitability of the mucous surfaces 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 for future investigation.

Gentlemen,—In turning, to-day, to the subject of when, how, and by what agency the secretory mechanism of the pancreas is excited during digestion, we must from the beginning be prepared to meet with 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 changed by a previous agency. It has consequently to adapt itself to varying chemical conditions. The difficulties of investigation which arise from these sources are, however, largely counterbalanced by the following advantage. The intestinal canal is completely separated from the lumen of the gland, and 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, the effects of solutions of neutral and alkaline salts of the alkali metals on the one hand, and of water saturated with carbon dioxide gas on the other. We found that a species of antagonism existed in the effects of these substances upon the pancreas. The saline solutions proved to be weaker excitants of pancreatic juice than water, the carbon dioxide distinctly stronger. These results directed our attention to the effects of acids, and we may now proceed to our first important experiment upon this subject. The dog which I exhibit to you possesses a permanent pancreatic fistula. As you see, the secretion at present is hardly worth mentioning, two or three drops in the minute, and even this is quite easily accounted for: the animal was fed fifteen hours ago. I now introduce into the stomach 150 c.c. of 0·5 per cent. solution of hydrochloric acid by means of the sound. The dog remains perfectly still and makes no protest whatever against the procedure. Two or three minutes after the injection you notice that the drops from the pancreatic fistula fall faster. We can already count twenty-five in the minute, and the flow grows quicker and quicker. In order to meet the objection that water and fluids generally, act here as the exciting agents, 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. By their means its activity can be excited 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 its intensity, I give here an example from the work of Dr. Dolinski, who took the investigation in hand.

The dog had been fed twenty-two hours before, and pancreatic juice had ceased to flow. A volume of two hundred and fifty c.c. of hydrochloric acid of the strength of the gastric juice was poured into the stomach by means of the sound. 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 ,,	0·6 ,,
7·0 ,,	1·0 ,,
8·0 ,,	0·2 ,,

7·5 c.c.	0·8 c.c.
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 an equal volume of water (250 c.c.) was poured in : no secretion followed for thirty minutes. Then another 250 c.c. of the hydrochloric acid solution was 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. Those investigated were phosphoric, citric, lactic and acetic, in addition to the hydrochloric.

The constancy and intensity of the acid effect stands out as a very remarkable fact. The idea, therefore, at once occurred to us that we had discovered the specific excitant of the pancreatic gland, and remembering that the contents of the stomach are normally acid, it seemed likely that this acid reaction probably served as a connecting link between two neighbouring compartments of the alimentary canal. But all these interesting and promising hypotheses had to be proved and established experimentally.

In the first place, the effects of hydrochloric acid of different strengths from 0·05 to 0·5 per cent. were tried, and with the following results. Quantities of 250 c.c. of HCl of the strengths given below were poured into the stomach :

	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 is possible that we had not reached the highest degree of gland activity with acid of 0·5 per cent. strength. 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 distinctly acid, acts as an excitant of the gland. The gradation in the effects, and the great sensitiveness to the acids, confirmed us in the belief that they behave not merely as general and indiscriminate stimuli, but as specific excitants of the pancreas. This conclusion appeared all the more justified since the gastric glands remained perfectly indifferent to the same acids.

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 they possess. It naturally was not difficult to test this supposition. To begin with, we satisfied ourselves that pure gastric juice was just as powerful an excitant of the pancreas as an acid solution of equal strength. Solutions of different sugars, of peptone, and of egg-white proved, when introduced into the stomach, to be excitants of the pancreas only when they had a strong acid reaction. If neutral or alkaline, their secretory effects were no greater than that of water, in some cases even less. Finally, our hypothesis was conclusively established when, by neutralising the gastric contents, we succeeded in destroying the exciting effect. If at the height of digestion, when pancreatic juice is flowing freely, one introduces by means of the sound, or through a fistula, a solution of sodium carbonate, or lime-water, or pancreatic juice into the animal's stomach, after a few minutes a diminution of the normal flow is observed which often lasts for a long time. I give here an example from one experiment:

The secretion of pancreatic juice 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 ,,
70 c.c. of the dog's own pancreatic juice 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 a striking instance of how the work of one segment of the alimentary canal is connected with and dependent upon that of a previous one. Thus, the saliva which moistens every dry food, acts by virtue of its content of water, as an excitant of gastric secretion. It is thereby ensured that the psychic secretion of gastric juice which ushers in digestion is followed by a flow produced by the influence of the saliva. This is further maintained by the effect of the gastric contents on the pyloric mucous membrane. Finally, the acid of the gastric juice acts in its turn as an excitant of the pancreatic gland, thus continuing the influence exerted by the digestive glands upon each other.

We are, therefore, justified in saying that the acid is a specific excitant of the pancreatic gland. Where, however, is its seat of action? There are several possibilities. The acid either acts reflexly through a nerve centre, by virtue of its effect on the end apparatus of centripetal nerves in the mucous membrane, or locally through a peripheral nervous mechanism, or it may be absorbed into the blood and stimulate the gland cells directly, or, finally, by its action on the duodenal mucous membrane it may produce an excitant which is absorbed and reaches the gland in the last-named way. Theoretical considerations led us at the outset to accept the first hypothesis. Thus acid solutions injected into the rectum produce no effect on the pancreas, nor do they when retained in the stomach and prevented from entering the intestine. It seemed to us, moreover, that if absorbed from the duodenum into the blood-stream the acid could only act on the pancreas by reducing the alkalinity of the blood. In normal digestion, however, the alkalinity of the blood is increased. So far we were right, though, as will be seen, we overlooked what has proved to be the correct explanation.

The negative effect on pancreatic secretion, of acids acting on the mucous membranes of the rectum and stomach, was observed by Dr. Popelskii. The following are the results obtained in 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 „

Experiments were also performed on a dog (*Dr. Popelskii*) the stomach of which was divided into two parts near the pyloric region, each having a fistula cannula leading into it. When acid was introduced into the cardiac segment the pancreas remained at rest. On the other hand, when it was poured into the pyloric portion, a secretion of pancreatic juice appeared, but only after the acid had passed on into the duodenum. This agreed with the fact that the flow of pancreatic juice augments and declines in curve form, obviously dependent upon the entry of the acid food mixture into the intestine. It appeared therefore probable, in the first instance, that the effect of the acid upon pancreatic secretion was due to a central reflex through nervous channels. Further experiments have, however, led to different conclusions.

It was in the next place shown by Popelskii * that the acid effect on the duodenum could be obtained after the following operations or combinations of them were carried out—namely, division of both vagi, section of the splanchnic nerves on both sides, destruction of the spinal cord, and extirpation of the solar plexus. He concluded that the secretion arose from a peripheral reflex through scattered ganglia of the pancreas, situated mostly near the duodenum. The same results were obtained by Wertheimer and Lepage,† who accepted Popelskii's explanation. They found, however, in addition, that the supposed peripheral reflex could be obtained from the jejunum and upper ileum, the effect diminishing in intensity with the descent along the gut. No effect whatever could be obtained from the last two feet or so of the ileum. Atropin did not abolish the secretory effect.

The foregoing experiments were repeated in a modified way by Bayliss and Starling,‡ who confirmed the results of Popelskii, Wertheimer and Lepage. Bayliss and Starling, however, found in addition, that the secretory effect could be obtained from a loop of jejunum after severing all the mesenteric nerves supplied to it. They were in consequence led to the conclusion that the result was not dependent on a reflex through the nervous system. The only other connection between the denervated loop of intestine and the pancreas was by way of the blood-vessels. But Wertheimer and Lepage had shown that the acid of itself, if introduced directly into the circulation, had no effect on the pancreas. Thus Bayliss and Starling were led to conceive that the acid produced some substance by its action on the mucous membrane which, when taken into the blood-stream and carried to the pancreas, excited its cells to activity. This hypothesis was at once confirmed by the most convincing experiments.

* Pflüger's *Archiv.*, xxxvi. 215.

† *Journ. de Physiol. et de Path. Générale*, 1901. ‡ *Loc. cit.*

The mucous membrane of the loop of jejunum was scraped off and rubbed up in a mortar with sand and 0·4 per cent. hydrochloric acid. The extract was filtered, neutralised, and injected into a vein, with the result that a copious flow of pancreatic juice quickly appeared from the cannula inserted into the pancreatic duct. Active extracts were obtained from the mucous lining of all those parts of the intestine which (in the hands of Wertheimer and Lepage) yielded positive effects from the acid, but were not obtained from the lower ileum or large intestine.

To the substance thus extracted the name *Secretin* has been given. It is not of the nature of a ferment, since boiling does not destroy it. It is suggested that it pre-exists in the mucous membrane in an inabsorbable form—*prosecretin*—which is then transformed into secretin by the action of the acid.

With the use of ordinary extracts of the mucous membrane a fall of blood-pressure accompanies the effect on the pancreas. This fall is due to some substance other than the *secretin* itself. It is, however, possible to obtain secretin free from the vascular depressant. By occlusion of the aorta, to temporarily shut off the blood supply from the alimentary canal, shedding of the lining epithelium into the lumen of the gut can be caused. An acid extract of this desquamated epithelium, made in the same way as the extract of the whole mucous membrane, gives the secretory effect without the lowering of blood-pressure. *Secretin* probably acts directly on the cells of the pancreas. Its effect, at all events, is not removed by a previous injection of atropin. This latter is of importance, since, as we saw, the same applies to the acid influence. The general name *Hormone* (ὁρμαω, *I set in motion*) is given to a specific chemical excitant, such as secretin.

The foregoing results have been verified by numerous workers. They have also received strong confirmation from an observation of Enriques and Hallion,* who found that if blood, taken from the carotid artery of a dog after acid had been introduced into its intestine, be injected into the jugular vein of another dog, a secretion of pancreatic juice is evoked. It should be added, however, that Wertheimer † and also Fleig ‡ obtained the acid effect from an isolated intestinal loop, even when the blood returning from it was not allowed to re-enter the general circulation. These investigators hence infer that the effect must also reach the pancreas through nervous channels as well as *via* the blood-vessels. Their experiments, however, do not appear to wholly exclude a humoral influence by way of the lymphatics.

That the acid forms a connecting link between gastric and intestinal

* *Compt. Rend. de la Soc. de Biol.*, lv. 233 (1903).
† *Journ. de Physiol. et Path. Générale*, 1901.
‡ *Compt. Rend. de la Soc. de Biol.*, lv. 462.

digestion is undisputed, but why is the acid and not something else employed to serve in this manner? Naturally, we cannot claim to have solved this question conclusively, we can only bring forward certain hypotheses. As is known, the pancreatic ferments act best in an alkaline medium. When the medium is weakly acid their effects are less, and with any pronounced degree of acidity soon become nil. It may be that the pancreatic juice neutralises the acid which caused it to flow, merely in order to provide a suitable medium for the activity of its ferments. But at the same time the juice protects itself against the destructive action of the pepsin, for which a neutral or alkaline medium is very unsuitable. Thus the idea of Brücke that the bile arrests the action of pepsin in the duodenum and so provides favourable conditions for intestinal digestion may also be applied to the pancreatic juice. At the same time another important significance of this relationship lies near.

For a peculiar and as yet unexplained 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 derived from the sodium chloride of the blood. An increase of alkalinity thus arises in the blood, and this condition, in order to preserve the mean chemical composition of the fluid, must be removed. The hydrochloric acid would, however, if not neutralised, again be absorbed, after fulfilling its function in the alimentary canal, and this in turn would lead to a marked reduction 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 of 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 radicle of the sodium chloride is abstracted by the peptic glands and passed into the cavity of the stomach, the basic radicle, the sodium, is simultaneously used in the preparation of pancreatic fluid. 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 it be true that the flow of pancreatic juice excited by acid, is poured out with the object amongst others, of neutralising the stimulus by which it is evoked, 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. Estimations of the amount of ash, as well as titration, both of the ash and of the unaltered pancreatic juice, have unquestionably shown that a connection exists between the nature of the secretory excitant and the amount of inorganic substance in the pancreatic fluid. The juice called forth 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 also shows a very high degree of alkalinity both in the ash and in the fluid itself. The "acid" juice retains these characteristic properties even when the hourly quantity of secretion varies. This occurrence is perfectly analogous to one previously described, where we saw in the first lecture that the ferments of the juice adapted themselves to the kind of food ingested at the time. With bread the amylolytic ferment, and with milk the fat-splitting ferment, was found to be increased. Likewise here, an acid evokes the production of alkali, while the organic constituents which are not required are remarkably reduced. The juice, however, which is poured out in response to acids is never devoid of ferment- or potential ferment-properties. It is always produced for digestive purposes, and never merely for the neutralisation of acids.

That under normal circumstances the work of the pancreas is intimately dependent upon, perhaps chiefly regulated by the acid produced in the stomach, is shown by the close correlation between the curves of secretion of gastric and pancreatic juice on ordinary foodstuffs. Thus the production of gastric juice for flesh and for bread in each case is most rapid in the first two hours, after which it declines. The same applies to the outflow of pancreatic fluid for these foods. Further, the qualities of the latter juice—low percentage of organic constituents and of ferments—are those of juice secreted in response to the acid stimulus. On milk, gastric juice is poured out less rapidly, reaching a maximum after three hours, after which the curve begins to fall. The flow of pancreatic juice for milk exactly corresponds.

Apparent discrepancies in reality support this view. The quantity of gastric juice poured out on bread in the first hour is, on the average, twice as great as in the second. The reverse holds good for the pancreatic secretion, the maximal of which falls in the second hour. But this is accounted for by the fact that the mixture of bread and acid only leaves the stomach in any quantity from the second half of the first hour onwards. Another difficulty is that the rate of outflow of gastric juice, is maximal for flesh, but of pancreatic fluid, for bread. This divergence is explained, however, by the fact that much more of the acid of the gastric juice is combined by the proteins of flesh than by those of bread.

That a non-nutrient substance, namely the acid, has proved itself to be the strongest excitant of the secretory apparatus of the pancreas, does not, however, preclude the possibility that there may also be other excitants, either identical with those which act on the gastric glands, or wholly different, since the sphere 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 excitants of the pancreas, for, as we know, the gland has special relations to these substances. So far, we have been unable to prove an exciting effect for starch. Solutions of varying concentrations evoked no more juice than water alone. The question, however, requires further investigation, for it is quite possible that the precise conditions required for the starch effect may 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 output of the ferment without increasing the total quantity of juice. Some experiments of Dr. Walther support this hypothesis. When a dog was fed 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 experiments the fat-splitting ferment behaved in just the opposite way—the flesh juice possessed a greater, the bread juice a less degree of fat-splitting action.

Nor is the possibility excluded that the continuation of starch digestion may depend on some entirely different condition—for example, the production of lactic acid from the carbohydrate constituents of the food. Possibly this is the explanation of the production of lactic acid, the meaning and importance of which have been but little cleared up. Science has not attempted, and could not up to the present venture to reproduce a synthesis of normal digestion—that is to say, to combine the often conflicting requirements, not only of the different food-stuffs, but also of the different sections of the digestive canal and of the body as a whole.

In contrast to the experiments with starch, those dealing with the influence of fat upon the pancreatic gland yielded much more direct and simple results. Indeed, the mere comparison of known facts made it very probable that fat acts as an independent exciter of the pancreas. The secretion of gastric juice is restrained by fat, and we could hardly conceive that, under normal conditions, a pancreatic secretion for fat could be wholly caused by the acid of the gastric juice. Dr. Dolinsky poured oil into the stomachs of dogs, and constantly obtained a more or less considerable flow of pancreatic juice. When we remember the strong inhibitory effect of fat on gastric secretion, the constancy of this latter result seemed to afford good assurance that we had here 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 the following experiment devised by Dr. Damaskin complies with the strictest requirements. A perfectly healthy dog, having two fistulæ—one a gastric, the other a pancreatic—was last fed twenty hours before the experiment. Below the orifice of the pancreatic duct a metal funnel and graduated cylinder were suspended. The gastric fistula was closed by a cork through which a glass tube was led, and this in turn was connected by an india-rubber tube to another funnel. The latter funnel was hung up at a suitable height, and contained 110 to 115 c.c. of oil. The india-rubber tube was provided with a T-piece, the transverse arm of which was connected to a second india-rubber tube. At the beginning of the experiment the tube between the funnel and the T-piece was clamped with a Mohr's clamp, so that the oil could not flow down. The other 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 shut himself in the room with the dog and patiently waited. The animal soon gave up hope of receiving food to eat, and finally slept. Here I should remark that sleep exercises no influence on the activity of the pancreas. When, therefore, the acid secretion from the stomach ceased, the experimenter cautiously closed the outflow tube and opened that to the oil funnel. So long as the stomach cavity remained unclosed, either no pancreatic juice was secreted, or at most 0·5 to 1·0 c.c. in fifteen minutes; but in three to five minutes after pouring in the oil, the flow distinctly increased, and after fifteen to thirty minutes attained a rate of 7 to 10 c.c. in fifteen minutes. During this time, a very small quantity of alkaline mucus was secreted by the stomach, which collected in the lower section of the india-rubber tube. The secretion of pancreatic juice after the administration of fat apparently takes place even when every trace of acid 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 was found to contain only 15 to 20 c.c. of oil and 3 to 5 c.c. of alkaline mucus, while later, only mucus mixed with small quantities of oil flowed out. In other cases, either early or late, together with the mucus, 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 preclude the idea that an acid reaction, rapidly set up in the intestine by cleavage of the fat, acts as the excitant of the pancreas. The intestinal contents, for an hour or still longer, showed no trace of acid reaction. The experiment affords good ground for concluding that fat is an independent exciter of the pancreatic gland. The investigations of Dr. Walther go still farther, and show that fat excites not only a free secretion of pancreatic fluid, but also causes an increase of the fat-splitting ferment. In the first two hours after a meal of milk, a juice uncommonly rich in fat-splitting ferment is secreted, If the milk be deprived of its fat by filtration, the juice possesses a very low fat-splitting power, without other alteration in the duration or rate of secretion. When, however, the milk is again mixed with its fat—*i.e.*, when it is synthetically reconstructed—the fat ferment in the pancreatic fluid increases to the normal amount characteristic of "milk juice."

It has also been shown that alkali soaps—for instance, solutions of sodium oleate—when introduced into the stomach of the dog, excite or augment the flow of pancreatic juice from a permanent fistula (*experiments of B. P. Babkin* *). This effect has been further investigated by Fleig,† who finds that the seat of influence of the soaps is the mucous membrane of the duodenum and upper jejunum. Extracts of these membranes made with soap solutions of 1–10 per cent. strength, when injected into a vein evoke a secretion of pancreatic juice analogous to that produced by secretin. The immediate excitant of the pancreas is a substance resembling, but not identical with, acid "secretin." It is absorbed into the blood-vessels and acts directly upon the gland.

If the blood from an isolated loop of intestine into which soap solution has been injected, be led away and not returned to the circulation, no secretion of pancreatic juice is evoked, even though the nerves of the loop be uninjured. On the other hand, Savitsh found that atropin arrests the soap effect, and concludes therefrom that it is a reflex through the nervous system.

Of substances foreign to the intestine, chloral hydrate, if injected into the duodenum of the dog in doses of 1 grm. dissolved in 5-10 c.c. of water, evokes a vigorous secretion of pancreatic juice from a cannula placed in the duct (*Wertheimer and Lepage*).‡ The filtered contents of the loop after chloral injection, also extracts of duodenal or jejunal mucous membrane made by boiling with alkaline solutions of chloral hydrate and a small quantity of chalk, are effective when injected into the circulation (*Falloise*).§

Fleig suggests the generic name "krinin" for stimulating sub-

* *Versamml. Nord. Naturf. i. Helsingfors*, 1902.

† *Compt. Rend. de la Soc. Biol.*, lv. 1201.

‡ *Ibid.*, lii. 668.

§ *Bull. de la Cl. Sci. de l'Acad. Roy. de Belg.*, 1903, 1106.

with lateral duodenal fistula as well as pancreatic. Secretion from the latter began, one to one and a half minutes after feeding with bread or flesh, and continued for ten to fifteen minutes, the duodenum all this time being empty and alkaline in reaction. Corresponding results were also obtained with a dog having a lateral fistula alone. Within one to one and a half minutes from the beginning of feeding with flesh or bread, a clear colourless fluid, strongly alkaline and capable of actively digesting egg-white, commenced to flow from the fistula. Sham feeding appears, therefore, to excite a flow, although only a moderate one, of pancreatic juice.

Similar considerations have to be borne in mind regarding the relationship of water to pancreatic secretion. Water poured into the stomach excites a flow of pancreatic juice. But how? Is it by independently exciting the gland, or because it has led to a flow of acid gastric juice? In experiments to decide this question the same method was adopted (*Dr. Damaskin*) as in those with 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, either a beginning or a distinct increase of the secretion of pancreatic juice. If one waits for a minute or two longer, and then empties the stomach, some water, or at all events a fluid, sometimes neutral sometimes alkaline, is 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, until 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 secretory mechanism of the pancreas.

Finally comes the question; How do other chemical excitants of the gastric glands act—namely, those 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 into the stomach the secretion began after the same length of time, and was in no case greater than with water.

If we now sum up these facts, we find that some excitants are common to both the gastric glands and the pancreas. Amongst these are to be included the psychic effect probably—*i.e.*, the contemplation of food and drink—and at all events the fictitious feeding effect. In addition, both organs have their own specific stimuli; for the gastric glands, the extractives of meat; for the pancreas, acids, fats, soaps, and chloral hydrate.

We must, however, dwell a little longer on the inhibitory phenomena which in certain cases became evident 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 they 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 pancreatic juice 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 the influence lasted. The solution to be investigated was passed into the stomach of a dog by means of the tube. An hour later the animal received its ordinary meal, and the resulting pancreatic secretion was compared with the normal. In every case a marked diminution of the secretion was 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, and brings it down to an unusually low level.

The fact that some substances diminish the secretion of this gland is very remarkable, and undoubtedly deserves our consideration. But how we are to interpret the mechanism of inhibition remains obscure. It is at present difficult to decide whether we have to deal only with a local effect on the peripheral terminations of reflex-transmitting nerves, or with an influence produced through the blood.

Such are the facts which have been collected concerning the normal excitants of the pancreatic gland. We are justified in characterising most of them as new, although the idea that acids and acid chyme exert a special stimulating effect was expressed long ago. But the mere expression of an opinion is very far from working out the precise facts. Moreover, the idea obtained no general recognition, because it was not founded on any definite basis. Till recently, articles and text-books mentioned only a stimulating effect of food as a whole.

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 in reality exhausted. Much, very much, remains to be achieved before we can congratulate ourselves on a complete conquest of the territory. What is gained already is very valuable if only for its use as a sign-post to guide future research. We have very many more inquiries before us than we had a short time ago, and all these mean progress in our investigations, because they testify to the existence of a wide field of research which we have merely studied from a general point of view, but which we now wish to submit to exhaustive inquiry. The questions are so many that we must group them together for consideration.

In the second lecture we learned of the great complexity, and at the same time marked 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. In doing so the requirements of the several food constituents. and the conditions necessary for the welfare of the digestive canal, as well as for the organism as a whole, must be borne in mind.

We have already spoken of the foods and subdivided them into their separate constituents, but we have not by a long way brought all of them under consideration. We must therefore study them individually and determine their importance more fully. It is from the effects of the elementary constituents that each separate point of the curve of secretion after a complex meal must be explained. To solve this problem we must combine successively the individual constituents with each other, and synthetically build up the food step by step, while at the same time we have to submit the properties of the juice at every phase to an exact analysis. In the case of a complex food we shall then be better able to draw conclusions from the properties of the juice as to what has been the effective excitant. For example, from the qualities of the pancreatic juice we can decide already with tolerable certainty whether its secretion has been caused by acids or not. A correspondence in the results of both methods—the analytic and the synthetic—would furnish the best assurance of their reliability.

The systematic investigation of the constituents of the food in these ways 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, (1) why, and (2) in what way gland activity varies, can only be obtained when an exact investigation of the contents of the digestive canal is thus joined hand in hand with observations upon secretory activity; when, for instance, for every given period of digestion, and for every section of the digestive canal, we know precisely where a particular constituent of the food is to be found, and to what alterations it is then being subjected. Under the second head, questions dealing with the seat of action of the elementary food constituents, their mode of working, and the combined results of these local specific excitants have to be considered. This category also embraces the chain of phenomena in the central nervous system set up by the peripheral impulses from the digestive canal, as well as by impulses from other organs. But the questions in both groups are interwoven in the closest manner. Furthermore, similar questions in all probability apply to such digestive fluids as the bile and the succus entericus, the physiology of which will be considered later. Experiments of Dr. Bruno, in which the entry of bile into the intestine was observed, have shown a relationship between this event and the nature of the food quite as exact and intimate as any we have already learned for the gastric and pancreatic juices.

Although much more remains to be done, we have reason to be satisfied with what has been accomplished. Our results, I hope, have for ever done away with the crude and barren idea that the alimentary canal is universally responsive to every mechanical, chemical, or thermal agency, regardless of the particular requirements of each phase of digestion. Instead of this hazy conception, we now see delineated an intricate mechanism which, like everything else in nature, is adapted with the utmost delicacy and precision to the work which it has to perform.

An essential advantage to the digestive process is derived, as we have already seen, 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 connected with the first and strongest secretory impulse to the gastric glands. Through the medium of its effect upon these latter the stimulus is further transmitted to other digestive organs. The fluids, differing in reaction, which are secreted under these influences, transform a considerable part of the food into a soluble half-fluid condition, and thus allow the chemical constituents of the mixture to take effect. In consequence of this, the initial rate of gland activity is modified so as to harmonise with the altered components of the food, which by this time are 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, a certain equilibrium is maintained, both in regard to the quantity and the strength of the digestive medium as a whole. The transformation of one constituent is favoured, that of another restrained: a species of contest for the reagent needed, is fought out between the several components of the food. The secretory work which began with the ingestion of food is thus passed on from stage to stage along the alimentary canal, thanks to a suitable linking 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. This period has more than elapsed, and, although my prediction has not perhaps been wholly fulfilled, there is no reason to be dissatisfied with the results which have accrued. In far-off lands, both East and West, a lively interest has been taken in our researches. With the assistance of many European and other colleagues as well as our workers here, numerous investigations have been taken up and started on the right way, and this must rapidly lead to a complete accomplishment of the task.

We are not dealing with questions concerning the nature of life, or of the physics or chemistry of the cell. The pursuit of these will furnish, for a long series of generations, themes of ever-engrossing and insatiable interest, before their final solutions are achieved. In our department of biology, however, that is, in organ physiology in contrast to cell physiology, one may reasonably hope that there are many territories where the reciprocal relations of the individual parts of the system (for example, the digestive canal) and the correlation of the whole towards external objects (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 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 overlooked these elementary structures and primary functions and investigated the rules and laws of their working in the mechanism, as a whole. We have simply learned how certain forms of apparatus may be thrown into activity, and within limits we know how to work them.

LECTURE IX.*

BILE AND SUCCUS-ENTERICUS.

Later researches on the digestive glands—The multiplicity of functions attributed to the bile is an indication of our lack of knowledge of its physiology—Method of studying bile 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 the pancreatic juice—The *succus entericus* has also the same function—A ferment of ferments, the ENTEROKINASE—Mechanical excitation elicits a secretion of *succus entericus*, but only of its watery constituents—Pancreatic juice is a specific excitant of enterokinase—The favouring influence of *succus entericus* upon the action of pancreatic juice depends upon the conversion 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.

GENTLEMEN,—Since the delivery of the preceding lectures, our investigations into the physiology of digestion have been carried on without interruption, and our later results have shown 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 in certain respects been made matters of direct research. The results have in nearly all cases been communicated to this society; consequently, the facts of which I am about to speak will be already known to many of you. I think it desirable, however, to bring them all under review. It is only in this way that the general bearing of the investigations can be made clear, and that

* The subject-matter of Lectures IX. and XII. was delivered as an address at the anniversary meeting of the Society of Russian Medical Men in St. Petersburg, 1899–1900. The address was dedicated to the memory of S. P. Botkin in the names of Professor Pavlov and the following collaborators: J. O. Lobasov, A. N. Volkovitsch. J. C. Soborov, J. C. Savriev, A. A. Walther, L. B. Popelskii, A. R. Krever, G. G. Bruno, N. N. Kladnitski, S. H. Wulfson, W. W. Nagorski, D. L. Glinski, N. P. Shepovalnikov, A. S. Serdiukov, P. O. Shirokich, E. A. Ganicke, and A. P. Sokolov. It was afterwards published as a separate pamphlet under the title "EXPERIMENT: The Only Adequate Method for Present-day Medical Research." For the purpose of incorporation in the second English edition of these lectures it was considered desirable to subdivide and redistribute the matter therein dealt with.—(*Translator*.)

each single piece of work can find its proper place in the scheme as a whole.

It will be understood that even at this stage purely physiological questions have taken the first place in our researches, but our field has naturally grown wider and wider. My former lectures dealt mainly with the chief digestive organs, the gastric glands, and the pancreas. During the interval we have penetrated still further into the physiology of these glands, but in addition we have included the study of the remaining digestive secretions, namely, the saliva, the bile, and the succus entericus. We have also made observations on the movements of the food along the digestive canal.

In dealing with the gastric glands and the pancreas we had no need to inquire into the chief physiological functions of their secretions, since these were already fully known. We were therefore free to direct our whole attention to a study of the factors which determined the normal activity of these glands. But in the case of some of the other fluids it was necessary to establish at the outset, their functional importance.

The results of our later investigations into the work of the salivary glands, the pancreas, and the stomach have, for the sake of continuity of subject, been transferred to earlier chapters of this book.

I therefore now turn to the BILE. You all know, gentlemen, that the greater the number of remedies recommended for a disease, the less useful is any one of them. The reason of this is quite plain. When a really good remedy is known we want no other. The same criterion may be applied to our knowledge of the organs of the body. When numerous 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 we learn at once the uses of the gastric juice, of the pancreatic juice, and so on. But when we come to the bile we have to read whole paragraphs about its supposed uses, and perhaps not even then learn its chief function. Mention is 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 semi-digested proteins, and so on. Are all these correct, however? In how far is any one essential, and the others not? To such questions no satisfactory answer could be found. Further, the teacher has 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, and 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 digestion gives place to the alkaline pancreatic.

But how are we to set about determining what are the digestive functions of the bile? One of the most direct ways is to examine how much and what kind of bile is poured into the alimentary canal. It is remarkable that this method has never been correctly applied, although numbers of physiologists have worked at the subject. 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 till required for use. Experiments performed on dogs with the aid of 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 then conducted into the gall-bladder. These experiments have led the authors to very different conclusions regarding the formation of the bile, but in all cases it was seen to flow continuously 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 are the functions of the bile during digestion, one must observe how it enters the alimentary canal and not how it accumulates in the gall-bladder. It was on these latter lines that we proceeded, after bringing the natural orifice of the bile duct (with a piece of the surrounding mucous membrane) to the exterior.

The operation we adopted, after some preliminary trials, was as follows. The wall of the bowel opposite the orifice of the duct was surrounded by an incision (see Fig. 20, *a*), the flap cut out and folded back upon its serous coat where it was fastened with sutures. This done, the intestine was closed at the point in question and the displaced orifice stitched into the edges of the abdominal wound, where it healed. The operation is not an easy one. In performing, it the abdomen is opened in the linea alba, just below the ensiform cartilage. The duodenum is then drawn forwards as much as possible and a white streak along the bowel sought for. This corresponds to the course of the common bile duct, and ends below in an oval patch, also whitish. The middle of this patch indicates the point of entry of the bile duct with the smaller pancreatic duct into the bowel. The pancreas opposite this spot is to be carefully separated from the duodenum, avoiding injury and ligaturing the blood-vessels before division. When the smaller pancreatic duct is thus brought into view it is to be double-ligatured and divided.

On each side of the oval patch a short incision is made lengthwise through all the coats of the bowel, and about 7–8 mm. apart. These are then joined by a transverse cut, 5–7 mm. below the papilla. The tongue-shaped flap thus formed contains the orifice of the duct at the middle of its inner face. The flap is then folded back at its base, bringing the

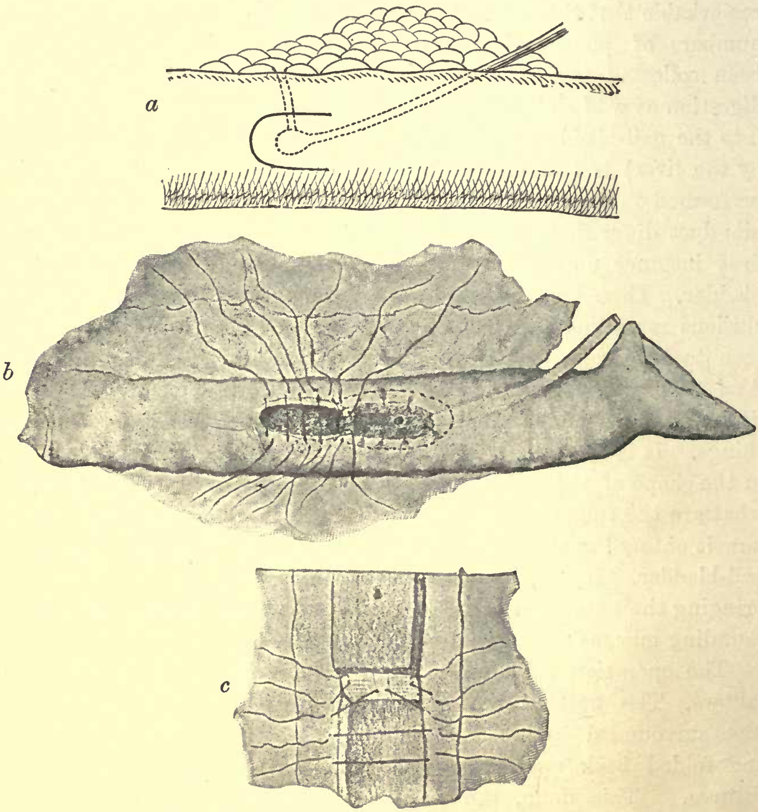


FIG. 20.—Showing the different stages in transplanting the orifice of the bile duct outwards. In (*b*) a flap of mucous membrane is reverted over the bowel.

orifice outwards, and its serous surface is fastened to that of the bowel by four or five sutures. The opening into the bowel is now closed. To do this the mucous membrane at the base of the reverted flap is carefully cut away, and the sides drawn together by sutures laid as shown in Fig. 20, *b* and *c*. The displaced orifice is then sewn into a part of the abdominal wound, the remainder of which is closed by layers of sutures. The wound usually heals in seven to ten days, but should a small fistula into the bowel remain, it can be easily remedied by a later operation, care being taken to remove the protruding mucous membrane from the fistular orifice. The bile is collected by means of a funnel, held in position by india-rubber bands.

A study of the entry of bile into the intestine showed that it is regulated by the same laws that govern the flow of the other digestive juices. (*Experiments of Drs. G. G. Bruno and N. N. Kladnitski.*) In the fasting animal not a drop of bile flowed from the duct. But when the dog had eaten, the flow began after a definite time, which

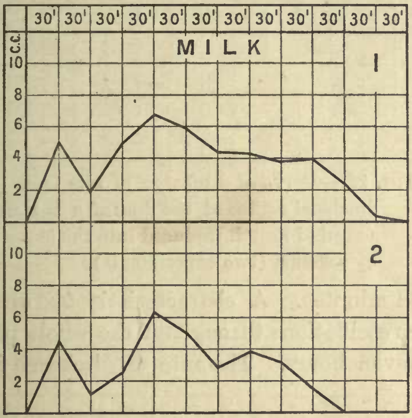


FIG. 21.—Curve of discharge of bile from the duodenal orifice of the duct of a dog after a meal of milk (two experiments).

varied for the different kinds of food. The fluid continued to escape as long as digestion lasted, with fluctuations in quantity and quality, dependent upon the nature of the food. Examples are given in Figs. 21, 22, and 23 of the curves of discharge of bile into the intestine of a dog fed with milk, flesh, and bread respectively. The features are more or less typical for each food. In the curve for milk three elevations are usually seen. The first begins after a latent period of fifteen minutes, reaches its maximum in half an hour, and lasts one hour. The second and largest undulation occupies, including rise and fall, the whole of the second and third hours, its maximum being reached at the end of the second. The third elevation occurs in the fourth or fifth hour, and merely marks a slight interruption in the decline of the outflow, which quickly comes to a stop, at or soon after the end of the fifth hour. The discharge for flesh is usually more prolonged. Its latent period is much longer—average 41 minutes—and its maximum is reached in half an hour from the beginning of outflow. Then comes a slow and gradual decline, not infrequently broken by sharp oscillations towards the end of the flow, which lasts well into, or even beyond, the sixth hour. The terminal fall is somewhat abrupt. The outflow for bread is still longer than for flesh. Its latent period is not markedly different;

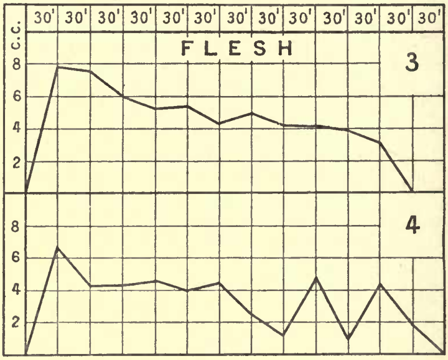


FIG. 22.—Curve of discharge of bile from the duodenal orifice of the duct of a dog after a meal of flesh introduced into the stomach by a fistula (two experiments).

the average is 38 minutes. A characteristic feature is the constant presence of sharp oscillations throughout the whole period, which, as a rule, lasts over seven hours. The rate of discharge is slower, but the

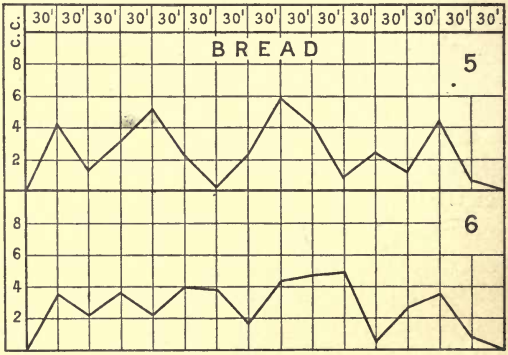


FIG. 23.—Curve of discharge of bile from the duodenal orifice of the duct of a dog after a meal of bread introduced into the stomach by a fistula (two experiments).

total bile ejected is greater for the same weight of food than in the case of flesh or milk.

Obviously the discharge of bile into the intestine is determined by the mode of passage of the food from the stomach into the duodenum, and lasts for the same length of time.

The curves of secretion above given may satisfactorily be explained on the following lines (*Bruno*). Thus in the digestion of milk there are three chief phases: *first*, a passage of unchanged milk through the pylorus into the duodenum. The initial rise in the "milk" curve corresponds to this period, and is due to the exciting effect of its fat. The quantity of bile at this stage coincides with the quantity of pancreatic juice; further, the bile is concentrated, and augments the action of pancreatic steapsin more effectively than at any other time. The *second* phase corresponds to the coagulation in the stomach of the greater part of the milk taken, with its separation into clot and whey. The decline of the first wave in the curve of discharge is no doubt due to arrest of the escape of milk through the pylorus owing to this coagulation, with possibly also the escape of whey, a fluid largely deprived of its stimulating properties owing to the absence of fat. The *third* phase consists in dissolution of the clot of casein by the pepsin-hydrochloric acid of the stomach with the formulation of protein digestive products and the liberation of fat. The rise of the second or chief wave of discharge in the milk curve is no doubt due to the stimulating effect of these products when they enter the duodenum. Its fall is due to the decrease in the quantity of these substances escaping from the stomach. The third elevation of the "milk" curve may be explained by the final passage of the residue of digestive products retained for a time in the stomach owing to their difficulty of solution.

The curve for flesh is more uniform, largely owing to the fact that it is mainly composed of one kind of food constituent. The series of elevations sometimes seen towards the end of the "flesh" curve, and normally present throughout the whole course of the "bread" curve, are to be explained by the mode of passage of these foods through the pylorus, after being acted upon by the gastric juice. Such elevations are less obvious in curves where the periods between the records are longer. They are hardly seen in curves marked at hourly intervals, since each period includes several of the smaller waves. If the periods are half the length of those given—namely 15 minutes—the undulations are still more obvious. One cannot resist the conclusion that the bile has quite as important a part to play as any other digestive juice in the chemical elaboration of the food. But although the discharge of bile into the bowel is clearly related to the passage of food from the stomach into the duodenum, the presence of food alone does not seem sufficient to excite a flow. Nor is the entry altogether determined by the reaction of the duodenal contents. Acids brought into the stomach in the intervals between meals and allowed to pass on into the bowel do not evoke a discharge of bile from the gall-bladder.

In our further investigations we gave the constituents of the food separately to the dog to eat, or brought them directly into the stomach. It then became evident that neither water nor raw egg-white nor boiled starch, whether solid or fluid, caused a flow of bile into the duodenum. On the other hand, fat, the extractives of meat, and the products of gastric digestion of egg-white, set up a free discharge of the fluid. The bile, therefore, resembles other digestive juices in that it possesses its own special group of excitants, which stimulate it to flow into the intestine.

But the discharge of bile into the bowel is not to be confused with its secretion by the liver. Observations on the latter, made long ago by Rutherford,* in which bile was collected by means of a cannula placed in the ductus choledochus, showed that acids, when applied to the duodenal mucous membrane, excite an increased secretion. The importance of this observation was not appreciated at the time, nor indeed till recently, when attention was drawn to it by the discovery (*Henri* and *Portier*)† that "secretin," so active in promoting a flow of pancreatic juice, also exerts, after intravenous injection, a powerful excito-secretory effect on the bile, provided the blood pressure be not severely lowered. Since then, the observation has been abundantly confirmed by several observers (*Enriquez* and *Hallion*,‡ *Wertheimer*,§ *Fleig*,|| *Falloise*¶). The acid effect is also obtained from the upper and middle segments of the jejunum, but not at all from the lower ileum, colon, or rectum, nor from stomach. The fluid mostly employed was hydrochloric acid of the strength of 0·5 per cent.; but other acids in weak solution are also effective—namely, sulphuric, nitric, phosphoric, acetic, and even oxalic.

The explanation of the acid effect had already been indicated by the fact that secretin (obtained by extraction of the mucous membrane of the duodenum and upper jejunum with 0·4 per cent. hydrochloric acid) if injected into a vein produced a copious flow of bile. It thus acts by chemical influence, transmitted through vascular channels, and this has been confirmed by the discovery that the blood returning from a loop of intestine into which acid has been introduced, is capable of exciting or augmenting the flow of bile from the liver of a second dog if intravenously injected.

The stimulating effect of acid extracts is not confined to those made with hydrochloric acid. Any of the acids mentioned above may also be used, and will yield active extracts. It has further been shown that chloral hydrate, when injected into a loop of the intestine, strongly excites a flow of bile from the liver, but, unlike acids, is also effective when injected into the rectum or into a vein. A larger dose is, however, required in these latter cases (*Wertheimer*, *Falloise*). In using chloral, 3 to 5

* *Trans. Roy. Soc. Edin.*, xxix. 191.
† *C. R. d. l. Soc. d. Biol.*, liv. 620.
‡ *Ibid.*, lv. 233.
§ *Ibid.*, lv. 286.
|| *Bull. d. l'Acad. Belg.*, 1903, 1095.
¶ *Ibid.*, 1903, 1757.

centigrammes per kilo. of body weight are injected into the duodenum of the dog, in solution of the strength of one part to five or ten of water, the duodenum being ligatured at its junction with the jejunum. The flow of both bile and pancreatic juice is augmented after a pause of two to three minutes. The maximum effect is reached in ten minutes for both; but while in the case of the pancreas the influence passes off after half an hour, the effect on the outflow of bile remains strong for thirty to forty minutes, with perhaps a slight dip in the curve after the first maximum. The effect only begins to pass off after an hour to an hour and a half, and finally disappears about an hour later.

If the contents of a loop of bowel into which the chloral has been injected be removed, filtered, and injected into a vein, the secretion of bile, like that of pancreatic juice, is much augmented. Furthermore, an extract of the mucous membrane made with chloral is effective. The results, therefore, in both variations of the experiment must depend on a chloral "secretin."

Having ascertained the mode of entry of bile into the intestine, we have still to ask, What is its true function? In seeking an answer to this question, 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 fact the that in many text-books of physiology they are consigned to small print. The bile possesses but a weak direct chemical action upon the food constituents. Different investigators have long ago shown that it has a slight amylolytic action. In addition, Dr. Gegalov has recently discovered in this laboratory that the bile of carnivora contains a proteolytic ferment, but its action is only a weak one. The latter observation has been extended to human bile (*Tschermak* *), likewise another concerning the existence of an oxidising ferment in this fluid. But these properties cannot be considered of major importance.

There remains the possibility of a chemical effect upon the 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 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. Likewise there are investigations, originally begun by Professor Nencki in his Berne laboratory and carried on by Heidenhain, Rachford, Williams and Martin, which show that the bile favours the action of the ferments of the pancreatic juice. But the majority of these experiments dealt with extracts of the pancreas, and

* *Zentralbl. f. Physiolog.*, xvi. 329.

consequently in the main with zymogen, not with the ready-made juice. It was open therefore to doubt, whether they would hold good for the actual conditions of digestion. Rachford * alone carried out experiments with the ferments of pancreatic juice, but only with those of the rabbit, and not with all of them. We shall, however, see that in the favouring action of bile upon the ferments of pancreatic juice we have discovered one of the main features 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, a constant and decided accentuation of the activity of the enzymes of the latter is produced. The effect is most pronounced on the fat-splitting ferment, the action of which on the average is increased two to threefold, less on the other two, which are only increased about twofold.

These observations have been confirmed and extended by more recent workers. The augmentation of the fat-splitting ferment, which at times may be as great as fourteenfold, is not destroyed by boiling, and therefore is not due to an enzyme. It was long ago attributed by Rachford to the influence of the bile salts, and this has been lately verified by v. Furth and Schütz,† who ascribe it in particular to the salts of cholic acid. The possibility of the result being due to any impurity adhering to the bile salts has been excluded by the observation that the sodium salts of synthetised glycocholic and taurocholic acids possess the same influence (*Magnus*).‡ It would seem that lecithin also promotes the fat-cleavage (*Hewlett*).§ Thus the bile proved itself to be a constant and powerful auxiliary of the pancreatic juice, a fluid in itself already so complex and so important for digestion.

In another way, I am also able to bring forward a striking proof of the close relationship between the bile and the pancreatic juice. I ask you to examine the following curves, in which the hourly rate of secretion of pancreatic juice is compared with the corresponding entry of bile into the intestine, the diet being the same. Their similarity is most striking. Is it not obvious that the two fluids have reciprocal chemical relationships towards each other, and in consequence must act hand-in-hand? Their discharge at one and the same place into the intestines of many animals, or, as is often the case, their admixture beforehand in a common excretory duct, is not without purpose.

But a further important *rôle* in the digestion and absorption of fats is played by the bile. By means of its salts—sodium glycocholate and sodium taurocholate—oleic acid is held in aqueous solution even without undergoing saponification, still more if there be present an amount

* *Journn. of Physiol.*, xii. 72.
† Hofmeister's *Beitr.*, ix. s. 28.
‡ *Ztschr. f. Physiol. Chem.*, xlviii. 376.
§ *Johns Hopkins Hosp. Bull.*, xvi. 20.

of sodium carbonate equivalent to the fatty acid (*Moore and Rockwood*,* *Pflüger*).† Of the ordinary fatty acids contained in food, oleic is the only one directly dissolved to any extent in this way, but its presence enables the others—palmitic and stearic—to be brought likewise into solution Pflüger found in his later experiments that 100 c.c. of ox-bile aided by an equivalent of sodium carbonate, dissolved 15 grms. of mixed oleic and stearic acids, or 19 grms. of mixed oleic and palmitic acids, at body temperature. He suggests that the fatty acids are held in loose

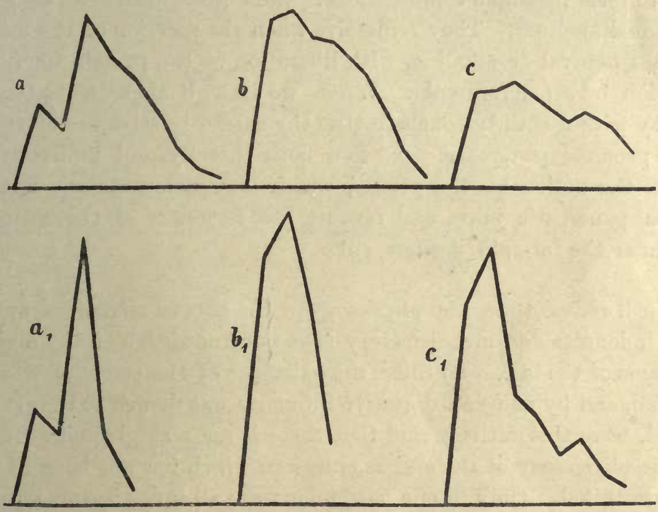


FIG. 24.—Curves representing in each case the hourly rate of pancreatic secretion (upper series) and the entry of bile into the intestine (lower series); *a*, a_1, after the ingestion of milk; *b*, b_1, after flesh, and *c*, c_1, after bread. In comparing the curves, their general form only is to be taken into account. The scale of the ordinates was different in the different cases.

combination with the bile acids, probably with their amino groups—combinations which are dissociated during absorption from the bowel with liberation of the bile acids for further duty. Dissociation is likewise effected by saponification, the soap going into aqueous solution without the assistance of the bile salts. Even free dilution with water is capable of effecting hydrolytic dissociation of the combination between bile acids and fatty acids. By virtue of the foregoing property of the bile, the whole of the fat of the diet may be presented for absorption in simple aqueous solution.

* *Journ. of Physiol.*, xxi. 58.

† *Archiv f. d. ges. Physiol.*, lxxxii. 303; lxxxvi. 41; and lxxxviii. 333.

The experiments dealing with the inhibitory action of bile on pepsin have also been repeated and the effect 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. The mere reduction of acidity, or better, the neutralisation of the chyme, would of itself restrain the action of the pepsin, but the effect of the bile is not limited to this. The salts of taurocholic acid unite with the albumoses and unaltered native proteins to form insoluble combinations. These precipitates can only occur in an acid medium. They redissolve when the reaction of the medium becomes neutral or alkaline, with liberation of the protein for further digestion by other ferments. When we link all these facts together we may with certainty conclude that the chief digestive use of the bile is to promote pancreatic digestion both directly and indirectly. 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.

Until recent times the physiology of the SUCCUS ENTERICUS was still more indefinite and unsatisfactory than our knowledge of the digestive functions of the bile. By some, the existence of the secretion was even doubted, and by many all digestive influence was denied to it. It may, indeed, be authoritatively said that there is not a single point concerning the physiology of the succus entericus which has not been at some time contested. Only in one particular were all investigators agreed—namely, in regard to the very slight, or almost insignificant importance of the digestive action of the fluid. It was considered to have at most a weak solvent effect on starch, and an inverting action on cane sugar. But quite recently it has been the good fortune of our laboratory at one stroke (*experiments of Dr. N. P. Shepovalnikov*), to elevate to a high position the digestive importance of this fluid, long known to physiologists, but for which they had discovered no precise use. This research started with the same question which proved to be so fruitful in the case of the bile. Does the succus entericus also act as an adjuvant to the pancreatic juice? This seemed likely, since close investigation very strikingly showed 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 improbable that the succus entericus would be found to activate one or other of the remaining ferments, in a manner similar to that in which the bile activated the fat-splitting. Our anticipations were fully borne out by facts. The succus entericus undoubtedly possesses to a striking degree the power of augmenting the activity of the pancreatic ferments, and more especially the proteolytic. In the case of the latter, the increase is often astonishing. Any one who has convinced himself of this accentuating influence by experiment will never doubt for a moment that it is the most important function of the succus entericus. In view of the novelty and significance 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 juices. 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 we were dealing in point of fact with a ferment. We had, therefore, discovered a ferment, not for any constituent of the food, but a FERMENT OF FERMENTS. I proposed that it should be given 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 by the secretion of the duodenum and by that of other portions of the small intestine. The proteolytic ferment, on the contrary, is most aided 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 lay open in which we could investigate the subtle problems concerning the adaptation of these combined fluids to the substances submitted for digestion.

With regard to the stimuli which evoke a secretion of succus entericus our observations also go to show (*experiments of Dr. W. Savitsh*) that, with the exception of fresh meat-juice, the introduction of food-stuffs into a Thiry fistula made immediately below the entry of the bile and pancreatic ducts has no effect. If the foods, however, be mixed with pancreatic juice, a flow occurs, and increases up to a certain point, after which it declines. The proportion of ferment in the juice is not affected by the total quantity of fluid secreted. Bile and gastric juice, if similarly introduced, do not increase the secretion.

On the other hand, feeding with cream by passing it into the stomach promotes a flow of succus entericus in a detached loop.

Delezenne and Frouin * likewise observed in a Thiry fistula of the duodenum, a secretion lasting from the third to the seventh hour after a meal, but not if the animal had been fasting. From fistulæ made in

* *C. R. d. l. Soc. d. Biol.*, lvi. 319.

the middle or lower segments of the jejunum, mere traces appeared even after feeding, and none at all from the ileum. These observers also found that a weak solution of hydrochloric acid (0·4 per cent.), if injected into one loop of duodenum, produced a marked flow of succus entericus from another, probably through the agency of a "secretin." Thus an acid extract of duodenal mucous membrane, boiled and neutralised, evoked a secretion when injected into a vein. Soaps, ether, and chloral also exerted a similar effect, greater in all cases during digestion. With regard to these results, it appears not improbable that different segments of the bowel may react differently to the same stimulus.

Mechanical stimulation, for instance the presence of a tube in the fistula, also elicited a secretion, a result which from our previous experience appeared quite exceptional. A review of all the facts, of everything that we had learned in connection with other secretions, taught us to believe in two fundamental features of gland activity, namely, adaptation and response to specific excitation. At first sight these seemed to be absent in connection with the succus entericus, but on closer examination they stood out prominently. Thus, it was found (*experiments of Dr. Savitsh*) 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 discovered in the ferment constituents of the pancreatic juice. If the secretion produced in an isolated loop of intestine under the stimulus of the cannula be studied for several consecutive hours, till at length the juice contains little or no kinase, and if now a few cubic centimetres of pancreatic juice be poured in and left for half an hour, the fluid subsequently secreted will have 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 conclude that in the case of the succus entericus, the secretion of the watery part is as sharply separated from that of the ferment as in other glands. 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 for the purpose of aiding its passage along the intestine. We have already learned of analogous phenomena in the case of the salivary glands. One may also regard the severe diarrhœa which occurs in certain acute forms of enteritis as the result of some powerful stimulus to this water-secreting and cleansing function of the intestinal glands. The flow is excited by the extreme irritation of the mechanical or chemically injurious contents of the bowel.

Additional light is also thrown upon the question of the formation of succus entericus by results obtained from repetition of the well-known experiment of Moreau. It will be remembered that this investigator closed off by ligatures, three adjoining loops of intestine of equal length. The nerves proceeding to the middle loop were divided without injury to its blood-vessels. The whole was replaced in the abdominal cavity, and after some hours it was found that the middle loop was distended with fluid, while the others contained none or mere traces. Similar results have recently been obtained by Wertheimer,* and also by Falloise.† The latter found the fluid to contain enterokinase, maltase, amylase, and sometimes lactase, but in no case either lipase or proteolytic ferment. Further, the fluid contained another ferment, erepsin, to which we shall immediately refer. For these reasons Falloise concludes that it is a true secretion produced by the intestinal glands, and not a mere exudation from the blood-vessels.

The bile and the succus entericus thus play the *rôle* of adjuvants to the pancreatic juice, and the significant fact appears that their assistance is variable, being now greater and now less. What is the meaning of this assistance, and why is it variable? It was long ago observed that pancreatic juice, secreted immediately after the formation of a fistula of the old type, often acts very weakly or not at all on proteids. It was conceived that the operation caused some injury to the gland and brought about an abnormal condition in its secretion. But, as has already been related in the second lecture, Vasiliev and Jablonski likewise saw in our animals, under the influence of certain diets, a very weakly acting juice. It was also remarked in the experiments of Shepovalnikov that the kinase worked all the more energetically the weaker in general was the activity of the pancreatic juice. We 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. Lintvarev, starting from this idea, have fully confirmed our 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.

* *L'Echo Med. du Nord.*, vi. 493. † *Archiv. Inter. d. Physiol.*, i. 261.

As already stated, the later observations of Delezenne and other investigators show that the proteolytic ferment of the pancreatic juice is normally secreted in the inactive form, so that we must now look upon enterokinase as a necessary co-worker of trypsinogen. The question of the nature of enterokinase activity has also been brought under investigation by Bayliss and Starling * who confirm our view that the kinase is a co-ferment and not simply a "complement" to the trypsinogen.

With regard to the significance of this mode of secreting the proteolytic ferment of pancreatic juice, it may be of interest to state that experiments of E. A. Ganicke show that juice, mainly containing *zymogen*, preserves its ferments uninjured even after several hours in the thermostat, while in one activated by succus entericus, or in which *trypsin* already existed, they are very easily destroyed, especially the amylolytic and fat-splitting. 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 protein ferment is made active by the kinase, new conditions arise which protect the fat-splitting and starch ferments, namely, the presence of protein food and of bile. This latter was proved also by the experiments of E. A Ganicke.

It was further shown that the augmenting effect of bile upon the fat-splitting ferment to some extent depends on definite conditions of diet. The relationships of the amylolytic ferment were, however, less obvious in this respect. Additional experiments are, however, desirable, and indeed necessary, to reinvestigate these questions.

The newly discovered kinase, as we have seen, soon displayed its useful *rôle*, 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 asserted by Pachon—has any significance, I am unable to say. The observations of Delezenne† which pointed to the existence of an activating substance in leucocytes, seemed to add interest to them; but they have not been confirmed by other workers, on the contrary they have been disproved by Starling and Bayliss‡ and also by Hekmar.§ These observers have shown that entero-kinase is only produced by intestinal mucous membrane. At all events the importance which is ascribed to the *rôle* of the spleen by Herzen, especially in his later contributions, is without doubt excessive, and does not correspond with the actual facts; for, as has already been shown by Dr. Popelskii, with egg white in tubes, and by myself, with fibrin, the fresh pancreatic juice collected from animals previously

* *Journ. of Physiol.*, xxxii. 129. 1905.

† *C. R. d. l. Soc. d. Biol.*, liv. p. 283; also *Compt. Rend.*, cxxxv. 328.

‡ *Journ. of Physiol.*, xxx. 61. § *Archiv. f. Physiol.*, 1904, 343.

deprived of their spleens (dogs and cats) contains large quantities of proteolytic ferment. 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 15 centimetres high and 1·5 centimetres in diameter. Moreover re-investigations of the question by Frouin* and also by Prym† have failed to show that excision of the spleen influences the activity of the pancreas in any way.

Naturally these new results concerning the interaction of the digestives juices have compelled us to repeat all our earlier experiments upon the quantitative production of the pancreatic ferments under different conditions.

But still another *rôle* in the digestion of proteins has been discovered for the succus entericus. It had long been known that peptones and albumoses disappeared from an intestinal loop, but could not be detected, as such, in the portal blood. It was believed, as you know, that these substances were reconverted into native proteins and added to those of the blood. Cohnheim,‡ however, showed that contact with the intestinal mucous membrane or mixture with extracts of it, caused a disappearance of albumoses and peptones, not by re-formation into albumen or globulin, but by further cleavage into crystalline, biuret-free bodies. Amongst the latter were found leucin, tyrosin, lysin, histidin, arginin, and ammonia salts. The cleavage was found to be produced by a ferment, to which the name *Erepsin* ('Ερειπω, *I break down*) has been given. It was uncertain from Cohnheim's results whether erepsin acted as an intracellular ferment or was secreted into the intestine. Salaskin § and others have, however, obtained similar results with pure succus entericus, and erepsin must therefore be reckoned amongst the ferments of this juice. These observations have also been extended to human succus entericus by Hamburger and Heckma.|| Erepsin is unable to act on primary albumoses or on native proteins with the exception of casein, which latter is feebly digested.

The ferment acts best in an alkaline medium, the optimum degree of alkalinity being somewhat less than that for trypsin. Peptones in Kuhne's sense are rapidly broken down, but albumoses require weeks to destroy the biuret reaction. Acting on the products of gastric digestion of proteins as they leave the stomach, erepsin produces the same derivatives as trypsin. The degree of cleavage effected in the bodies which the ferment is capable of attacking is comparable to that of

* *C. R. d. l. Soc. d. Biol.*, liv. 418 and 798.

† Pfluger's *Archiv.*, civ. 433.

‡ *Zeitsch. f. physiol. Chemie*, xxxiii. 451.

§ *Ibid.*, xxxv. 419.

|| *Jnl. de Physiol. et Path. Gén.*, iv. 805.

boiling mineral acids. Cohnheim* found that after successive digestion of syntonin with pepsin-hydrochloric acid and erepsin, the amount of nitrogenous products precipitable by phosphotungstic acid was almost the same as in the acid cleavage. Kossel and Dakin† also obtained fully as much arginin from the erepsin digestion of clupein as from boiling it with acids.

Arginase, a ferment first discovered in liver extracts by Kossel and Dakin,‡ has also been found in the intestinal wall. It has the property of cleaving arginin into urea and ornithin. Whether the ferment occurs in the lumen of the intestine or not, remains undecided. Kutscher and Seeman § found a very small proportion of arginin amongst the cleavage products occurring in the intestinal contents, a fact which the presence of arginase would readily explain.

It is also remarkable that portal blood, returning from the intestines, is particularly rich in ammonia-compounds. This ammonia must arise by the deamidation of amino-compounds, whether in the lumen of the bowel or in its mucous membrane, has not been ascertained.

Of enzymes capable of acting on other food-stuffs, Boldirev || has discovered the presence of *lipase* in the natural succus entericus periodically secreted in fasting animals. All local excitation of the mucous membrane must be avoided, otherwise a large quantity of fluid, not true succus entericus, is secreted. The natural juice is capable of cleaving monobutyrin in one per cent. aqueous solution; also emulsified fat, such as that of milk. The effect is due to an enzyme, but the enzyme is not aided by the presence of bile. That the cleavage is not due to traces of pancreatic lipase is shown by its occurrence in the intestinal fistulæ of animals deprived of the pancreas. Its presence here also explains the absorption of the fat of milk to the extent of 50 per cent. after removal of the pancreas.

Numerous carbohydrate ferments, in particular those which reduce the double sugars to mono-saccharides are present in the bowel. The first of these is *Invertin* (Invertase or Sucrase) which splits cane sugar into dextrose and lævulose. The intestine is the only organ of the body in which this ferment is produced. Much more of it is found in extracts of the mucous membrane than in the intestinal secretion. Apparently the cleavage occurs chiefly in the act of absorption. The second is *Maltase* which cleaves maltose into two molecules of dextrose. It appears also to effect a similar cleavage of iso-maltose. Both Maltase and Invertin are more abundantly present in the upper than the lower part of the small intestine. A third enzyme of the same class is

* *Zeitsch. f. physiol. Chemie*, xxxv. 136. † *Ibid.*, xli. 321.

‡ *Loc. cit.* § *Zeitsch. f. physiol. Chemie*, xxiv. 528.

|| *Inaug. Dissert.*, St. Petersb. 1903; also *Zentralbl. f. Physiol.* xviii. 460.

Lactase, which splits milk sugar into dextrose and galactose. It is always present in the young of mammalian animals, not in those of other species. It is also re-formed in adult mammals, if milk sugar be given with the food. Lactase only occurs to any extent in the jejunum and not at all in the ileum.

It is worthy of remark that the foregoing ferments do not act directly on the starch molecule, but supplement, as in the case of maltase, the work of other primary digestive enzymes which have this power. The same remark applies to the specific proteolytic enzymes of succus entericus. A small amount of ptyalin, however, seems to be present both in intestinal juice and in extracts of the mucous membrane. The juice secreted by Brunner's glands unquestionably contains a diastatic enzyme.

Thus the chemical agencies of intestinal digestion are linked together so that the individual members relieve and mutually assist 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 found easy of application and lead to fruitful results. It is only when we are able to bring into view a complete train of normal occurrences in any one portion of the organism, that we can at once distinguish the accidental from the essential, the artifical from the natural, discover new facts, and detect bygone errors. Constantly to remember that all parts of the organism work together, sheds a flood of light on any special field under review.

LECTURE X.

[ADDED BY THE TRANSLATOR.]

THE PASSAGE OF FOOD THROUGH THE ALIMENTARY CANAL.

DEGLUTITION: MOVEMENTS OF THE STOMACH.

Our knowledge of the motor functions of the alimentary canal till recently was very incomplete—The regulatory mechanism of the pylorus recognised independently by Hirsch and by v. Mering—The act of deglutition—The discharge of the reflex—The passage of food through the pharynx—The function of the epiglottis—The descent through the œsophagus — The auscultation of swallowing — The normal human stomach—The entry of food—The movements of the cardiac portion—The work of the pyloric part—The passage of food through the pylorus —The pyloric reflex—The stimuli to which the sphincter of the pylorus responds—Periodic movements of the stomach in fasting.

In the course of 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.

It became necessary, in order to fully understand the variations in the curves of secretion of the digestive juices, to know where, in what amount, and in what condition, the food occurs at any given moment. But how incomplete has been our knowledge of the motor functions of the digestive canal, and yet 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! Yet this great mass of work could not in the smallest degree satisfy our requirements. It offered to us for analysis a long series of facts without rational connection. As to why one kind of food is held back while another is moved forwards, or why one is propelled quickly and another slowly, there was no reply; and yet the complex food mixture is somehow sorted out 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 requisite 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 elementary conditions is this selective transmission of the food effected, with the purposiveness of a delicate and conscious mechanism?

The steps of the actual progress, and the mechanism of the movements, have been till recently as little brought under investigation as the stages of the secretory work of the digestive apparatus. The credit of having begun this investigation belongs to two German workers (*Hirsch* and *v. Mering*), who independently 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 discharge of food from the stomach is temporarily restrained by a reflex from the duodenum, whereby the pylorus is closed each time after a portion of the stomach contents has passed into the intestine. Our investigations have started from the same point, namely, the pyloric reflex, and to a certain extent have followed similar lines, but before referring to them, a short account of the essential features of the act of swallowing and of the motor functions of the stomach may be given.

In the Act of Deglutition, food, previously brought into a suitable condition in the mouth, is propelled through the pharynx and œsophagus by means of a complicated reflex, which requires for its normal discharge the fulfilment of certain conditions.

The act consists of two phases differing widely in character: the first a rapid projection of food through the pharynx, the second a slower progress through the œsophageal tube.

By a study of its mechanism (*Wassilieff*,* *Kahn* †) it has been shown that in all animals there are certain regions of the bucco-pharyngeal mucous membrane from which the reflex is readily discharged by mechanical contact. One particularly sensitive area always lies in the normal path of the bolus from the mouth to the pharynx.

In the rabbit this chief area is on the fore part of the soft palate, and is innervated by the second division of the fifth cranial nerve. In dogs and cats the chief area is on the dorsal wall of the pharynx at the level of the fauces, the afferent nerve being the glossopharyngeal. In monkeys the most sensitive region is at the side of the fauces before and behind the tonsils, its nerve being furnished by the fifth cranial. Experiments on the rabbit have shown that if local anæsthesia of this area be induced by the application of cocain or chloral hydrate solution, the act of swallowing is rendered impossible for the time being (*Wassilieff*).

* *Zeitsch. f. Biol.*, xxiv. (1888).

† *Archiv. f. Physiol.*, 1903, suppl. vol. p. 386.

Other less sensitive or subsidiary areas, from which the reflex is, as a rule, less readily discharged, also exist, and serve for the dislodgment of secretions or of food particles deviated from the normal path. In the rabbit they are situated as follows: (*a*) on the dorso-lateral wall of the pharynx above the level of the velum palati (glossoph. nerve); (*b*) on the whole dorsal surface of the epiglottis (superior laryngeal nerve); (*c*) on the mucous membrane of the lower part of the pharynx and adjoining part of the œsophagus (sup. and inf. laryngeal nerves).

In the cat and dog the secondary areas occur on (*a*) the dorsal surface of the velum palati and neighbouring parts of the pharyngeal mucous membrane (second division of the fifth cranial nerve); (*b*) on the dorsal surface and base of the epiglottis (sup. laryngeal); (*c*) at the entry of the larynx and lower part of the pharynx (sup. and inf. laryngeal nerves).

In monkeys the corresponding areas are situated at (*a*) the entry of the larynx; (*b*) the dorsal surface and base of the epiglottis; (*c*) the posterior wall of the pharynx.

In considering the physiology of swallowing, it is to be remembered that the pharynx serves for the most part as an air inlet. Its communications with the nasal passages and trachea are then open, those with the mouth and the œsophagus are closed, the former by the contact of the soft palate with the dorsum of the tongue, the latter by the apposition of the cricord cartilage with the back wall of the pharynx.

During deglutition the respiratory function of the pharynx is temporarily interrupted, its communications with the nose and the trachea are closed, those with the mouth and the œsophagus are opened. These changes in the disposition of the tube are essential to the main reflex of swallowing, and upon their timely performance depends the safe passage of the food through the pharynx.

The closure of the nasopharyngeal orifice is effected by the elevation of the soft palate aided by the advancement of the posterior wall of the pharynx and the approximation of the palato-pharyngeal folds, these latter embracing the uvula between them. The muscles concerned in the movements are the levator palati, the superior constrictor, and palato-pharyngeal.

The closure of the larynx is provided for in three ways. The arytenoid cartilages with the true vocal cords approximate to meet each other in the middle line, while the former bend forwards to touch the epiglottis. The false vocal cords likewise approach each other and come into contact, descending at the same time so as to lie upon the true cords. In addition the whole larynx is drawn upwards and forwards beneath the tongue. The epiglottis is thereby depressed, the cushion at its lower part tightly fitting into the vestibule of the larynx.

The pharynx is brought into communication with the mouth by the same movement which closes the naso-pharynx.

The opening of the œsophagus to receive the bolus is determined by the upward and forward movement of the larynx. That this aperture is normally closed is shown in frozen sections, and is also supported by a very general experience, namely, that in passing an œsophageal tube, a difficulty is here met, which is readily overcome by directing the subject to swallow.

It has been customary since the time of Magendie to describe the act of swallowing as consisting of three stages. During the first, the bolus is said to be formed by the tongue and rolled back to the entry of the fauces; during the second it is rapidly shot past the entry of the larynx; during the third it is slowly carried down the œsophagus.

Strictly speaking the act begins with the discharge of the reflex produced by contact of the bolus with the sensitive mucous membrane near the entry to the pharynx. The forming of the bolus and bringing it into position at the root of the tongue are only necessary to the act of swallowing in the same way that bringing food to the mouth is necessary to the act of chewing. It would seem, therefore, more rational to divide the reflex into two phases, the first consisting, as already stated, of the rapid passage of the bolus through the pharynx, with the requisite preparations, the second of its descent through the œsophagus.

The muscular force by which the *first stage* is started and food projected through the pharynx is said by Ludwig, Kronecker, and others to be chiefly contributed by the mylohyoid and hyoglossus muscles. That these muscles contract at the beginning of swallowing is unquestionable, and division of the nerves supplying the mylohyoids has been shown to render the act difficult for several days. Afterwards the animals (dogs) learned to raise and throw forward their heads so as to get the food back to the fauces, and thus start the deglutition reflex (*Kronecker* and *Meltzer* *).

One result, at all events, of contraction of the mylohyoids is to raise, draw forward and fix the hyoid bone and with it the whole larynx, thus providing for the opening of the œsophagus to receive the food. Previous to this the bolus has been formed and rolled back to the fauces, when no doubt the contraction of the mylohyoids aids in giving it a thrust onwards, but whether they effect more than this may be doubted. Wassilieff † found that the act of swallowing could take place without the aid of the mylohyoids. Moreover other forces are unquestionably concerned. One of these is a rapid jerk imparted by a revolving movement of the root of the tongue, executed with great speed

* *Archiv. f. Physiol.*, 1883, suppl. vol. p. 328.

† Wassilieff, *loc. cit.*

round the arc of a circle which has for its centre the hyoid bone. In addition, the superior constrictor muscles at the back of the pharynx, the palato-pharyngei at the sides, and the tensor palati above, all contribute by a combined movement to bring pressure on the bolus from every side, and thus aid the propelling force of the tongue.

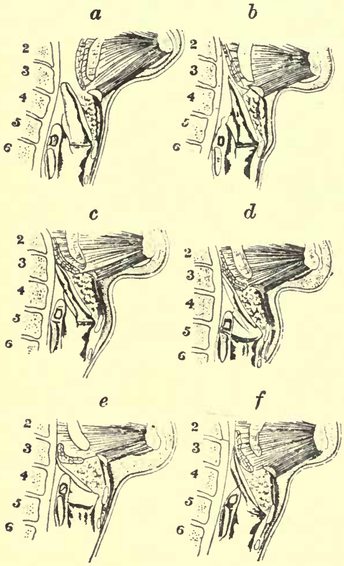


FIG. 25.—Position of epiglottis and root of tongue at different stages of swallowing (*Eykmann*).

The distance to which the bolus is carried by the initial thrust varies with its consistence. According to Kronecker and Meltzer a liquid bolus is forthwith shot down to the lower end of the œsophagus. Neither Schreiber * nor Cannon and Moser † were able to confirm this view. The latter investigators believe that liquids are projected well into the thoracic œsophagus, but not to its lower end, while solids and semi-solids reach no further than the cervical œsophagus.

The function of the epiglottis in deglutition has been the subject of much discussion. Magendie, Longet, Schiff and others, have shown that after its complete removal, swallowing can be accomplished without difficulty and without the entry of substances into the larynx. On the other hand, it has been conclusively proved by Czermak, Arloing, Passavant, Anderson Stuart, Rethi ‡ and others, that the basal or laryngeal part of the cartilage is pressed tightly into the orifice of the larynx, in the way described. The tip or pharyngeal part of the epiglottis projects beyond the glottis and takes no part in its closure, but recent investigation shows that it is not without use in swallowing. At the beginning of deglutition the root of the tongue is applied to the anterior face of the epiglottis, the pouch between the two being obliterated. It is held by some investigators (*Stuart* and *McCormick* §), that in this position, the bolus glides over the concave posterior face of this part of the epiglottis without the cartilage itself descending.

Others, including Kanthack and Anderson, have convinced them-

* *Archiv. f. Exp. Pathol. u. Pharmakol.*, xlvi. 414 (1901).

† *American Jnl. of Physiol.* i. p. 435.

‡ *Résumé* of literature given in article by P. H. Eykmann, Pflüger's *Archiv.*, xcix.

§ *Jnl. of Anat. and Physiol.*, 1892.

selves (the latter by passing a finger into the throat) that the cartilage moves backwards and downwards at this stage. This has also been indubitably shown by Rethi,* who dotted the margins of the epiglottis with points of Indian ink, and after swallowing found dark streaks on the back wall of the pharynx produced by the sweep down-

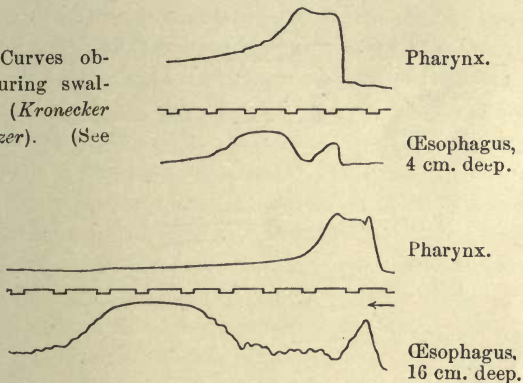


FIG. 26.—Curves obtained during swallowing (*Kronecker* and *Meltzer*). (See p. 174.)

wards of the tip of the cartilage. The same observer saw in addition, that the sides of the epiglottis were embraced by the lateral walls of the pharynx at this stage. Lastly Eykmann,† by means of X-rays, has been able to photograph the movements in the early stages of swallowing, and has shown that the tip of the epiglottis sweeps backwards and downwards in the immediate wake of the bolus, touching the posterior wall of the pharynx as it descends (see Fig. 25).

Reference has been made to the arrest of breathing which takes place during the act of swallowing. It is a reflex, accomplished chiefly through the glossopharyngeal nerve. Marckwald ‡ showed that if this nerve be cut and its central end stimulated, an immediate and absolute arrest of respiration occurs. The mode of inhibition is remarkable inasmuch as the muscles of respiration are stopped in whatever condition the efferent impulse finds them, whether it be one of inspiration, or one of expiration, or midway between the two acts; that is to say, there is no refractory phase. The arrest lasts for five or six seconds, sufficiently long for at least one complete act of deglutition, after which respiration begins again, notwithstanding a continuation of the stimulus. Similar excitation of the superior and inferior laryngeal nerves also brings about cessation of respiration, though with less certainty.

The *second stage* of the swallowing reflex begins with the entry of food into the œsophagus. For this to take place, the opening of the

* *Sitzungsb. d. K. Akad. d. Wissensch. in Wien*, 1891.

† Pflüger's *Archiv.*, Bd. xcix. p. 513 ‡ *Zeitsch. f. Biologie*, 1889.

upper end of the tube by the forward movement of the cricoid cartilage is essential. If the movement be prevented by holding the larynx between the fingers, swallowing cannot occur. The importance of this movement of the larynx was known to Haller and the earlier writers, but its effect in opening the œsophagus was first experimentally proved

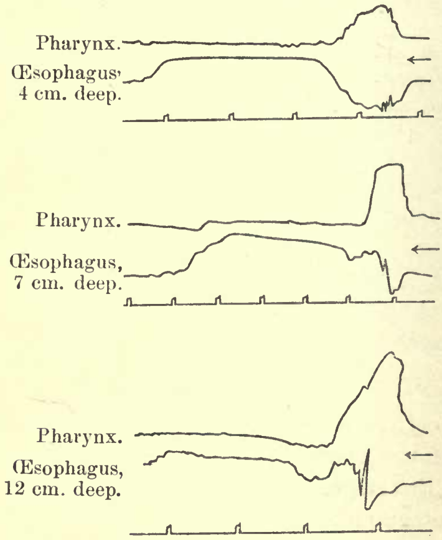


FIG. 27.—Curves obtained during swallowing (*Schreiber*). (See p. 175.)

by Schiff. Schreiber, Eykmann and others have recently called attention to it. Simultaneously with the mechanical opening of the orifice of the œsophagus, there is also a relaxation of its muscular walls, no doubt in conformity with the general law of peristaltic movement to be mentioned later, namely, " contraction behind, relaxation in front," of a particular stimulus applied to the mucous membrane of the tube.

This relaxation would explain the so-called "negative injection mark" mentioned by Kronecker and Meltzer and seen in the tracings given above of Schreiber (Fig. 27).

The investigations of these observers were carried out by means of small india-rubber bags tied to the ends of two hollow metal sounds, one of which was introduced into the œsophagus, the other into the pharynx. The balloons were gently inflated and the upper ends of the tubes connected to recording tambours. A mouthful of water was then swallowed, when records such as are shown in Figs. 26 and 27 were obtained. In each tracing the upper curve is from the pharynx, and the elevation shown upon it is due to the pressure of the bolus. Of the two waves seen on the lower curve, the first was attributed by Kronecker and Meltzer to the effect of the bolus in shooting past the balloon in the œsophagus, the second to a wave of peristalsis following later, which served to sweep the passage free of retained particles and press food into the stomach when it reached the lower end of the tube.

Schreiber, however, who employed similar methods, doubts whether the first elevation or "injection mark" on the œsophageal curve can be due to the pressure of the bolus on the ground that it may be absent from the normal and is sometimes present in the so-called "empty" swallowing. Moreover, the injection mark usually shows a negative phase. Kronecker and Meltzer observed this only at the top of the œsophagus, and none of their published tracings show it. Schreiber found it well marked at 7 cm. down the tube and relatively well marked (Fig. 27) as low as 14 cm.

The negative injection mark is followed at once by a positive wave, the curve returning to the base line and then passing into an elevation. This occurs before the bolus has reached the œsophageal bag, and would be accounted for, by an increase of pressure produced by the descending bolus and transmitted in advance through the lax œsophagus.

The forces concerned in the above passage of foods through the œsophagus are two, namely the initial thrust imparted by the contraction of the muscles of the tongue, fauces, and upper pharynx, and secondly, the wave of peristaltic contraction which starts in the lower constrictors of the pharynx and travels down the œsophagus to the cardia. The extent to which these two forces come into play varies with the animal and with the consistence of the bolus.

Liquids, in most animals, are shot by the first impulse a considerable way down into the œsophagus, usually to the level of the heart. From thence the descent through the lower segment of the tube is relatively slow and accomplished by peristaltic action. This holds good for the cat, dog, horse and man. Solids and semi-solids are projected by the first impulse no further than the top of the œsophagus, the remainder of the descent being due to peristaltic contraction. The rate of passage is greater, however, in the cervical and upper thoracic regions than in the lower part. Thus in the cat a bolus reaches the level of the heart, that is more than two-thirds of the whole way, in 4–4½ seconds, while for the remaining portion, 6–7 seconds are required. Liquids reach the level of the heart in 1½–2 seconds, after which the descent is very slow, the total time varying from 9–12 seconds.

Cannon and Moser,* to whom we are indebted for these latter observations, studied the passage of foods through the œsophagus by means of Röntgen rays, bismuth subnitrate being added to render the substances opaque. For liquids, either milk or water mixed with the bismuth, for solids, small pieces of meat dipped in the powder, or a gelatine capsule

* *Loc. cit.*

filled with it, and for semi-solids a thin paste of bread and milk were used.

Kronecker and Meltzer had previously concluded from their observations that liquids are propelled the whole way down the œsophagus by the initial impulse, reaching the cardia in less than one-tenth of a second. They supposed the wave of peristaltic contraction to be a reserve force following after the bolus to ensure the clearing of the passage of residues adhering to its walls. Schreiber, who used a similar method, found the time to be much longer than Kronecker supposed, namely 6·8 to 7·4 seconds, of which 0·6 to 1 second was taken up by the passage through the pharynx, the remainder through the œsophagus. These observations harmonise with those of Cannon and Moser.

When food reaches the lower end of the œsophagus it does not always pass at once into the stomach. On the contrary, it is sometimes retained for a considerable time before entering, one minute or more in the cat (*Cannon* and *Moser*). Then the cardia opens to allow it to pass through. Immediately above the diaphragm there is a dilatation of the œsophagus—the phrenic ampulla—where such foods lodge. With frequent small acts of swallowing the cardia may only open to every third or fourth peristaltic wave. Meltzer's later observations with the aid of a speculum introduced into the stomach of a dog show that in this animal fluids do not trickle through but enter periodically with the arrival of a peristaltic wave.

More recent observations have been carried out by Hertz and Morton * with the aid of Röntgen rays on fourteen healthy young men. For liquids, milk was used to which carbonate of bismuth in the proportion of 2 oz. to half a pint, was added ; for solids bread baked of flour mixed with the same salt. In the upright position liquids were seen to pass rapidly through the pharynx and upper œsophagus, an ordinary mouthful forming a bolus about 2 inches in length. The progress was arrested above the cardia, where the bolus, presenting a horizontal upper surface and tapering lower end (see Fig. 28), was seen to gradually enter the stomach. The average time required till it completely disappeared from the œsophagus was $5\frac{3}{5}$ seconds, with variations ranging from $4\frac{3}{5}$ to $8\frac{3}{5}$ seconds. Half of the whole time was occupied in the descent, half in the passage through the cardia. The total time varied as much as 3 seconds in the same subject.

In the lying position swallowing was less rapid and the delay at the cardia longer. In the completely inverted position with the head down the rate of ascent through the œsophagus was only one-third that of the ordinary.

* *British Med. Journal*, 1908, vol. i. p. 130 ; also *Guy's Hosp. Reports*, lxi. p. 389 (1907).

Solids such as the bismuth bread, when fully chewed and swallowed in the ordinary way, behave as liquids, but with a slightly increased tendency to adhere to the walls of the gullet. Dry solids, such as *cachets* filled with bismuth carbonate, moved along very slowly, in some cases taking as long as 15 minutes to make the descent. If taken at intervals of 1 minute several could be seen in the œsophagus at the same time.

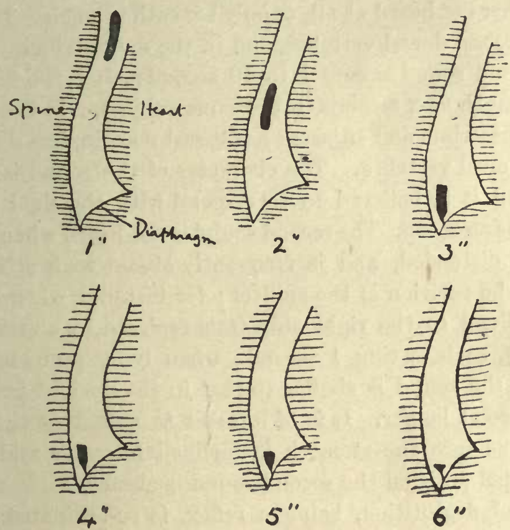


FIG. 28.—Diagram of the passage through the œsophagus of a bolus of milk mixed with carbonate of bismuth as seen by X-ray examination (Hertz). The time after swallowing is indicated in seconds beneath each figure.

The act of swallowing has also been investigated by auscultation. C. W. Hamburger (1868) * seems to have been the first who used this method; then followed Zenker (1869),† and Kronecker with Meltzer ‡ (1883). The last-named observers described two sounds heard at the side of the vertebral column on a level with the eighth dorsal vertebra. One occurred immediately after the act of swallowing, the other 6 seconds later. The first sound was taken by them to indicate the arrival of the bolus at the lower end of the œsophagus, the second its entry into the stomach under the influence of the wave of œsophageal peristalsis. According to these authors, the results harmonised with those obtained by means of the balloon method.

Hertz § has re-investigated the sounds of swallowing in four healthy

* *Med. Jahrb.*, xv. (1868).

† *Berl. Klin. Woch.*, 1884. (This and the foregoing reference are quoted from Kronecker's article on "Deglutition" in Richet's *Dictionnaire de Physiologie.*)

‡ *Loc. cit.* § *Loc. cit.*

young men. Two are audible, the first a short sharp sound, heard best beneath the chin, and also, though less distinctly, over the front of the neck and cervical spinal column. It is simultaneous with the contraction of the mylohyoids, and is believed to be caused by the impact of the bolus against the posterior wall of the pharynx. The sound is fainter with a small bolus, and in empty swallowing or in swallowing solids, is either not heard at all, or only beneath the chin. It is inaudible below the second dorsal vertebra, and in the epigastrium.

The second sound occurs 4 to 10 seconds after the first, the time varying as much as 2 seconds in the same subject. It is heard loudest over the epigastrium and adjacent left costal margin, less distinctly over the tenth dorsal vertebra. The character of the sound is described as trickling, and it is believed to correspond with the final entry of the bolus into the stomach. The second sound is not heard when the stomach is empty or distended, and is frequently absent with solids. It also varies with the position of the subject; for instance, when lying on the back or inclined to the right side it is replaced by a series of squirts (two to five), each lasting 1 second; when lying prone or inclined to the left side the sound is similar to that in the upright posture, but is delayed 1 second longer. It is of interest to note that the opening of the œsophagus into the stomach is inclined forwards and to the left. In the inverted position the second sound is absent.

The act of deglutition, being a reflex, is co-ordinated by a nerve centre. This has been shown to be situated in the medulla, close to the respiratory centre but distinct from it, since the one can be destroyed without abolishing the activity of the other.

The afferent channels through which the reflex can be discharged are numerous. The chief of these have been already indicated when speaking of the areas of mucous membrane from which it is normally evoked. The efferent nerves to the pharynx and œsophagus, according to recent investigations (*Kahn*) are all derived directly or indirectly from the vagus. This at least holds good in the cat the dog and the monkey. It is also supported by clinical observations in cases of localised paralysis in the human subject. The muscles of the tongue concerned in deglutition are supplied by the hypoglossal nerve, the mylohyoids by the third division of the fifth.

As is well known, a complete act of swallowing can be elicited very readily by proximal stimulation of the superior laryngeal nerve. In the peristalsis which follows, the mode of propagation of the wave along the œsophagus is different from that in the intestine. In the one case the impulse traverses nervous channels, in the other it is transmitted by muscular continuity. Thus Mosso found that if the œsophagus be divided into two or more parts by transection, or if a segment be cut out, leaving the nervous connections undamaged, a wave of peristalsis will pass from the upper to the lower segments. Wild had previously arrived at a different conclusion from finding that peristalsis was arrested by a ligature placed round the tube.

Meltzer,* however, finds that the degree of narcosis affects the results and that there are two forms of œsophageal peristalsis. One of these (primary) corresponds to that just described in being very sensitive to anæsthetics, but differs in requiring complete integrity of the tube. The other (secondary) consists of a sequence of single reflexes started from point to point by distension of the œsophagus and propagated through the nervous channels. The secondary reflex is more resistant to narcosis, but is destroyed by section of the nerves on one side, whereas the primary is not. Kahn finds that a wave started by introducing a bolus into the œsophagus traverses the tube in 6–7 seconds.

To these two forms of contraction Cannon adds a third, propagated through the smooth muscle and independent of the integrity of the vagus nerves.

The lower segment of the œsophagus in higher animals differs in many respects both structurally and functionally from other parts of the tube. In no way is this more evident than in its nerve-supply. Auerbach's plexus is found between its muscular layers and it is under autonomic nervous control. Division of the vagi in dogs causes paralysis and relaxation of the upper segments, but the lower end passes into a state of spasmodic contraction which lasts for several days, after which tone returns to a more or less normal condition and swallowing is again possible. In frogs after section of the vagi the whole œsophagus becomes tonically contracted (*Goltz*).†

We have now to consider THE MOVEMENTS OF THE STOMACH. In the previous lectures we have had occasion to examine the accuracy and delicacy with which the stomach discharges its first duty towards the food received into it. This duty consists in dissolving and preparing the material for a further and more complete digestion by agencies which are to act upon it lower down in the alimentary canal. To this end the dissolved food has to be passed onward from the stomach in appropriate quantities, at suitable times, and in favourable conditions.

A second duty, no less important than the first, is thus required of the stomach, namely, that of propelling and regulating the transmission of its contents into the intestine. To fully appreciate this second duty in its relation to the first, some reference must be made to the anatomy of the organ.

The stomach, as a whole, is a horn-shaped sac, consisting of two chief

* *Zentralbl. f. Physiol.*, xix. 993.

† *Archiv. f. d. gesammte Physiol.*, vi. 616 (1872).

divisions which differ widely in structure and function. They are named the upper, chief, or cardiac part, into which the œsophagus opens, and the lower, smaller, or pyloric part, from which the duodenum leads off.

The cardiac portion, or chief stomach, is nearly cylindrical, and lies to the left of the vertebral column, with its axis descending almost vertically from the entry of the œsophagus. The greater curvature forms its left border, the lesser curvature its mesial or right border.

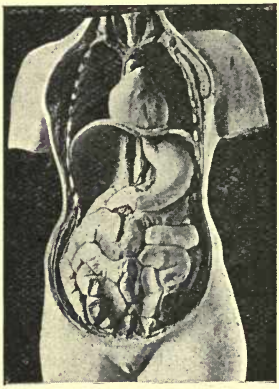


FIG. 29.—Normal position of stomach and small intestines, hardened *in situ* (*His*).

The lower end of the œsophagus, after passing through the diaphragm, takes a bend towards the left, before opening into the stomach. Its orifice—the cardia—is sometimes irregularly roundish, sometimes slit-like, and is directed towards the left. In consequence, food on entering it, is guided towards the great curvature, along which it passes towards the pylorus. This fact was first observed by Dr. Beaumont in the case of Alexis St. Martin.

The lesser curvature continues, in its upper part, the direction of the right wall of the œsophagus, being normally somewhat inclined to the left side. It is therefore the part first touched by an instrument when passed into the stomach. The rounded upper end of the chief stomach, situated to the left of the cardia, is known as the fundus. It extends upwards and backwards to occupy the dome of the diaphragm, and usually contains gas. Between the fundus and œsophagus there is a depression or cleft, more marked in the distended condition, to which the name *incisura cardiaca* is given. The remainder of the cardiac portion is known as the body.

The pyloric part of the stomach usually lies in front of the vertebral column, its axis taking a sharp bend to form almost a right angle with that of the cardiac portion. The boundary between the cardiac and pyloric portions is marked, on the lesser curvature by a sulcus, the *incisura angularis ;* on the greater curvature, by a prominence or elbow, where the change in the direction of the axis occurs. Not infrequently a groove or depression is seen which extends from the *incisura angularis* towards the greater curvature marking the division between the two parts on the anterior and posterior walls. It is said that the circular layer of muscle fibres is thickened along this line, constituting what has been called by older writers the *transverse band*, and by some modern writers *the sphincter of the pyloric antrum.*

The pyloric part gradually narrows towards its junction with the duodenum, but not uniformly. Its cavity shows dilatations separated by shallow constrictions. One of these is situated on the greater curvature, at the bend between the cardiac and pyloric portions. It is named the *pyloric antrum* (*Willis*) or *pyloric vestibule*. The

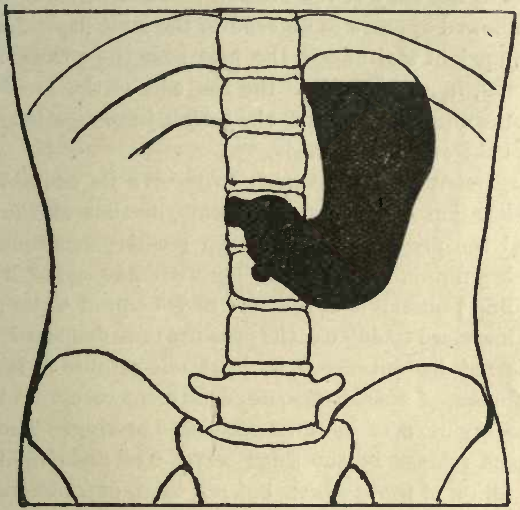


FIG. 30.—Shadow of the normal stomach (after Rieder). The black crescent at the lower margin of the pyloric part indicates the level of the umbilicus.

remaining narrower and more tubular portion is named the *pyloric canal.* It extends backwards and slightly upwards from the pyloric antrum to the duodenum, the first part of which takes the same direction.

The food reaching the lower end of the gullet is driven through the cardia under a certain degree of pressure by the œsophageal peristaltic waves. It is then guided to the left, and descends along the greater curvature of the stomach. The food subsequently swallowed lies, at all events in some animals, within this, forming layer after layer concentric to the first (*Grützner*),* the size of the cavity adapting itself to the quantity of its contents. A stratification is thus produced, which remains throughout the greater part of digestion, the mass being acted upon by the gastric juice from the periphery inwards. In consequence, the interior remains long unacidified, and here salivary digestion may continue for fully two hours (*Cannon*). A difference of opinion exists in regard to the mode of stratification. Grützner, from observations on rats fed with foods differently coloured, holds the view above expressed.

* *Archiv. f. d. gesammte Physiol.*, cvi. p. 463.

Ellenberger and his pupils,* whose first observations date from an earlier period, have shown that the later portions of a meal are spread out in layers over or above the part first swallowed. Probably the mode of layering is not the same in all animals, and in many there is a mechanism by which liquids are allowed to reach the pyloric vestibule without being delayed in the body of the stomach. In the human stomach the food first swallowed appears to descend to the most dependent position, which in the upright attitude is the part near the pyloric region. It may be accepted, in any case, that the contents of the greater stomach remain for hours unmixed, and that the gastric juice digests and dissolves the mass from the exterior inwards.

The enlargement of the stomach to receive its contents is accomplished by relaxation of its muscular coats, so that at the end of an ordinary meal the pressure within is no greater, sometimes even less, than at the beginning. Thus in a dog with 240 c.c. of liquid in its stomach, Kelling † observed a pressure of 7·6 cm. of water; when the quantity was increased to 460 c.c. the pressure recorded was 7·0 cm. The adjustment is not instantaneous, at least one minute is required, and under the influence of anæsthetics, no adjustment occurs, so that in this condition the organ may be distended to bursting. The surviving excised stomach relaxes in the same way. The abdominal walls also relax during filling of the stomach, but not to an extra-visceral increase of pressure in the peritoneal cavity.

The cardiac orifice, as a rule, opens to each ordinary act of swallowing, but if a series of acts be made in rapid succession it appears to remain open for some considerable time. On the other hand, when the acts of deglutition are weak or small, it only opens to every third or fourth, as already stated.

There can be no doubt that the opening is due to a reflex, but the mechanism is not fully understood; nor does a muscular sphincter in the ordinary sense seem to exist. The reflex, however, responds to stimuli both from the œsophagus and from the stomach. Thus the cardia opens easily to gentle mechanical stimulation of the mucous membrane of the œsophagus, also to fluids of neutral or alkaline reaction at a temperature in or about that of the body. On the other hand, it closes against strong or rough contact and offers considerable resistance to carbonated and cold water. For example, water at body temperature enters at a pressure of 2 to 7 cm. of water column, whereas cold water requires a pressure of 16 to 18 cm. and carbonated waters 20 to 40 cm. Very strong resistance is offered to corrosive or irritant liquids; hence in accidental swallowing, one of the sites of greatest damage is at the lower end of the œsophagus, immediately above the cardia.

* *Archiv. f. Physiol.*, 1889, p. 137, and 1891, p. 212; also Scheunert, *Archiv. f. d. gesammte Physiol.*, cxiv. p. 93.

† *Zeitsch. f. Biol.*, xliv. 160 (1903).

From the lower side, the cardia opens to increase of pressure within the stomach. Thus if fluid be poured into the stomach of a dog by means of a tube inserted directly through its walls, an escape takes place at the cardia each time when the pressure reaches 25 cm. of water. Since this does not occur if the animal be narcotised, the effect is not due to mechanical pressure alone; on the contrary, an active opening of the cardia occurs to permit the escape. The cardia also actively opens in vomiting even before the abdominal muscles contract to put pressure on the stomach contents. Further, it has been observed by Cannon * in the cat, particularly when the stomach is well filled, that a periodic escape and return of contents to and from the œsophagus occurs. This does not happen if the fluid passing into the stomach is acidified or becomes acid from secretion of gastric juice. Cannon infers, therefore, that the acid of the gastric juice plays a *rôle* in determining the closure of the cardia. The acid closure persists under the influence of anæsthetics and after the following operations have been carried out, namely, destruction of the thoracic spinal cord, section of the vagi and section of the splanchnic nerves. It must therefore be dependent on a local nervous mechanism.

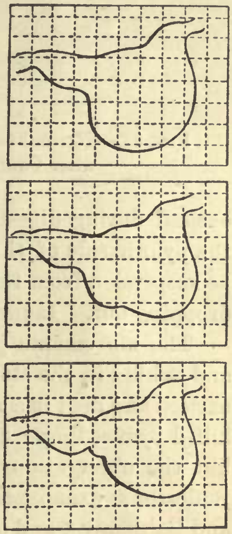


FIG. 31.—Waves of contraction seen in excised stomach of dog (*Hofmeister* and *Schutz*).

The nervous regulation of the cardia from the œsophageal side is effected through the vagi. After section of these nerves, spasmodic contraction of the lower œsophagus and cardia sets in, which prevents swallowing for several days. Kelling † also observed that a higher pressure is required for the entry of liquids under these conditions, and all discrimination is lost—water, whether warm, cold or carbonated, entering at a pressure of 20 to 40 cm.

Soon after food enters the stomach, gentle waves of contraction are seen as shallow indentations which course along the greater curvature, gradually deepening as they approach the pyloric end. These waves begin near the middle of the stomach and temporarily end about two centimetres from the *pars pylorica* (*Hofmeister* and *Schütz* ‡), in what has been termed the pre-antral constriction (see Fig. 31). Each is quickly followed by a contraction of the pyloric antrum, beginning with a closure

* *American Jnl. of Physiol.*, xxiii. p. 105.

† *Loc. cit.*

‡ *Archiv. f. experim. Pathol. u. Pharmak.*, xx. p. 1 (1886).

of its sphincter and extending along the canal to the pylorus. These waves in the dog take about 34 seconds to travel from their origin to the pylorus, and succeed each other at intervals of 15 to 18 seconds. There can be no doubt that they serve to propel liquefied food into the pyloric antrum, the transverse band or sphincter of the antrum being sufficiently relaxed to allow of this, but not to permit the passage of solids. It is, indeed, probable that liquids pass into the pyloric antrum between the folds into which the mucous membrane is here thrown. Thus if the stomach of the rabbit be excised during digestion and divided into two segments by a cut at the pyloric side of the preantral constriction, the cardiac portion may be suspended from the end of the œsophagus, without its solid contents dropping out. Liquefied food under these conditions escapes.

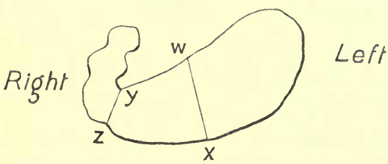


FIG. 32.—Normal stomach of cat, after Cannon.

The movements just described were first observed by Hofmeister and Schütz in the stomach of the dog during digestion. The organ was excised and kept in a moist chamber at 38° C., the animals having been killed by bleeding. Similar contractions have been seen by Rossbach,* but the observations have received their strongest confirmation from radioscopic examinations carried out by Cannon † in the cat, by Roux and Balthazar,‡ and others. To render the movements visible, a salt of bismuth, the subnitrate, carbonate, or oxychloride, was mixed with the food.

In Cannon's description the divisions drawn between the different regions of the stomach are not those generally followed, and consequently his results appear to be less in harmony with the account of Hofmeister and Schütz than they really are.

Thus Cannon divides the stomach (Fig. 32) into cardiac and pyloric portions by the line *wx* (which appears to be arbitrarily drawn), the line *yz* marking the beginning of the antrum. The middle region between the lines *wx* and *yz* is named pre-antral part of the pyloric portion. The term fundus is also used as being synonymous with cardiac portion.

Within five minutes after finishing a meal of bread mixed with milk or water or gravy to a thin consistence, bismuth subnitrate being added, Cannon saw in the cat a slight annular constriction near the duodenal end of the antrum, moving towards the pylorus (Fig. 33). This

* *Deutsches Archiv. f. klin. Med.*, xlvi. 296.
† *American Jnl. of Physiol.*, i. p. 359.
‡ *Archiv. d. Physiol.*, xxx. 85 (1898).

was followed by others at regular intervals. These movements began as very shallow depressions about the middle of the greater curvature, and travelled slowly as waves towards the antrum. The indentations became more marked in their progress and deepened still further when they swept round the bend in the pyloric part. Each wave took 36 seconds to pass from the middle of the stomach to the pylorus, others following at regular intervals of 10 seconds, so that, commonly, three and sometimes four were observed in progress at the same time. The waves continued to run in this manner during the whole time of gastric digestion, often for over seven hours. This gave, at the rate of 300 per hour, in round numbers 2000 for one meal. During their passage the antrum appeared to elongate, while the pre-antral part or body of the stomach was reduced in diameter so much as to become tubular.

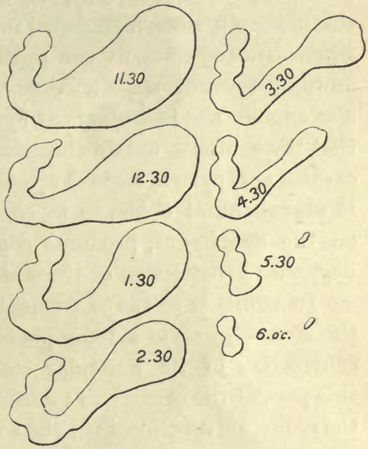


FIG. 33.—Changes observed by Cannon in the stomach of the cat after a bismuth meal given half an hour before the first tracing shown here.

The smaller waves in the cardiac portion serve, no doubt, to bring liquefied food into the antrum, and from investigations carried out by Schemiakin * it appears that the passage is intermittent, being regulated by the rhythmic activity of the sphincter of the antrum already described. Schemiakin found that this sphincter is capable of effecting a complete separation between the two parts of the stomach, so that not even a drop of liquid may pass from the one to the other during its closure. Of the existence of this sphincter there can be little doubt: Kelling † has seen it, not only in dogs with gastric fistulæ, but also in the human subject by means of the gastroscope. In the latter case the constriction appeared as a triangular cleft, above which coarser particles of food lay. If these by any chance passed into the antrum they were returned to the cardiac end. Cannon saw in the cat a complete division of the stomach into two parts at the transverse band, towards the end of a meal, also in the act of vomiting. He corroborates the return of solid particles by means of observations made with a hard pill of starch and bismuth subnitrate given with softer food. Each time the pill reached the pylorus the sphincter

* *Archiv. d. Sciences Biolog.*, x. 87 (St. Petersburg), 1904.

† Volkmann's *Samml. Klinisch. Vortr.*, Nr. 144 (Leipzig); also *Zeitsch. f. Biol.*, xliv. 161.

closed and a reflex wave swept it back to the antrum, or even into the body of the stomach. Magnus * likewise saw a division of the stomach in cats fed with strongly spiced foods, and in a later research found it to be a constant and remarkable effect produced by the administration of morphine. The observations of Dr. Beaumont on Alexis St. Martin, which bear upon this point, may also be recalled. He found the stem of a thermometer, when introduced into the stomach, to be at first obstructed when directed towards the pyloric end, then tightly seized and drawn onwards towards the duodenum. The existence of a separation would also explain the fact observed by Sick † in the human subject, namely, that the contents obtained separately by fractional extraction from the cardiac and pyloric regions are different in composition. Finally there is experimental evidence to show that excitation of the vagus nerve on the œsophagus, produces complete closure of the sphincter in the dog, with constriction of the stomach into two parts.

In addition to the movements above described, the cardiac part of the stomach exerts a tonic pressure on its contents, due to a gradual contraction of its muscular coats. About three hours after a meal this part of the organ was noticed to be reduced in size by Cannon, and the reduction continued till the contents no longer cast a shadow on the screen. The object of this tonic contraction is to "feed" the pyloric portion as long as any food remains capable of being pressed on.

The movements of the Pyloric Portion have been incidentally referred to in the previous paragraphs. The chief duty of this part of the organ is to receive liquefied food from the greater stomach, mix it, and propel it into the intestine. Along with this, a regulation of the acidity of the contents before passing into the duodenum no doubt also takes place. Thus it is known that the injection of dilute acids into the pyloric part evokes a secretion from its glands.

The waves of contraction already described press the contents towards the pyloric sphincter, which opens at intervals to allow the food to pass into the duodenum. What determines the opening is not satisfactorily settled, but it does not usually occur on the arrival of every wave; indeed, as a rule, not oftener than to every third or fourth.

That the passage is intermittent, was known to Schiff, and this has been confirmed by many subsequent investigators. Hirsch,‡ v. Mering,§ Tobler || and others examined the outflow by means of fistulæ laid

* *Archiv. f. d. gesammte Physiol.*, cxxii. 210 (1908).

† *Deutsch. Archiv. f. klin. Med.*, lxxxviii. 169.

‡ *Zentralbl. f. klin. Med.*, 1892, 993.

§ *Verh. d. XII. Kongr. f. inn. Med.*, 1893, 471, and *Therap. Monatsh.*, vii. 201 (1893).

|| *Zeitsch. f. physiol. Chemie*, xlv. 185 (1905).

in the upper part of the duodenum and saw the contents escape by jets of half a c.c. to a few c.c. about every quarter of a minute. They also observed that when the escaping fluid was collected and re-introduced into the lower segment of the bowel the sphincter at once closed and the pylorus opened less frequently; under these circumstances the stomach retained its contents longer and digested them more fully.

It thus appeared that the passage of food from the stomach to the duodenum is regulated quantitatively by a reflex from the latter. But the nature of the response was not fully appreciated till the investigations of Dr. A. S. Serdiukov placed it beyond doubt that it is due to a chemical effect produced by contact of the acid chyme with the duodenal mucous membrane. Thus a solution of sodium bicarbonate previously introduced into the stomach may be kept there for an unlimited time if one continuously injects into the duodenum (through a fistula) either small quantities of acid solutions, or of pure gastric juice. If, however, no acid be injected into the duodenum the alkaline solution generally leaves the stomach very quickly. This cannot be accounted for by a mechanical reflex from distension, for if all the other conditions remain unaltered, and a solution of sodium bicarbonate be poured into the duodenum, the escape of the solution from the stomach is not prevented. Further, it has been observed that the passage of acid solutions out of the stomach is markedly slower in the case of dogs with a pancreatic fistula than in those in which the duct opens into the duodenum. Hence 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. But the acid food allowed through by the pylorus causes an increased flow of pancreatic juice, of bile, and of succus entericus, thus rapidly leading to its neutralisation. It is only when this has been achieved that the escape of a further portion of contents from the stomach is permitted. This regulatory action ensures a more complete preparation of the food in the stomach, and provides for an orderly transition from the acid gastric to the alkaline intestinal digestion. If it were otherwise, and the acid contents of the stomach passed without control into the duodenum, the bile, on mixing with them, would 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. Injurious action of the stomach contents upon intestinal digestion is prevented by their neutralisation, while, on the other hand, the pancreatic juice, owing to the entry of its powerful adjuvants, the bile and the succus entericus, is afforded conditions for exercising its 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 other investigators who have worked at the subject (*v. Mering* and *Marbaix*) clearly realised the chemical nature of the reflex which regulates the passage of the food into the intestine. On the contrary, they misinterpreted it by thinking of a mechanical reflex, acting from the duodenum, which determined a closure of the pyloric orifice.

There are, however, other conditions which have an effect on the sphincter similar to that of the acid. In the experiments of v. Mering it was found that milk, a neutral fluid, when introduced into a duodenal fistula caused a reflex closure of the pylorus. He was thus led to suppose that the result was due to mechanical distension of the bowel. Marbaix,* who also believed in the mechanical reflex, found that milk and yolk of egg were much more effective in producing it than water or egg-white. The results of both observers were, however, due to the fat contained in the milk and egg-yolk. This has been shown by the experiments of Lintvarev, who finds that fats, fatty foods and soaps produce a reflex closure of the pylorus by contact with the duodenal mucous membrane similar to that of acids, and quite apart from a possible mechanical effect. It is probable, however, that mechanical distension is not without influence. Tobler obtained closure by inflating a small india-rubber bag placed within the duodenum. We may conclude, therefore, that when the upper part of the bowel contains as much food of any kind as can be conveniently dealt with, the pyloric sphincter allows no more to enter it.

But not only is the sphincter influenced from the duodenal side, it is likewise affected by conditions acting from the gastric side. This is shown, in the first place, by the difference in its response to liquids and solids. To the former it opens in the way described, but if hard particles or pieces of undigested food reach the pylorus the sphincter closes and remains tightly closed. The most instructive observations on this point we owe to Cannon (*loc. cit.*), who, along with the bread mixture, gave, as previously mentioned, in certain experiments one or more hard pills of bismuth, mixed with starch paste and dried. The pellets could be seen in the pyloric canal, driven onwards by the peristaltic waves of contraction. When they arrived at the pylorus, although the liquefied bread mixture was escaping at the time, the pellets were at once arrested by tightening of the sphincter. Not only were they prevented from entering the bowel, but they were also carried back into the antrum by a current reflected from the closed orifice. The sphincter, which opens on the average four times a minute, was seen to open only

* *La Cellule,* xiv. 251 (1898).

seven times in twenty minutes when a hard pellet had reached the pylorus. The presence of hard particles delayed the exit of softer food as well. Thus the bread mixture which ordinarily begins to pass into the duodenum within fifteen minutes from the beginning of a meal, did not appear there, when administered after a pellet, till the lapse of forty-two minutes.

The difference in the rate of passage of digested food-stuffs from the stomach into the bowel has also been taken to imply an influence acting on the sphincter from the gastric side.* Carbohydrates, as we know, begin to leave the stomach very soon (within fifteen minutes); the escape is rapid and the stomach is found empty, as a rule, within three hours.

With fat, of the same consistence and fed in like quantities, none, as a rule, enters the bowel before the end of the first half-hour; the escape is slow, and after six hours not more than half the whole meal has left the stomach. Proteins, such as lean meat boiled and minced, when made of the same consistence as the bread and fat, begin to pass into the duodenum even more slowly than fats. (In over 50 per cent. of the experiments none had left within half an hour, while in the remainder very little had passed through at the end of an hour.) Later, the proteins pass out more rapidly than fats, but much less so than carbohydrates. In six hours the stomach is usually empty. Proteins given before, or mixed with carbohydrates, delay the exit of the latter. Fats mixed with either carbohydrates or proteins, delay the escape of both.

But the acid reaction of the food, acting on the stomach mucous membrane near the pylorus, is claimed by Cannon † to be the most important factor in determining the opening of the sphincter. His reasoning is as follows. The digested food which escapes through the pylorus in jets, is always acid. Carbohydrates, which do not mask hydrochloric acid by combination with it, escape early because of the earlier development of free acidity. Proteins, on the other hand, escape late for the opposite reason. If, however, proteins be administered as acid-proteins, their discharge from the stomach is hastened, whereas if carbohydrates be rendered alkaline by mixture with 1 per cent. sodium carbonate solution, their entry into the duodenum is retarded. Again, dilute hydrochloric acid, applied to the mucous membrane through a pyloric fistula, causes an opening of the pylorus and escape of contents. The same happens when the acid contents are brought into contact with the membrane near the pylorus by tilting an excised stomach which is suspended in warm oxygenated Ringer's fluid. Cannon points out that the effect of the acid in causing, as he claims, an opening of the pylorus from the gastric side, and a closure from the duodenal side, brings the

* Cannon, *Am. Jnl. of Physiol.*, xii. 387.

† *Ibid.*, xx. 283.

response of the sphincter pylori into line with the Bayliss-Starling law of peristalsis in the intestine, namely, relaxation in front and contraction behind the seat of a given stimulus. Against this it should be remembered that the explanation does not account for the escape of water, which passes through the pylorus almost at once and without acidification, nor for the rapid escape of unboiled or lightly boiled egg-white. A more probable reason appears to be that foods pass through the pylorus in the order in which they are liquefied and prepared in the stomach by the digestive juices acting upon them.

Other conditions which appear to affect the rate of passage from the gastric side are the temperature of the liquid, and in the case of saline solutions, the degree of concentration of the salt. Liquids at body temperature, and isotonic solutions as compared with hypertonic or hypotonic, escape quickest. Lastly, Marbaix found that during closure of the pylorus from the duodenal reflex, distension of the stomach with an additional quantity of water, milk or gas, caused an immediate opening of the passage.

The pylorus not only opens to allow the escape of foods out of the stomach, but also to permit the passage in the reverse way of digestive juices from the intestine. This happens in fasting animals with great regularity, and is associated with a periodic activity of the digestive glands—pancreas, liver, intestinal glands. Each secretory period (which is accompanied by periodic movements to be mentioned below), lasts about 20 minutes, and is followed by a pause of 1½ to 2 hours. In dogs which had previously fasted more than twelve hours, a quantity of mixed juices varying from 100 to 300 c.c. could be collected from a gastric fistula in an observation period of twelve to fifteen hours.

When much fat (particularly acid fat) is given with the food, and when large quantities of gastric juice or of dilute hydrochloric acid (0·5 per cent.) pass from the stomach into the bowel, a similar return of intestinal fluids takes place. The action of the fat is due to its cleavage into fatty acids. Both the fatty acids and the hydrochloric acid produce their effects indirectly by causing a free secretion of bile, pancreatic juice, and succus entericus, which neutralise them, whereupon the pylorus opens and the fluids pass into the stomach. The mixture of juices is richly supplied with the ferments natural to them and may exert important digestive functions in the stomach. The foregoing investigations were carried out by Dr. Boldirev * and have been confirmed by Dr. Asbekov.† There can be little doubt, however, that the conditions observed by Quincke in 1889 ‡ in the case of a child

* *Archiv. d. Sciences Biologiq.*, St. Petersb., xi. 1904.

† *Dissert.*, St. Petersb., 1904 (quoted from *Jahresb. d. Thier-Chemie*, 1904, p. 479).

‡ Quoted by Marbaix, *loc. cit.*

on whom the operation of gastrotomy was performed were similar. During fasting the pylorus was frequently seen to remain open for fully ten minutes, and all this time bile and other intestinal fluids passed to and from the stomach. A similar return of intestinal juices into the human stomach has been obtained by giving oil (*Boldirev*) or cream in considerable quantities. Marbaix also found that when he attempted to inject more than 10 c.c. of milk into the duodenum through the fistula it was returned with a force equivalent to 10–15 cm. of water. This force would be sufficient to overcome intra-gastric pressure, which is usually under 10 cm.

We have hitherto confined our attention to the movements of the stomach during digestion, nor was it suspected till recently that movements of the organ occurred at other times. In experiments on the movements of food in the stomach and intestines, the following observation was, however, made by Dr. P. O. Shirokich. In fasting animals, characteristic propulsive movements are discharged from time to time, the stomach being empty and its reaction alkaline. These movements have been more fully investigated by Boldirev, and have also been observed by other workers in the St. Petersburg Institute (*Kaznelsohn*, *Edelmann*, &c.). They occur periodically in animals which have fasted more than twelve hours.

The movements are much more energetic than those which take place during digestion. The active periods continue for about twenty minutes, and consist of from 5 to 15 propulsive waves, the phase of contraction in each lasting from $\frac{1}{2}$ min. to $1\frac{1}{2}$ min., the pause from 1 to $1\frac{1}{2}$ min. The intervals between the periods vary from $1\frac{1}{2}$ to 2 hours. These spontaneous 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, in an œsophagotomised animal, a fictitious meal be given. Consequently, when ingestion of food is about to take place, or is actually happening, the periodic movements are arrested, clearly with the object of allowing the food to remain in the stomach and be digested in a suitable manner. For instance, milk lapped up by the dog, in contrast to that introduced unobserved through the fistula, does not pass at once into the duodenum, although propulsive movements may have been in progress immediately before. The spontaneous movements also cease when acid fluids are poured into the stomach through the fistula, namely hydrochloric (0·5 per cent.), or lactic, butyric and acetic in equimolecular strengths. But they are more effectively arrested by the action of acids in the duodenum; for example, they are stopped and do not recur for half to one hour by irrigation of a loop of duodenum for ten minutes with 0·1 per cent. HCl. Irrigation with a stronger acid (0·5 per cent. HCl) also stops the movements, but they return with abnormal characters, these latter being removed by dilute sodium carbonate solution. It should be added that at sight of food, the arrest of the movements is instantaneous, taking place long before the secretion of gastric juice begins.

The periodic movements involve both cardiac and pyloric regions of the stomach, and may occur in either region independently of the other, as seen in a dog with the organ divided by operation into two parts. These movements are accompanied by similar movements of the intestine and, as already stated, by a spontaneous flow of bile, of pancreatic juice and of succus entericus. Apart from their physiological interest, the occurrence of periodic movements of the stomach during fasting may throw light upon the spasmodic pain which takes place some hours after a meal in cases of gastric and duodenal ulcers.

LECTURE XI.

[ADDED BY THE TRANSLATOR.]

THE PASSAGE OF FOOD THROUGH THE SMALL AND LARGE INTESTINES.

The SMALL INTESTINE—Methods of studying the movements—The different movements observed and their probable uses—The rate of passage of various foods through the small intestine. The LARGE INTESTINE—Methods of study—The movements observed—Rate of passage of different foods—Defæcation.

GENTLEMEN,—In studying the movements of the intestine *in situ* the methods employed have been: (1) the acute experiment in which the abdomen is opened and the viscera exposed to view, precautions being taken to prevent drying and cooling by keeping the air warm and moist or by immersing the whole abdomen in a bath of normal saline maintained at a temperature of 37° C.; (2) the fistula method, in which permanent openings into the bowel are made at different levels, and samples of the contents taken for examination; (3) the method of radioscopic examination with the fluorescent screen, supplemented by radiophotographs in certain cases. To render the intestines visible in the last-named observations, a salt of bismuth (the subnitrate, carbonate or oxychloride) is administered in considerable doses with the food. Valuable knowledge has also been obtained by the examination of the intestine removed from the animal, and suspended in warmed physiological fluids charged with oxygen, or by taking strips of the muscular coat and observing them in the same way (*Magnus*).

When examined under normal saline the intestines of the living animal are for the most part quiescent. But if the observation be extended over some hours, two kinds of movement are always to be observed, whether the animal has fasted or has been previously fed.

That most commonly seen is the PENDULAR MOVEMENT described by Ludwig. This consists of narrowing and lengthening of the tube, alternating with shortening and widening, rhythmically repeated in the same loop of intestine over and over again (*pendelnder modus*). A to-and-fro movement is thus produced in the long axis, and with this, partial constrictions of the bowel appear simultaneously at several points. The movements may be observed at any part of the small intestine, but are generally first seen in its upper parts, and are more marked when partly filled with contents. Consequently they are livelier some three or four hours after the animal has been fed. As a rule they are less vigorous in the ileum.

When studied by inserting a small rubber bag into the bowel and recording their effects, the pendulum movements produce a rhythmic compression and relaxation, which on the whole moves slowly as a wave down the intestine (*Bayliss* and *Starling* *). The contractions occur at the rate of 10 to 12 per minute and simultaneously involve both the longitudinal and circular coats of muscle fibres. It is difficult to estimate the rate of progress of the wave owing to its multiple origin, but Starling has found it approximately to vary from 2 to 5 cm. per second. Each contraction with subsequent relaxation lasts 5 to 6 seconds.

These rhythmic movements persist after nicotine is injected into the circulation or cocaine applied to the bowel, both of which drugs paralyse local nervous mechanisms. From this it has been inferred (*Bayliss* and *Starling*) that they originate in, and are propagated along the muscular coats of the bowel; that is to say, are both myogenic and myodromic. The view that they are myogenic in origin has been contested by Magnus † on the following grounds. If the longitudinal and circular coats of muscle be separated in the intestine of the cat, Auerbach's plexus generally clings to the former. This layer retains its spontaneous movements if fed with oxygenated nutrient fluid. The other does not, though it is directly responsive to stimuli. Moreover, the less damaged the Auerbach's plexus, the nearer normal are the rhythmic movements. Further, in the intestine of the embryo guinea-pig spontaneous movements appear only after the plexus of Auerbach is developed in connection with the longitudinal coat. Lastly, preparations have been made from the longitudinal muscular fibres of the stomach, free from adherent nerve cells, and were found to be devoid of rhythmic movement though excitable directly (*Sick*).‡

The second form of movement is the true or co-ordinated PERISTALTIC WAVE. It appears as a localised constriction of the wall of the intestine, which travels downwards over a more or less extensive tract of bowel. The constriction at any one spot gives way immediately to relaxation,

* *Journ. of Physiol.*, xxiv. 99.

† Pflüger's *Archiv.*, cii. 349.

‡ Magnus points out that when Auerbach's plexus is absent, the smooth muscle of the intestine is tetanisable, gives superposition of contractions, shows no refractory period, and on continued excitation with the galvanic current manifests neither spontaneous movements nor rhythmic contractions. If Auerbach's plexus is present the converse holds good in all of these particulars.

during which the next adjoining ring of muscle fibres enters into contraction. In life, the progress of the peristaltic wave is always downwards, never in the reverse or antiperistaltic direction. The rate at which it travels is slow, namely 1 to 2 cm. per minute, and a very striking feature in the case of intestines examined under normal saline, is the rarity with which the wave spontaneously occurs. It can, however, be readily elicited by inserting a suitable bolus into the lumen of the bowel. Such a body has been found to be propelled forwards at the rate of $\frac{1}{2}$ to 2 cm. per minute, and takes 2 to 3 hours to travel the whole length of the intestine.

The force which thus comes into play has been measured by introducing through a fistula, a wax ball to which a thread was attached, and causing it to move a weight suspended over a pulley. A weight of 8 grms. was lifted and the bolus moved on with an average speed of 27·5 cm. per hour: that is approximately half a centimetre per minute. Similar experiments by Cash with a weight of 10 grms. as the maximum, gave a speed varying in fasting from $\frac{1}{10}$–$\frac{1}{2}$ cm., after feeding from $1\frac{1}{2}$–2 cm. per minute.

The peristaltic movement is a definite reflex evoked by mechanical excitation of the mucous membrane, and when closely examined is seen to consist of a contraction of the muscular fibres above the spot excited, accompanied by relaxation of the coats below. No matter how elicited the peristaltic wave manifests these two features, contraction above the point of stimulation, relaxation below. This law of intestinal movement was first clearly enunciated by Bayliss and Starling,* though Nothnagel† had recognised the occurrence of a dilation of the intestine below, with contraction at or above, the point of excitation, and Mall ‡ drew the inference that local contraction seemed to have a tendency to produce dilatation below.

Intestinal peristalsis is annulled by the injection of nicotine into the circulation and by the local application of cocaine. Since these drugs paralyse peripheral nerve mechanisms, it is inferred that the reflex is mediated through the nerve plexus of Auerbach.

Both the pendular and peristaltic movements continue after all extrinsic nerves of the intestine have been severed (see Fig. 35), and also after extirpation of the cœliac plexus (or division of the mesenteric nerves peripheral to this point), with subsequent degeneration of the post-ganglionic nerve fibres as far as Auerbach's plexus, the latter remaining intact.

* *Loc. cit.*

† Virchow's *Archiv.*, lxxxviii., Heft 1; also "*Physiologie u. Pathologie d. Darmes*" (Berlin, 1884).

‡ *Johns Hopkins Reports*, vol. i. 37.

Cannon,* by means of X-rays, observed peristaltic movement in the cat in two forms—a slow advance, often with many halts and accompanied by segmentation, and a rapid sweep through several turns of the gut without pause. The latter was frequently seen in the duodenum following a preceding period of segmentation, and, after giving an enema of soap-suds, in other parts of the small intestine also.

With the object of testing the law of forward direction in the propagation of peristaltic movement of the small intestine, segments of bowel were cut out and reversed, the lower end being sutured into the position occupied previously by the upper and conversely (*Mall*). In every case the direction of the peristaltic wave was also reversed with the operated segment, so that the contents at the region of its upper junction with the normal intestine were acted upon by opposing forces, the result being that this part of the bowel became enormously dilated, and impaction followed, ending in death. The bowel at the dilated part was found post-mortem to be filled with solid particles, pieces of hay, sand, and other indigestible materials. The mucous membrane in the same region was greatly ulcerated or absent. These experiments were repeated by others (*Mühsam*,† *Sabbatani* and *Fasola*,‡ *Prutz* and *Ellinger* §), and all agree that the direction of peristalsis in a reversed segment of bowel is as above stated. On the other hand, the later observers have found that if easily digestible foods, such as lean meat and fat be given, little or no ill-effects follow the reversal, whereas if indigestible substances, such as particles of bone, cork, straw, be mixed with the food, obstruction, dilatation, impaction and death ensue.

These results accord with those which follow total removal of the muscular coats of the small intestine for considerable lengths (as much as one metre having been stripped off) leaving merely a narrow band along the mesenteric attachment (*Kreidl* and *Müller* ||). The animals lived for months in good health, fæces were passed at normal intervals after food had been eaten, and no obstruction occurred if care were taken in the feeding. On the other hand, if indigestible solids, such as particles of straw, &c., were mixed with the food, fatal impaction rapidly followed.

A third form of movement, THE SWIFT VERMICULAR WAVE, has long been known to occur under certain circumstances. It has usually been observed immediately after the death of the animal, and was first carefully described by van Braam Houckgeest,¶ under the name of "Roll Movement." This observer saw it in the last stages of asphyxia in the rabbit, following general convulsive movements of the body, when the

* *Loc. cit.* † *Mitth. a. d. Grenzgeb. d. Med. u. Chirurg.*, vi. 1900.

‡ *Archiv. ital. de Biol.*, xxiv. 1900.

§ *Arch. f. Klin. Chirurg.*, lxvii. (1902) and lxxii. (1904).

|| Pflüger's *Archiv.*, cxvi. (1906). ¶ *Ibid.*, vi. 266 (1872).

intestinal blood-vessels, after an earlier constriction, had become dilated and charged with venous blood. The movement usually began in the pyloric part of the stomach or first part of the duodenum, and consisted of a vigorous and rapid contraction (chiefly involving the circular coat of muscular fibres), which traversed the whole intestine in less than one minute. The contents of the bowel were swiftly driven before it into the cæcum. Not infrequently an earlier wave started from some part of the jejunum, and ran to the cæcum in advance of that which originated higher up. The "Roll Movement" was seen in life on stimulation of the vagus, the splanchnic nerves having been previously divided, but not on stimulation of the vagus without the latter, nor did it follow section of the splanchnics alone. It has also been found (*Bokai*,* *Booker* †) that the movement could be evoked by injecting into the lumen of the bowel the gases and organic acids of decomposition such as CH_4, H_2S, phenol and skatol, likewise the toxines of infantile summer diarrhœa. The passage of CO_2 into the bowel had a similar effect, whereas, on the other hand, the movement could be stopped by permitting the animal to breathe freely or by introducing oxygen into the lumen of the intestine.

It seems clear that the purpose of this movement is to rid the bowel as rapidly as possible, of irritating and dangerous contents. The procedure may perhaps be compared to that by which fluids are quickly passed through the stomach. There can be little doubt that the swift vermicular wave is a form of protective movement held in reserve, but ready to be brought into play when circumstances require it. The same probably applies in a less degree to the true peristaltic wave, which provides a force necessary for the propulsion of solid or semi-solid contents, but not essential for the transmission of the normal liquid contents through the small intestine. All observers agree that it is seldom seen under normal conditions in the jejunum or ileum.

The office fulfilled by the pendular movements has been made clear by Cannon's radioscopic observations on the cat. A noticeable feature in these investigations also, was the absence at any given moment of every form of movement from most of the loops of the small intestine. Within a few minutes, however, movements could be seen in one or other loop if examined some hours after taking food. These began by sudden undefined activity in the narrow masses of food within the bowel, followed immediately by division into many little segments. Then each particle quickly divided again, the halves of adjacent segments approaching and fusing together; this process was continued, the little particles dividing and joining again with others, while the large segments oscillated to and fro for more than half an hour without much change of position

* *Archiv. f. Exp. Path. u. Pharm.*, xxiv.

† *Trans. IXth Intern. Med. Cong.*, vol. iii.

in the contents of the bowel. The rate of division in slender masses was about thirty per minute, and each might be divided and re-divided more than 1000 times, while remaining at practically the same part of the intestine. In thicker masses the rate of constriction was somewhat slower, and the division not always complete.

By this rhythmic segmentation the movements ensure thorough mixture of the contents of the bowel with the digestive juices and bring every particle of food repeatedly into contact with the mucous membrane, thus actively promoting absorption. Since the pendular movements slowly advance down the intestine, they probably effect a corresponding forward movement of its liquid contents. This force, together with those contributed by the initial expulsion from the stomach, and by the peristalsis which appears to be a normal function of the duodenum, also possibly by the secretory pressures which propel digestive juices into the bowel, represent the normal forces which move the contents through the small intestine.

Mall has pointed out, in addition, that the rhythmic movements help to pump the blood into the rootlets of the superior mesenteric vein, and thus give important aid to the circulation. They also have a similar effect on the filling of the lacteal vessels with chyle, thus aiding the movement of the fluid in them. The loaded chyle vessels coming away from a loop of intestine absorbing fat, will soon be found empty if after opening the abdomen the intestinal movements be allowed to proceed. This may be prevented by slitting the tube open, thus rendering the contractions ineffective.

The actual transmission and rate of progress of foods through the small intestine, as observed by Cannon in the cat, are as follows: The food escaping from the stomach is ejected some little way (about 2 cm.) into the bowel, collecting at first for a short time in the bends of the duodenum before being hurried on into the coils of the jejunum. The time at which it begins to leave the stomach varies, being shortest with carbohydrates (10–15 mins.) and longest with proteins (30–90 mins.). After three to four hours the contents in the coils of the small intestine collect into a small number of unbroken segments of uniform width. By measuring the lengths of these strings a fairly accurate estimate of the quantity of food present can be obtained. Investigating in this way it was found that when similar quantities of different foods were given, mixed in each case with bismuth subnitrate, the total length of the shadows increased up to a certain point and then declined. With carbohydrates the maximum length observed (37·7 cm.) was reached in two hours, after which the quantity rapidly declined. With proteins the increase continued for four hours (maximum length 20·6 cm.), with fats for three hours (maximum length 14·8 cm.), the decline in both these cases being slower than with carbohydrates. At the end of seven hours the observations were brought to a close, when there remained of carbohydrate food 8·3 cm., of proteins 12·2 cm., of fats 7·6 cm. Curves showing the results of these observations are given in Fig. 34.

With a diet of mixed foods the rate of passage varied. When composed of carbohydrates and proteins, the rate was intermediate between

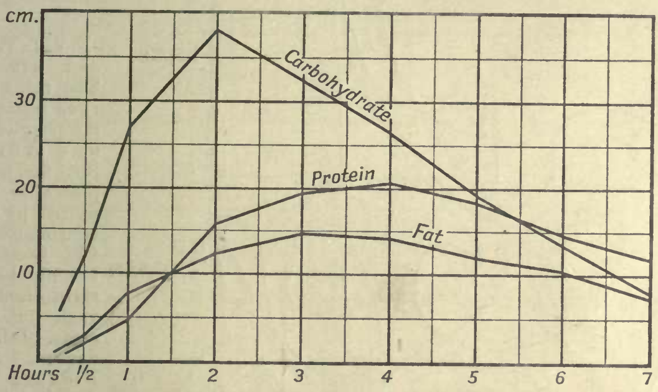
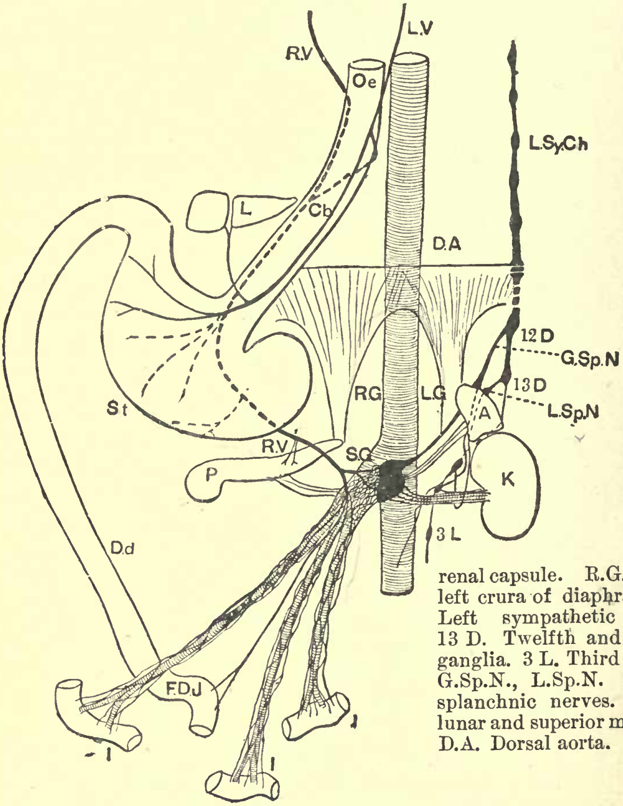


FIG. 34.—Diagram showing the rate of passage of different foods out of the stomach and through the small intestine (*Cannon*).

those for the two foods singly. With carbohydrates and fat the rate at first was more rapid than for the carbohydrates alone, but later became slower than that for either. Fats added to protein made the passage slower than for either alone. When the procedure was varied, the proteins being administered before the carbohydrates, the latter were retarded, but not if given before the proteins. Increase in the quantity of food accelerated the passage for carbohydrates, but slowed the rate for proteins.

In such experiments the length of food column in the intestine is obviously a resultant of two factors, namely, the quantity which passes through the pylorus and the amount removed by absorption from the bowel. The curves therefore give some information with regard to the disappearance by absorption, and teach not only that the escape of carbohydrates is the most rapid of the three classes of foods, but that their absorption is also the most rapid.

The discharge of proteins in the majority of cases is distinguished by a late beginning and a slow rise. At the end of half an hour eight times less protein than carbohydrate had passed out. Their absorption is also slow: thus at the end of one hour there is five times as much carbohydrate in the bowel as of protein, but at the end of two the proportion is reduced to twice as much, the absorption of the former having gained on the latter in the interval. The distinctive features of fat in these respects are a very slow discharge, with a long low curve indicating a small quantity in the bowel, and an absorption almost at the same rate as fat



R.V., L.V. Right and left vagi. The right vagus runs behind the œsophagus (Oe.) and stomach (St.), and in those places is represented by a discontinuous line. Cb. Connecting branch between right and left vagi. P. Pancreas. Dd. Duodenum. F.D.J. Flexura duodeno - jejunalis. I, I, I. Intestine. L. Liver. K. Kidney. A. Suprarenal capsule. R.G., L.G. Right and left crura of diaphragm. L. Sy. Ch. Left sympathetic chain. 12 D, 13 D. Twelfth and thirteenth dorsal ganglia. 3 L. Third lumbar ganglion. G.Sp.N., L.Sp.N. Great and small splanchnic nerves. S.G. Left semilunar and superior mesenteric ganglia. D.A. Dorsal aorta.

FIG. 35.—Nerve-supply of the small intestine in the dog (*M. H. Naylor*).

enters the bowel. At the end of seven hours little over half the meal had left the stomach, and after the first hour and a half the quantity present in the bowel varied very slightly within the period of observation.

The whole time required for the passage of food through the small intestine fluctuates considerably under different circumstances, and varies also with different foods. For the cat, Cannon found the average length of time, from the taking of a meal, at which foods appeared in the cæcum, to be as follows: Carbohydrates, 4 hours; proteins, 6 hours; fats, 5 hours. Allowing in the case of proteins one hour for the later discharge from the stomach, it would still seem that their rate of passage through the small intestine is slower than that of carbohydrates.

The same method has been used by Cannon * to investigate the effects on the passage of foods of cutting off extrinsic nervous influences from the stomach and intestines, either partially or completely. Three sets of experiments were performed. In the first the splanchnic nerves were divided on both sides, and short lengths excised aseptically,

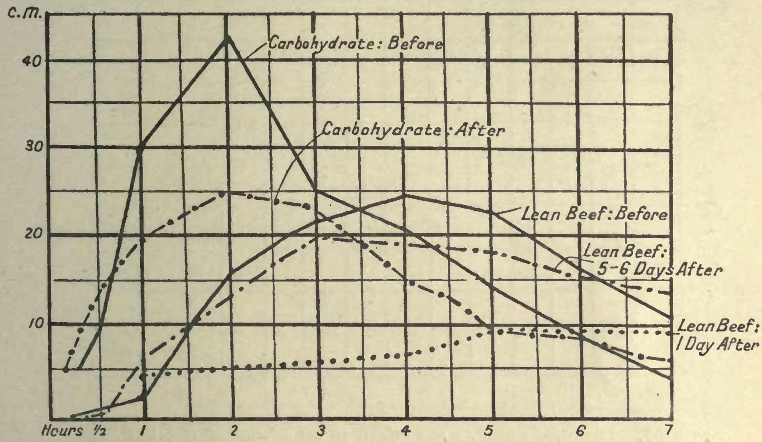


FIG. 36.—Diagram showing the influence of splanchnic and vagus section, upon the passage of food through the small intestine (*Cannon*).

with as little disturbance to the viscera as possible. In the second set the two vagi were severed, the right one below the origin of the recurrent laryngeal, the left in the neck, and usually at a later operation. In the third group of operations both sets of nerves were divided, the splanchnics and right vagus at one stage, and afterwards the left vagus.

The usual standard meals, representative of carbohydrates and proteins, were given at different periods afterwards, and the animals observed by X-rays. The results were as follows: After the removal of splanchnic influence neither the passage of carbohydrates nor that of lean beef was altered in any degree. Stomach movements, rhythmic segmentation, and intestinal peristalsis were all seen as in the normal animal.

On the other hand, after severance of the vagi the entry of carbohydrates into the intestine was distinctly retarded, and still more that of proteins, particularly within the first two days after the division of the second vagus. After complete removal of both splanchnic and vagus influence the results, as might be supposed, differed little from

* *Am. Jnl. of Physiol.*, xvii. 1906.

those which followed division of the latter nerves only. In one respect, however—namely, in regard to proteins—the passage, curiously enough, approximated more closely to the normal. In all cases the distinctive rates of discharge and progress were retained for the two classes of foods, carbohydrates and proteins.

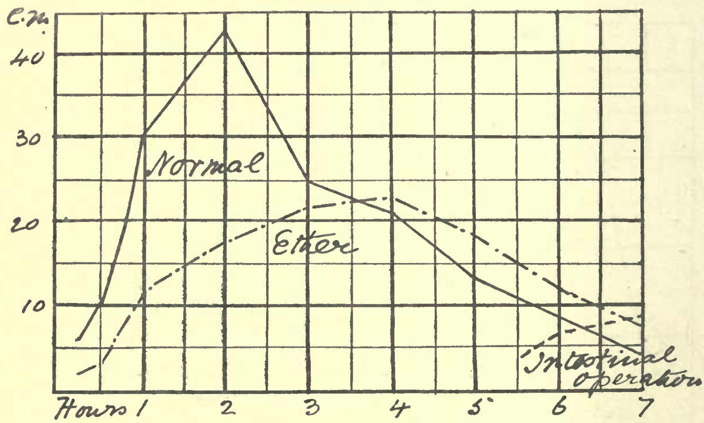


FIG. 37.—Diagram showing the effects of ether and of division and resuture of the bowel upon the passage of food through it (*Cannon*).

The total time required for the passage of different foods through the small intestine tallied, on the whole, with the foregoing. After splanchnic section carbohydrates were, on the average, very slightly retarded, while proteins, on the contrary, were much accelerated. After vagus section the delay for carbohydrates amounted to about one hour, that for proteins being much greater. Thus in two out of four cases lean beef had only reached the cæcum at the end of seven hours from the feeding, although it began to leave the stomach at the usual time. In the remaining two cases the delay was still longer.

The influence of certain operative procedures on the passage of food through the stomach and intestines was also investigated in the same way by Cannon and Murphy.* The normal rate of passage of a standard meal of mashed potato and bismuth was in the first instance observed. On subsequent days the different animals were submitted to one or other of the procedures, and the effect on the passage of a similar meal observed.

At the outset the *influence of ether* administered for half an hour was recorded (Fig. 37). The most marked alteration produced by ether in the passage of food through the alimentary canal is the slowing of the rate of discharge from the stomach. The curve rises slowly instead of abruptly. This is followed by a slow passage through the small

* *Annals of Surg.*, 1906, 513.

intestine. The food, which ordinarily reached the large intestine at the end of two or three hours, only arrived there after four, five, or six hours. Inhalation of ether, therefore, slows the active movements of the alimentary canal, but does not arrest them.

Secondly, the effect of a thirty-minutes *exposure of the bowel* to the

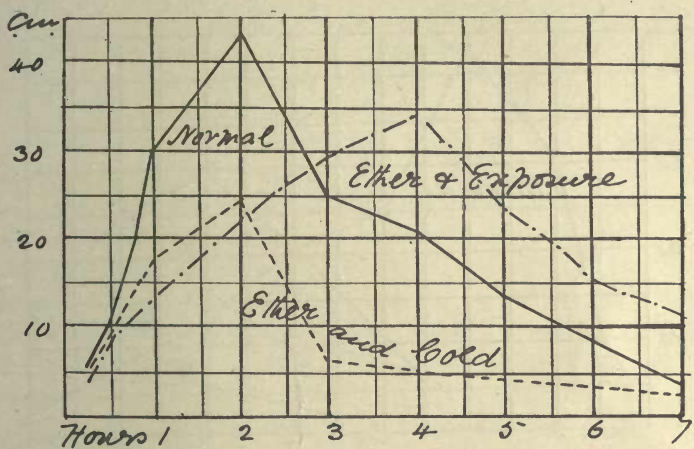


FIG. 38.—Diagram showing (*a*) the effects of ether followed by exposure of the bowel to air, and (*b*) the effects of ether followed by the application of cold to the intestine, upon the passage of food through it (*Cannon*).

air was observed, such as might occur in an operation, care being taken not to touch the viscera. At the end of this period the abdomen was closed, and after recovery from the anæsthetic a standard meal was given. After exposure to air the discharge from the stomach begins at the normal time, but the outgo is slow (see Fig. 38), though not so slow as in the case of ether alone. The passage through the small intestine is, however, much retarded; no food entered the large bowel until the end of six hours.

In the next observation *the intestines after exposure were cooled*, the animal being anæsthetised with ether. The cooling was effected by pouring at intervals into the abdomen sterile salt solution at a temperature of 20° C. In the curve showing the effect of cooling (Fig. 38), the discharge of food from the stomach, though not late in starting, is somewhat slow. The striking feature of the curve, however, is the rapid passage through the small intestine. Food appeared in the large intestine at the end of three hours, and one hour later almost the whole meal had reached the colon.

Next the *effect of handling the bowel* was studied, the handling varying from gentle to severe, and being accomplished sometimes in air, sometimes under warm normal saline.

The results are very remarkable (see Fig. 39); even the most gentle manipulation under warm salt solution arrested all movement of the stomach and intestine for fully three hours after feeding. Moreover, the

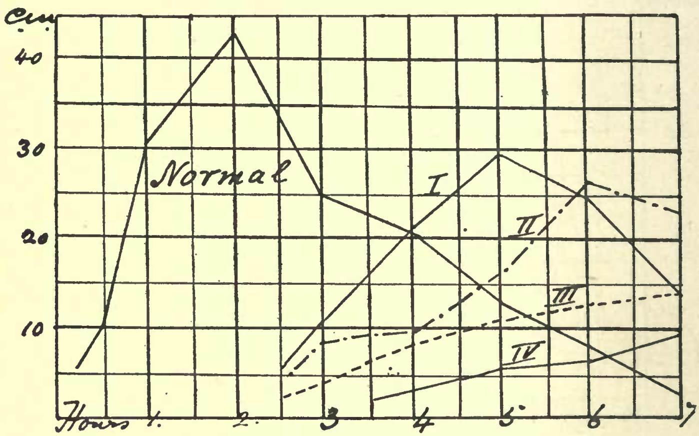


FIG. 39.—Diagram showing the effects upon the passage of food of (I) gentle handling under warm saline; (II) gentle handling in peritoneal cavity; (III) gentle handling in air; (IV) severe handling in air.

escape, when it began, was very slow, and became increasingly so with the severity of the manipulation. The appearance of food in the large intestine was also delayed, none arriving there before the end of seven hours. Manipulation of the stomach and intestines in these experiments produced, even under the most gentle and favourable circumstances, a far greater degree of inactivity than any of the other factors concerned in the operation, exclusive of the operation itself.

Lastly, the effect of the *section of bowel* was investigated (see Fig. 37), the two ends being sutured together again immediately after the division. For comparison, two operations were performed—one a high trans-section, the other a low one near the end of the ileum.

After a high intestinal section food did not emerge from the stomach before the lapse of five or six hours, and within the period of observation extremely little had entered the intestine. This remarkable delay was not due to arrest of the normal peristaltic waves of the stomach. These contractions were seen pushing food up to the pylorus at the rate of five or six a minute for more than five hours, but the sphincter held perfectly tight against the pressure, and refused to permit food to pass on into the injured gut. Cannon and Murphy have pointed out how remarkable it is that the period during which this protection is exercised corresponds closely to the time required for the primary cementing of the wounds of the intestine as determined by independent observers. From experiments made by Dr. Abbey on the healing of intestinal sutures in dogs, sheep, and other animals, the usual time required for the exudation of a firm gluey lymph able to afford efficient support to the wounded parts is usually about six hours.

In the intestinal section at the lower end of the small bowel food escaped from the stomach within two hours, but was delayed in the upper part of the small intestine, and even at the end of seven hours had not reached the lower end, although under normal circumstances the same meal appeared in the colon before three hours. Thus it would seem that a protective influence is exercised not only through the sphincter pylori, but that injury to any part of the small intestine is able to produce a blocking effect upon the passage of contents through the bowel itself which saves the damaged part until a certain amount of repair has taken place.

To the foregoing may also be added the influence of emotions on the movements of the alimentary canal. In his earliest observations on the cat Cannon * noticed the absence of stomach movements particularly in male animals when excited or resentful of the restraint necessary for examination. A marked case of inhibition induced by anxiety about its kittens was also seen in a female cat.

Further, arrest of the movements of the intestine, segmentation, peristalsis, and, in the case of the large intestine, of antiperistalsis, could be brought about at any time by covering the mouth and nose of the animal with the fingers, so as to cause some respiratory distress. Similar effects were seen in a dog when placed in unaccustomed surroundings (*Lommel* †). They have also been seen in the rabbit (*Auer*) and guinea-pig (*Cannon* ‡).

The nerve paths along which the inhibitory emotional influences pass to the intestine lie in the splanchnics. Thus arrest is at once produced by respiratory distress when the splanchnics alone are intact. On the other hand, when the splanchnics are severed and the vagi left intact no effect is produced unless the respiratory distress be pushed to a much further degree. The movements then become shallow and temporarily cease. With both sets of nerves divided it is impossible to arrest the movements by inducing respiratory distress (*Cannon* §).

* *Am. Jnl. of Physiol.*, 1898.
† *Münch. Med. Woch.*, 1903.
‡ *Loc. cit.*
§ *Am. Jnl. of Med. Sci.*, 1909.

Applications of the radioscopic method to the human subject have shown that stagnation of food in the stomach also occurs as the direct result of mental worry.

The contents of the human small intestine, after a bismuth meal, do not usually cast shadows. Exceptions to this rule are frequently found in the lower end of the ileum, where it joins the cæcum, and sometimes in the duodenum. In certain cases also in the jejunum short lengths of food, mixed with bismuth, have been observed and watched for over half an hour (*Hertz*). Well-marked segmentation was then seen to occur, the mass constricting into two, and each half subdividing into two more. The middle halves then joined up to form a new central piece, which, in its turn, was divided once more. The rate observed in one case was ten divisions in a minute and a half.

The whole time required for the passage of food through the human small intestine has also been determined by this method. From previous investigations in the case of a fistula close to the ileo-cæcal valve it was found (*McFadyen*, *Nencki*, *Sieber*) that green peas appeared on one occasion in $2\frac{1}{4}$ hours, on another in $5\frac{1}{4}$ hours, after a meal.

Observed by the radioscopic method, the time, after a mixed meal, at which food appeared in the cæcum was found by Hertz to vary from $3\frac{1}{2}$ to 5 hours, the average being $4\frac{3}{8}$ hours. Deducting half an hour for the delay in the stomach before escape began, and taking the length of the small intestine as $22\frac{1}{2}$ ft., this gave a rate of 5 ft. 7 in. per hour, or approximately 1 in. per min.—that is, much faster than the ball was moved by peristalsis in the observations mentioned earlier. The results obtained by the X-rays have been verified by auscultation. Sounds indicating the periodic entry of food into the cæcum are first heard from 4 to $4\frac{1}{2}$ hours after a meal.

From calculations based upon the length of column and the rate of division Cannon concludes that the sum total of the energy expended in the segmentation of different foods varies considerably. In the first seven hours after a meal, the expenditure in the case of carbohydrates far exceeds that for either proteins or fats. The difference, however, appears to be somewhat equalised in subsequent hours owing to the longer stay of the latter foods in the bowel.

THE LARGE INTESTINE.

With the object of studying the entry of food into the cæcum, the changes which it there undergoes, and the nature of the secretion produced, fistulæ were laid by Drs. Berlazki and Straschesco into the ileum at its lower end and into the colon immediately beyond the cæcum. Their observations show that the juice secreted is alkaline, that its amount is dependent on the mechanical properties rather than the chemical nature of the food, and that it contains small quantities of various enzymes, such as erepsin, amylase, maltase, and invertin. Of the constituents of a mixed diet, fats appear to reach the cæcum earlier than proteins, proteins earlier than bread, while milk passes through the small intestine quickest of all, fully 50 per cent. reaching the cæcum in 1 to 2 hours.

The extent to which absorption occurs in this part of the large intestine is indicated by the following data. Of the proteins of a meal, 9·6 per cent. reach the cæcum, where a further 2·6 per cent disappears; the corresponding figures for carbohydrates being 2 per cent., with an absorption of 0·4 per cent., and for fats 5 per cent., with a disappearance of 1·7 per cent.

The MOVEMENTS OF THE LARGE INTESTINE have in recent years been studied in animals mainly by two methods, namely, by direct observation in a warm saline bath (*v. Braam Houckgeest*,* *Bayliss* and *Starling*,† *Jacobi*,‡ *Raiser*,§ *Magnus*,|| *Elliott* and *Barclay-Smith*¶), and, secondly, by means of Röntgen rays after the administration of a bismuth salt added to a meal (*Cannon*, *Magnus*, *Hertz*,** &c.). In the human subject the latter method has been employed by Rieder,†† Hertz, and others.

When considering the knowledge acquired by examination of lower animals, it is important to bear in mind that the development of the large intestine varies considerably in different classes, and also that the anatomical nomenclature employed for the human subject is seldom strictly applicable to them. Moreover, structural divisions do not, as a rule, correspond with the functional or physiological activities displayed. In the case of some animals, the whole large intestine (cæcum, colon, rectum) falls into three main regions, from the point of view of function, the proximal, intermediate, and distal (*Elliott* and *Barclay-Smith*). In the first of these the contents are semifluid, of uniform consistence, and the movement most frequently seen is antiperistaltic in direction. In the second the contents are consistent, often nodular, especially in lower animals, while its chief movement is true or propulsive

* *Loc. cit.* † *Jnl. of Physiol.*, xxvi. 107.

‡ *Archiv. f. Exp. Path. u. Pharm.*, xxvii. 1890.

§ *Inaug. Diss.*, Giessen, 1895.

|| *Loc. cit.*

¶ *Jnl. of Physiol.*, xxxi. 272, 1904.

** *Brit. Med. Jnl.*, 1908, vol. i. p. 191.

†† *Münch. Med. Woch.*, No. 35, 1904; also No. 3, 1906.

peristalsis. The distinctive feature of the distal or third segment is that its cavity is under the control of, and can be evacuated by excitation of the pelvic visceral nerves. Its contents are nodular in lower animals. These subdivisions are present and well marked in herbivorous mammals, but are not always clearly defined in carnivora. Thus they are distinct in the rabbit, also in the rat (*omnivora*) and in the cat (*carnivora*), but not so in the dog. Each division corresponds approximately in length to one-third of the whole bowel. In the human subject the proximal division includes the cæcum, the ascending, and half the transverse colon. The middle includes the remaining half of the transverse and the descending colon, while the distal comprises the pelvic colon and rectum. Roith * subdivides the human large intestine into three regions, according to the amount, nature, and consistence of the contents, namely: (1) Cæcum and ascending colon, contents greatest and most liquid; (2) transverse colon, contents relatively less; in proportion to length not more than half, though actually greater; (3) descending and sigmoid colon, the former being often empty, the latter subject to wide variations.

In studying the movements of the lower bowel in animals, a suitable stimulus by which they may be evoked is of great value. The best and nearest to the normal has been found to be an injection of gruel or paste, of about the consistence of the bowel contents. Raiser used starch-paste, Elliott and Barclay-Smith a mixture of pea-flour and water.

The commonest movement seen in the proximal division is anti-peristaltic in direction. This was independently observed by Jacobi † and by Cannon ‡ as a normal occurrence in the cat. It has also been confirmed and extended to some other animals by Elliott and Barclay-Smith, but has not been seen in the dog, nor does it appear in the human subject (*Hertz*). The waves of constriction of which it consists usually begin near the junction with the middle division, and from thence move back towards the cæcum. Periods of activity alternate with periods of quiescence. The former continue on the average for about 4 minutes (2 to 5), the waves following each other at the rate of 5 or 6 to the minute. Thus about 25 waves act upon any portion of contents in each period. The quiescent intervals are not of uniform length, but usually last from 20 to 30 minutes. Under the influence of the waves the diameter of the tube is reduced to two-thirds or one-half. The movements are not arrested by large doses of nicotine, and are therefore by many considered to be myogenic. The wave of constriction is not preceded by relaxation as in direct peristalsis.

* *Mitth. a. d. Grenzgeb. d. Med. u. Chirurg.*, xix. 33, 1909.

† *Loc. cit.*, p. 147, 1890.

‡ *Am. Jnl. of Physiol.*, vi. 1902.

The food thus driven back towards the cæcum does not enter the ileum, the ileo-cæcal sphincter being competent to prevent a return. From time to time a contraction of the cæcum drives it onwards again into the proximal colon. This contraction may appear either as a constriction occurring near the middle of the cæcum and moving slowly towards the junction with the colon; or as a strong general contraction of the whole cæcum, which may even extend to the beginning of the colon. Segmenting movements have also been seen in the cæcum and proximal colon (*Cannon*). The combined effects of these movements secure a thorough mixture of the contents of the proximal division of the lower bowel; bring them repeatedly into contact with the absorbing mucous membrane; and prevent their too rapid transit to the lower divisions.

The food continues to accumulate in the proximal division till the column extends to the end of the region of antiperistalsis. Meanwhile the contents become more consistent and the antiperistaltic movements lessen or disappear. Soon constrictions at the end of the region of antiperistalsis cut off portions, which are passed in succession into the middle region of the bowel. Here they are driven forward by a co-ordinated wave of peristalsis—the only movement which this section exhibits—and are lodged in the lower division till evacuation occurs.

From the foregoing it will be seen that there are three main types of movement seen in the large intestine. First, the antiperistaltic contractions which normally occur in the proximal segment and move toward the cæcum, not preceded however, by the relaxation which always accompanies true propulsive peristalsis. Second, the co-ordinated peristaltic reflex, the characteristic movement of the intermediate region, but seen at times in all three divisions of the bowel. Third, the descending constriction of the distal segment due to progressive contraction of the circular muscle, accompanied by shortening of the longitudinal fibres and by downward movement of the distal colon. Along with these a segmenting or oscillatory movement has been seen (though not regularly) in the ascending colon; also a general contraction of the cæcum and ascending colon, the effect of which is to propel the contents distalwards and against the recurrent or antiperistaltic waves.

The ileo-cæcal orifice is controlled by a sphincter which, in the human subject, is supplemented by valvular folds of mucous membrane containing muscle. The sphincter consists of a thickening of the layer of circular muscle-fibres at the lower end of the ileum. In the cat the extent of this thickening is 10 mm. (*Elliott*).

The sphincter is innervated through the splanchnic nerves, the fibres arising from the lowest thoracic and upper two lumbar roots in the cat. Stimulation of the splanchnics causes a contraction, which is arrested by the effect of nicotine on the solar ganglion, where the fibres have relays. Neither the vagus nor the pelvic visceral nerves appear to exert any influence on the sphincter. Adrenalin and anæmia (caused by artificially reducing the blood-supply) have the same effect as stimulation of the sympathetics. Destruction of the spinal cord permanently paralyses the sphincter.

The question of a reverse passage through the ileo-colic orifice has long been discussed. Under ordinary circumstances it does not appear to occur. Food having once entered the cæcum does not in normal conditions return to the ileum. The remarkable observations of Grützner * seem, however, to be explicable only on the supposition that a reverse passage is possible, at all events, under certain circumstances. He found that particles of hair, charcoal, and unboiled starch injected with saline enemata into the lower bowel make their way into the small intestine, and may even ascend to the stomach. Sabbatani and Fasola † obtained confirmatory evidence, as did also Cannon, the last-named by radioscopic observations. Large and small enemata (25 c.c. and 90 c.c. respectively), both fluid and semi-fluid, containing a bismuth salt, were injected by Cannon into the bowel of the cat. The large enemata, sufficient to fill the lower bowel, were seen to pass through the ileo-colic sphincter and enter the ileum, the propelling force being the anti-peristalsis of the proximal colon. Several coils of the small intestine were filled with a continuous column, in which rhythmic segmentation was seen to occur as with food arriving there in the normal way. The smaller enemata lodged at first in the descending colon, and never entered the ileum. The composition of the fluid enemata was in the proportion of 2 grms. of starch, 10–15 grms. of subnitrate of bismuth, 100 c.c. of milk, the whole being boiled and cooled. For the semi-fluid enemata one egg was added before boiling.

The passage of food through the human large intestine has been observed by Rieder,‡ and has also been carefully followed by Hertz and his co-workers in sixteen healthy young men.

The contents of the ileum probably enter the large intestine by jets. Food remains long in the cæcum and ascending colon. Peristaltic and antiperistaltic movements are believed to occur in the human large intestine, but the latter have not been seen, and the former only during defæcation (*Hertz*). They probably occur too slowly to be observed radioscopically. The contents also move forwards very slowly, more than an hour being required to observe distinct progress, except after a meal, when the rate is much quicker. Thus in a series of hourly observations, made by Hertz, more movement took place in

* Pflüger's *Archiv.*, lxxi. (1898). † *Loc. cit.*

‡ *Fortschr. a. d. Gebiet. d. Röntgenstrahlen*, vii. 1.

one hour after dinner than in the preceding four. In one case nearly half the transverse and the whole of the descending colon (observed before breakfast to be empty) were filled up in three-quarters of an hour after the meal.

The first portion of an ordinary meal (breakfast) usually reaches the

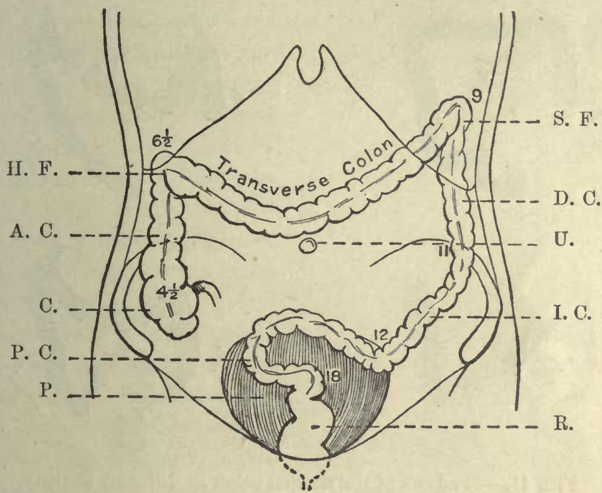


FIG. 40.—Diagram of normal large intestine, the pelvic colon being represented in the position it occupies when full. The numbers represent the hours after a bismuth breakfast at which the different parts of the colon are reached. C. Cæcum. A. C. Ascending colon. H. F. Hepatic flexure. S. F. Splenic flexure. D. C. Descending colon. I. C. Iliac colon. P. C. Pelvic colon. R. Rectum. U. Umbilicus. P. Pelvis. (*Hertz.*)

cæcum in from 3½–5 hours, the average being 4⅜ hours, as previously stated. The hepatic flexure of the colon is reached in from 5–8 hours, the average being 6½ hours; the splenic flexure in from 7–10 hours, the average being 9 hours. An intermediate point, the middle of the transverse colon, is reached in 8 hours. The beginning of the iliac colon is reached, on the average, in 11 hours. The fæces pass at the same rate through the iliac colon to reach the pelvic colon, where the movement is slower. Beyond this they do not pass till evacuation is about to occur.

It will be seen that if the first part of a meal reaches the cæcum in 4½ hours, and the whole stay in the stomach does not exceed that time, the end of the meal will reach the large intestine in a further 4½ hours. Thus the whole of the unabsorbed residue of a given meal would ordinarily be contained in the large intestine in 9 hours, the advanced part having reached the splenic flexure of the colon. This is confirmed by radioscopic examination (*Hertz*). At the end of 9 hours shadows of a bismuth meal are visible in the cæcum, the ascending and half the transverse colon. Somewhat later, when the descending colon is reached, the shadows of

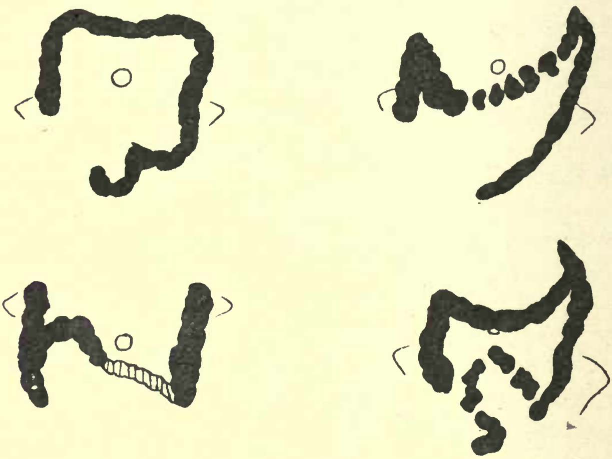


FIG. 41.—Shadows of the normal colon in different healthy subjects. (*Hertz.*)

the cæcum, ascending and half the transverse colon are comparatively faint, owing to the residues of the bismuth meal having been displaced by those of a subsequent ordinary meal. By the time the iliac colon is attained the shadows of the ascending and transverse parts are no longer visible. A faint shadow of the cæcum, however, usually remains.

The onward movement is less active at night. A bismuth meal taken at 10.30 P.M. had reached the hepatic flexure in 12 hours, whereas during the daytime in the same subject only 8 hours were required for the food to travel the same distance.

The nerves supplying the large intestine are furnished from two sources (Fig. 42), an upper set from the lumbar spinal cord, through the sympathetic chain, and a lower set from the sacral cord through the pelvic nerve. The fibres of the former emerge, as a rule, by four of the upper lumbar nerve roots (second to fourth in the cat and rabbit; first to fourth in the dog), enter the lateral chain of the sympathetic, from which they pass by a special strand on each side to the inferior mesenteric ganglion. The latter surrounds the artery of the same name, and in it the fibres have a cell station.

From the inferior mesenteric ganglion the filaments given off, proceed in three directions; some take an ascending course to communicate with the solar plexus and supply the upper part of the descending colon; others, the colonic nerves, proceed along the branches of the corresponding artery to the whole of the descending colon and rectum. Two of the largest branches, the hypogastric nerves, descend, one on each side, to communicate with the pelvic nerves on the sides of the rectum and assist in forming the pelvic plexus.

The lower or sacral autonomic nerves for the rectum and other pelvic viscera are given off from the sacral nerve roots (second and third in the cat and dog, third and fourth in the rabbit), and join to form a single relatively large nerve on each side, which soon divides and intercommunicates with the branches of the hypogastric nerves in the pelvic plexus. Branches proceed from this plexus, forwards to the bladder and urethra, upwards to the descending colon, and downwards to the rectum. Some of the latter twigs come off from the vesical branches.

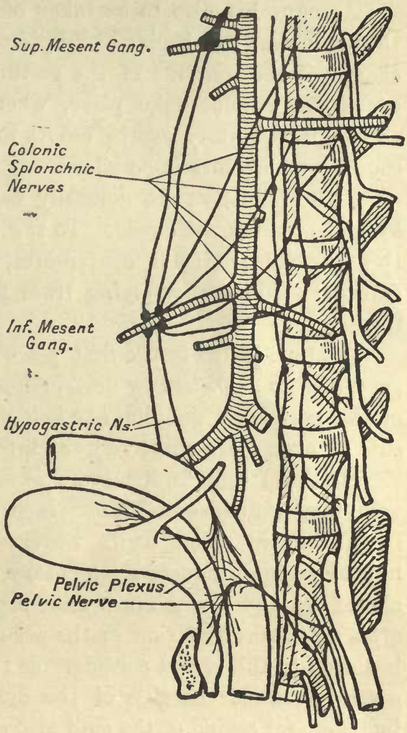


FIG. 42.—Nerve-supply of the rectum.

Stimulation of the nerves of the upper set produces inhibition of the movements of the whole colon and rectum, with relaxation of both muscular coats. The internal sphincter is also inhibited. These effects are best obtained in the isolated intestine (*Starling*) or after section of the pelvic visceral nerves. Langley and Anderson * obtained in the cat and rabbit, together with the above, a motor effect on the muscular coats and also on the internal sphincter. The pelvic visceral nerves were, however, intact.

Excitation of the lower set of nerves causes contraction of both coats of the descending colon and rectum, with increase of peristalsis and discharge of the contents. This effect is apparently limited in most animals to the parts named (*Elliott* and *Barclay-Smith*†); but in the dog (*Starling*), and possibly in the cat, the pelvic nerve is motor to the whole colon. The contraction is also accompanied by descent of the colon, produced

* *Jnl. of. Physiol.*, xviii. (1895). † *Ibid.*, xxxi. (1904).

by shortening of the recto-coccygeus muscle, the extent of the movement varying in different animals. Langley and Anderson obtained, in addition, dilatation of the internal sphincter preceding the contraction. In the dog the descent and shortening involve the whole colon, in the cat the distal half (*Elliott* and *Barclay-Smith*), in the rabbit only the last few centimetres, while in the rat these movements do not occur.

Account has also to be taken of the functions and nerve-supply of the sphincters which play an important *rôle* in the retention and discharge of the contents of the rectum. If either remains contracted, evacuation cannot take place, whereas when both are paralysed or relaxed, involuntary escape occurs and retention of fæces of ordinary consistence becomes impossible.

Both sphincters are normally held in a state of contraction and keep the anal outlet closed. To the maintenance of this tonic closure the internal sphincter contributes, as a rule, the larger share, the external sphincter supplying from 30 to 60 per cent. of the whole force.

The tone is due in the first place to a local mechanism. It is not permanently abolished by destruction of the spinal cord nor by removal of the peripheral ganglia, nor is it wholly annulled by nicotine, which cuts off even more effectively the influence of these ganglia.

The local tone is, however, normally augmented by reflex and by voluntary influences. These reach the sphincters through a centre in the lumbar spinal cord. Severance of the spinal cord above the lumbar region produces a temporary loss of tone, which soon disappears almost completely. A much more severe and lasting disturbance occurs after a destructive lesion or the removal of the lower part of the cord, but even in this case a considerable restoration of tone takes place after several months. Section of the dorsal nerve-roots belonging to the lumbo-sacral region of the cord also causes loss of tone.

The existence of pronounced local tone in the external anal sphincter (a striated and voluntary muscle) is remarkable. The muscle, however, shows peculiarities in several other respects. Thus it does not degenerate nor give the reaction of degeneration when its spinal nerve-supply is destroyed. It is much less affected by curare than other voluntary striped muscles. On excitation of the pudic nerve after the injection of a considerable dose of curare the external sphincter contracts long after the muscles supplied by the sciatic nerve have ceased to react. Again, its contraction in response to stimulation of its nerve is very slow, and characterised by a long latent period. Single induction shocks directly applied to the muscle, however, elicit a short, quick contraction. Lastly, the whole muscle contracts on stimulation of the nerve of one side. The contraction is, however, stronger on the side of excitation, and is prevented from spreading to the opposite side by division of the muscle.

The internal sphincter is furnished with nerves from both the sources which supply the rectum, namely, from the hypogastric and pelvic nerves. Stimulation of the former produces dilatation if the pelvic nerves be cut. In the experiments of Langley and Anderson in which these were intact, stimulation of the upper set gave variable results, namely, both dilatation and contraction or contraction alone. The results of excitation of the pelvic nerve have also varied in the hands of different investigators. Frankl-Hochwart * and Fröhlich obtained constriction of the internal sphincter in the dog, Langley and Anderson dilatation in the rabbit, and dilatation followed by contraction in the cat.

The external sphincter is innervated along a wholly different path, namely, by way of the sacral plexus and internal pudic nerve, the latter giving off the inferior hæmorrhoidal branch to the muscle in the ischio-rectal fossa. The roots along which the fibres emerge from the spinal cord are the first and second sacral in the cat, the second and third in the rabbit. Reflex dilatation and constriction of the anal sphincters can also be obtained by proximal stimulation of the divided sciatic and other nerves. The latter effect is the more easily obtained, and is at once prevented by severance of the pelvic nerves. Similarly reflex dilatation is prevented by division of the hypogastrics. These nerves therefore contain the respective efferent paths.

The normal afferent paths for reflex influences from the rectal mucous membrane appear to lie chiefly in the pelvic nerves. Langley and Anderson found that one-third of the fibres of these nerves are afferent since they remain undegenerated after section of the cauda equina above the level of the second sacral ganglia.

THE ACT OF DEFÆCATION has been investigated in various ways by different observers. As seen by radioscopic examination in the cat (*Cannon*), the emptying of the distal segment of the lower bowel is accomplished in the following way. The propulsive constrictions by which the fæcal nodules are moved into this region give place to a contraction which spreads downwards from the upper limit of the distal segment. The narrowing thus produced is preceded in the cat by a descent of the whole colon, together with a shortening of its pelvic portion, due to contraction of the longitudinal coat and recto-coccygeus muscle. The contents are thus driven into the rectum, to be soon expelled at the anal orifice, abdominal pressure aiding in the evacuation. After evacuation the colon returns, and the contents which remain appear to gradually occupy the whole tube. The proximal colon was never observed by Cannon to be empty, even after purgatives and enemata had been given.

* Pflüger's *Archiv.*, lxxxi. (1900).

Evacuation of the bowel is in the main a reflex act the afferent impulses of which are started by distension of the coats of the rectum and by excitation of its mucous membrane. The act comprises relaxation of the internal and external sphincters, increased peristalsis of the lower colon and of the rectum, together with compression, applied by descent of the diaphragm as an accessory force when necessary. Towards the end of the evacuation the sphincters contract, beginning with the

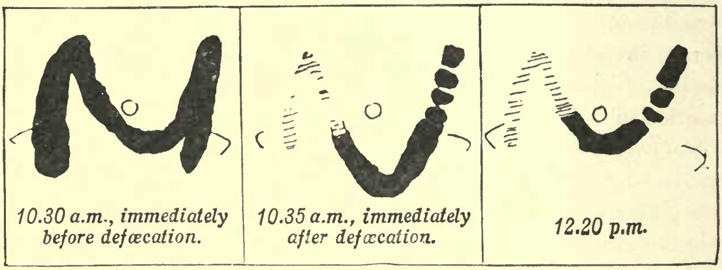


FIG. 43.—Shadows of the colon and rectum before and after normal defæcation. (*Hertz.*)

internal, thereby ensuring complete emptying of the anal canal. The centre through which the reflex is normally mediated is situated in the lumbar enlargement of the spinal cord. The act is possible, however, not only after severance of the spinal cord above the lumbar region, but also after complete removal of its lower part (*Goltz*, *Sherrington*). For some days after the former lesion the performance of the act is temporarily annulled, but soon the tone of the sphincters returns, and intermittent defæcation occurs regularly, though unconsciously, on the accumulation of fæces in the rectum. When the sacral cord is destroyed the sphincters remain patulous for months, and fæces if fluid, escape uncontrolled. Eventually the power of evacuation returns to a considerable degree, the fæces, when not too hard, being expelled periodically at approximately normal intervals. In this case it is supposed that the reflex is discharged through peripheral ganglia. Owing, however, to the loss of sensation in the lower bowel fæces tend to collect unperceived and to become hard through absorption of water. The reflex evoked under these circumstances is less forcible than normal, and often unable, without artificial assistance, to accomplish evacuation of the contents.

In man the whole of the large intestine below the splenic flexure is normally emptied during defæcation. The parts of the lower bowel more immediately concerned are, however, the pelvic colon, the rectum, and the anal canal. The nomenclature here followed is that under which the lower part of the large intestine is subdivided into *iliac* colon, *pelvic* colon, *rectum*, and *anal canal*. The first of these divisions extends from the end of the descending colon at the level of the iliac crest to the inner margin of the psoas muscle. From the latter point the pelvic colon deviates across to the right side and returns again, making a loop which is continued into the rectum opposite the third sacral vertebra. Thence the rectum descends to join the anal canal below the tip of the coccyx.

The fæcal residue which arrives at the splenic flexure is passed through the descending to the pelvic colon, which latter is filled from below up. Its contents are prevented from entering the rectum till immediately before evacuation by tonic constriction of the muscular coat at the pelvi-rectal junction, also by the fact that the two parts of the bowel meet here at an acute angle. The desire to defæcate is probably due to the entry of fæces into the rectum, this latter being accomplished by peristalsis of the colon started by the taking of food. It may also be evoked by expelling contents from the pelvic colon into the rectum through abdominal pressure. The normal intrarectal pressure, due to tonic contraction of the diaphragm and abdominal walls, also to the weight of the abdominal contents, is about 25 mm. Hg. It may on straining be increased to 100–200 mm. Hg. (*Keith*).

LECTURE XII.

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

It is desirable, in the interests of medicine, to employ the methods described in these lectures in experimental investigations into the pathology and therapeutics of the digestive canal—The fact that the beginning of the secretory work of the stomach depends upon a psychic effect harmonises with the experiences of everyday life, namely, that food should be eaten with deliberation and enjoyment—To restore the appetite has been from all ages the endeavour of the physician—The indifference of the modern physician to appetite—Probable causes of this—Curative remedies based upon restoration of appetite—The therapeutic effects of bitters depend upon the excitation of appetite—The usages of the chief meal are in agreement with physiological requirements—Physiological reasons for certain instinctive customs and empirical regulations—An acid reaction of food is of importance—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 harmonise the results of some of the previous investigations 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 its goal, and secure its most useful application, the methods we have applied, and from the same point of view, should be extended 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 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 alimentary canal. In pathological investigations thus carried out the functional diseases of the organs 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. In such experiments therapeutic remedies could also be tested, the whole process of healing and the final result observed, while the conditions of secretory activity during every phase of the healing process could be examined. It can hardly be doubted that scientific, that is to say ideal medicine, can only take its proper position when, in addition to an Experimental Physiology and Pathology, there shall also have 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 experiment in pathology and therapeutics of this kind, namely, on the dog whose vagi nerves were divided in the neck. Other similar cases I can call to mind. One of our dogs with the miniature stomach 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. In the latter it manifested itself by 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, furnished juice in appropriate quantity, at a time when local excitants almost completely failed. It is possible that the deeper layers of the mucous membrane, with the gastric glands, were still healthy, and thus capable of being thrown into activity by central impulses, while the surface of the membrane with the end-apparatus of the centripetal nerves was 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 desires 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 required, because the clinical study of the same subject (notwithstanding the attention devoted to it during the last ten years and the results derived therefrom) has encountered serious difficulties. We must not forget that the stomach-tube, the chief clinical instrument, is less effective 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, and at times impossible, to decide anything.

Hence the exact scientific study of therapeutic questions in this region still belongs to the future. This, however, does not exclude the probability that the later advances of physiology may fruitfully influence the work of the physician. But physiology naturally cannot altogether guide medicine, since the knowledge at its disposal is incomplete, and much more restricted than that of the wide field of clinical reality. But as a recompense for this, physiological knowledge is often able to explain the causation of an illness and the meaning of empirical curative methods otherwise obscure. To employ a remedy the mode of action of which is not clear is a wholly different thing from knowing precisely what is happening. 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 grow into what it must at length ideally 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 admitted that human instinct is the outcome of everyday experience, leading to the unconscious adoption of the most favourable conditions for life, this is particularly the case 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, having regard to the foregoing facts, instinct often brilliantly establishes its case before the tribunal of physiology. Perhaps the old and empirical requirement, that food should be eaten with attention and enjoyment, is of all, the most strongly emphasised and enforced. In every land, special customs designed to distract from the business of the daily life are associated with the act of eating. A suitable time of day is chosen, a company of friends, acquaintances, or comrades assemble. Certain preparations are carried out (in England a change of raiment is usually made, and often a blessing is asked upon the meal by the head 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 add enjoyment—in a word, everything is directed to divert the thoughts from the daily cares of life, and to concentrate them on the repast. From this point of view it is also clear 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 assists in alleviating the pressing strain of daily anxieties. Naturally this highly developed *régime* of eating is only found amongst the intelligent and well-to-do classes, first, because with them mental activity is more developed and the various questions of life more burning; and secondly, because with them also food is served in greater quantity than is required for the wants of the organism. With the poorer classes, where mental activity is less, and muscular activity greater, a constant lack of surplus nourishment ensures a normally keen desire for food, without the adoption of any special regulations or customs. The same considerations explain why the preparation of food is so elaborate in the case of the upper classes and so simple in that of the lower. Further, all the accessories of the meal—foretastes of the actual repast—are obviously designed to awaken the attention and interest, and augment the desire for food. How often do we see a person who begins his customary meal with indifference, afterwards taking it with obvious pleasure, his taste having been awakened by something piquant or, as we say, appetising. It was only necessary to arouse the organs of taste by a strong impulse for their activity to be continued by less powerful excitants. For a person who feels hungry such extra inducements are of course, unnecessary. The quelling of hunger in his case affords sufficient enjoyment of itself. It is often said, and not without reason, 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 only fasted for some hours will not eat everything with equal pleasure that dogs usually eat, but will pick out the food it relishes best. Hence a condiment of some kind is a general requirement, although naturally individual tastes vary.

This short discussion of the habits of different people with regard to the act of eating is sufficient to show that care has always been taken to direct attention to the food, to create an interest in it, and to promote enjoyment of the repast—that is to say, to excite an appetite. Every one knows that a normal, useful food is one eaten with appetite and perceptible enjoyment. Every other form of eating, eating according to prescription or from persuasion, soon becomes worse than useless, and the instinct rebels against it. One of the most frequent requests addressed to the physician is to restore appetite. Medical men of all times and in every land have held it to be a pressing duty, not only to combat the fundamental illnesses of their patients, but also to pay special attention to the restoration of appetite. I believe that in this they have been animated not only by a desire to free their patients from a troublesome symptom, but also by the conviction that a restoration of appetite of itself favours the return of normal digestive conditions. It may be said that physicians have striven to discover remedies for the restoration of appetite just as much as patients have wished to have it restored. Hence we have not a few remedies which are specially named "appetite stimulants." Unfortunately, medical science has latterly deviated from this the correct treatment of the appetite, and that which accords with the real conditions. Current text-books on disorders of digestion pay remarkably little attention to appetite as a symptom or to its special therapy. Only in a few is its importance indicated, and then merely in short parenthetic phrases. On the other hand, one meets 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, such views can only be designated 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 can most certainly and effectively be achieved by measures which restore the appetite. We have already seen that no other excitant of gastric secretion can compare, so far as quantity and quality of the juice are concerned, with the stimulus of a desire for food.

To a certain degree we can understand how contemporary medical science has come to regard so lightly the loss of appetite as a special object for treatment. The experimental method has penetrated more and more into medical science, with the result that many pathological agencies and therapeutic remedies are valued only in so far as they can be verified by laboratory experiments. Naturally a movement in this direction indicates a great advance, but even here progress is not made without mistakes and exaggerations. We must not consider an occurrence to be a mere picture of the imagination because it is not realisable under certain experimental conditions. Often we do not know all the conditions essential for its production, nor do we yet comprehend the connections between all the different functions of life as fully as may be desired. In the pathology and clinical treatment of digestion, assistance was sought in the laboratory, but nothing was there met with relating to appetite, and consequently this factor was overlooked in medical practice. As stated above, the psychic gastric juice obtained merely incidental notice in physiology, and this not even by all authors; and when it was mentioned it was related chiefly as a curiosity. Great importance was assigned, on the other hand, to the mechanical stimulus, the efficiency of which has now been shown to be purely imaginary. These contending factors have at length been assigned their proper places, and if clinical medicine maintains her worthy desire of following out the experimental investigation of her problems, she must in practice accord to appetite its old claim for consideration and treatment.

But notwithstanding the indifference of the physician to appetite in itself, many therapeutic measures are based on its promotion. And here the truth of empiricism has made itself irresistibly felt. When a patient is enjoined to eat sparingly, or when he is restrained from eating without express permission, or again, when he is (for instance, during convalescence) removed from his ordinary surroundings and sent to an establishment where the whole *régime*, 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, to prevent overfilling of a weak stomach, the oft-recurrence of appetite juice, plentiful in quantity and strong in digestive power, is of great importance. I may remind you here of one of our experiments in which food, given in small portions to a dog, 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, therefore, happen that the mucous surface of the stomach, that 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 remarkably shortened, or even wholly absent. A strong psychic excitation, a keen feeling of appetite, may evoke a secretory impulse in the central nervous system and send it unobstructed 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, has already been 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 advantage of removing a patient, the subject of long-continued atonic dyspepsia, from his customary surroundings, is also evident. Take, for example, a brain-worked individual, such as an official holding a responsible position, who cannot for a moment distract his thoughts from his daily work. He eats without observing 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 hurry of great cities. Such systematic disregard of 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 best, 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 in the midst of his old conditions. The fundamental cause of his illness still continues. 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 amongst the so-called intellectual classes of Russians that a proper conception of life generally, is often wanting, and where a wholly unphysiological indifference towards eating often exists. More methodical nations, like the English, have made a species of cult of the process 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 lies between the two extremes.

With the establishment of the fact that mental conditions influence the secretion of gastric juice, the effect of condiments enters upon a new phase. The conclusion had already been reached in an empirical way, that the food should not only consist 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 and learn how the food has been eaten, whether with or without enjoyment. But how often do the people who have charge of the supplies 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 interests of the public, direct attention especially to the feeding of children. If it be granted that the choice of food is determined by a particular taste, and that with this the beginning of digestion is closely linked, it would appear undesirable to accustom children solely to refined and unvarying gustatory sensations. This would in all likelihood interfere with their powers of adaptation to other conditions in after life.

The question of the therapeutic influence of so-called "bitters" appears to me to bear 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 did not justify their old and valued reputation; many of them were unable, on being directly introduced into the stomach, to produce a flow of gastric juice. In consequence, they became greatly discredited in the eyes of clinicians, numbers of whom 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 did not correspond with the actual state of affairs. The whole question of the therapeutic importance of bitters acquires a different significance when we link it with another, namely, 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 become, 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 the observation had been overlooked 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 effects 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 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 arouse no desire for eating, or 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 facilitate the awakening of pleasant ones. In either case there is no longer indifference; there is a foundation upon which an appetite for a particular food may be awakened, and in this a general physiological law is illustrated. The light appears brighter after darkness, a sound louder after silence, the enjoyment of vigorous health more keen after illness, and so on. This explanation of the appetising effect of bitters starting in the mouth, does not exclude the possibility of some similar influence coming 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 also 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 a keen desire 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, in the production of a certain psychic influence, which indirectly promotes a physiological secretory activity. The same probably applies to other substances, such as condiments. In any case, whether our explanation correspond to the reality 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 also have the assurance that the investigation has been correctly carried out; that is to say, that it has dealt exactly with the point at issue. 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, simply 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 corroborate our physiological deductions. After a *hors d'œuvre*, perhaps with a liqueur of brandy (especially customary in Russia), both of which are designed to awaken the appetite, the repast proper usually begins with something hot, generally a meat broth or soup of one or other kind. After this come the really nourishing foods—flesh meats 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 for 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. Thus human instinct has made provisions for the digestion of the chief food. 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, *kvas* * serves in this way with the Russian populace, while in Germany, where the price of meat is high, different kinds of soups are used, made of water mixed with flour, bread, &c. It has also 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 but very little; consequently, the meal must in every case begin with a strong chemical excitant—for example, with a solution of the extractives of meat. Otherwise solid foods, particularly if they do not consist of flesh, remain long in the stomach without any digestion whatever. It is 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 series, according to the influence of the chemical excitants, the following would be the order: first, the preparations of flesh, such as meat juice and the like; secondly, milk; thirdly, water.

The usual mode of terminating the repast is also, from the physiological standpoint, quite rational. The chief meal generally ends with something sweet, and everybody knows that sweets are 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 that have to 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. For example, one of the commonest seasoning substances is vinegar, which figures in a number of sauces and relishes. Further, many kinds of wine have a somewhat acid taste. In Russia, *kvas*, especially in the acid form, is consumed in

* *Kvas* 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

large 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 likewise, this instinct is 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 as well as 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 solvent action upon all the constituents of the food. In this way, where too little gastric juice is present, acids may either assist digestion in the stomach, or where it is wholly absent bring about vicarious digestion by the pancreas. It is easy, therefore, to understand why the Russian peasant enjoys his *kvas* with bread. The enormous quantity of starch which he consumes, either as bread or porridge, demands a greater activity of the pancreatic gland, and this is directly promoted by the acid. Further, in certain affections of the stomach, with loss of appetite, we make use of acids, both from instinct as well as under medical advice, 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 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 dictates 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 can now 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 protein substances; consequently, a combination of fat and protein-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 protein. Fat alone cannot by any means be counted as a heavy food, as may be seen from the large quantities of lard consumed with impunity in certain districts of Russia. This also is comprehensible, since the inhibitory influence of the fat does not in this case prevent the digestion of any other food-stuff, and is conducive to the assimilation of the fat itself. There is no struggle 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 in moderate amount, or fat as emulsion, is prescribed. And here medicine has brought to its aid, on empirical grounds, the restraining action of fat which has been so strikingly seen in our experiments.

Amongst the various articles of human food, milk takes a special position. 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. Milk, when compared with other foods in nitrogen equivalents, requires, as we already know, the weakest gastric juice and the smallest quantity of pancreatic fluid, consequently the secretory activity necessary for its assimilation is much less than for any other food-stuff. In addition, milk possesses a further important property. When introduced unobserved into the stomach of an animal it causes a secretion both from the stomach glands and also 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, whether the milk be brought unnoticed into the stomach or be given 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, I think, be accepted that milk excites not only a really effective, but also a very economic secretion, and also that the appetite is unable to stimulate this secretion into a more active or abundant flow.

The question 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 on the one hand the fat 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 belongs 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 is found that the increase during the first seven to ten hours after the milk (compared with the excretion beforehand) amounts only to from 12 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 utilised, 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. Riazantsev*); consequently, in the case of milk a much larger fraction of its nitrogen is free for use by the organism as a whole (irrespective of the organs of digestion) than with any other kind of food. In other words, the price which the organism pays in digestive work for the nitrogen of milk is much less than for other foods. How admirably, therefore, the food prepared by nature subserves its purpose 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 ousted 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 amount of 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. We learn in this way how much nutrient material was contained in the food, but the question of its digestibility remains as obscure as before. The experiment does not teach us how great an effort it has cost the alimentary canal to extract all the nourishment from the food. Neither can artificial digestion experiments settle the question of digestibility. Those in which food is normally ingested are quite different from those in the test-tube; in the latter we have to deal with only one juice, and not at all with the interaction of different juices and different food constituents. That we must here, as a matter of fact, make a distinction, is clear from the observations of Dr. Walther in our laboratory. Fibrin, which is regarded by all as the most easily digested protein, 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, in regard both to the quantity and the 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 the 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 organs. From this point of view those materials must be considered as less nourishing and less digestible which are in large part used up to make good the expenditure on the part of the alimentary canal entailed by their digestion; that is to say, 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 little doubt. But how do they act? 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 follow that we know the mechanism by which it occurs, and although medicine is liberal enough and comprehensive enough to make free use of empiricism in practice, yet it often thinks in narrow grooves when attempting the explanation of facts. It frequently tries to explain complicated healing processes in the simplest way, on supposed physiological data. And it is true that the present case affords an example of customary medical reasoning: the alkalies act favourably in digestive disturbances; therefore, they are succagogues. Naturally the stomach, after the administration 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. The effect is due to the fact of recovery, and not to 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 exerted by these salts. Indeed, their effects both on the stomach and pancreas proved in our hands to be inhibitory. 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 had survived the performance, one after another, 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 influence of this otherwise very effective 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. As regards 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 a particular 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 from the effects of activity, proceed best during rest. In the normal course of events, after a period of active work follows a pause, during which the silent work of restoration is accomplished. When, therefore, a remedy effectively restrains the excessive work of a diseased organ, it may silently 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. This 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 also followed in which mention is 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. Khizhin*).

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 most injurious 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 physiological experiment had no answer to the question. But the foregoing facts, it appears to me, contribute towards clearing up the situation. Every food determines a certain amount of digestive work, and when a given dietary is long continued, definite and fixed types of gland activity are set up which can be altered but slowly and with difficulty. 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 : one often hears of cases of sudden and unaccountable digestive disturbances. From the standpoint of modern physiology these might be explained by an activity of the secreto-inhibitory apparatus, which from some cause or other has been excessively and abnormally stimulated. In any case this mechanism is now a factor of which the physician has to take due cognisance.

LECTURE XIII.

THE PATHOLOGY AND EXPERIMENTAL THERAPEUTICS OF DIGESTION—THE METHOD OF EXPERIMENT IS THE ONLY ONE WHICH ADEQUATELY MEETS THE REQUIREMENTS OF MEDICAL SCIENCE TO-DAY.

The pathology of the stomach as studied by experimental methods—The protection of the mucous membrane of the stomach—Physiological function of the epithelium—Experimental production of gastric asthenia and of a condition the converse 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—Survival of vagotomised dogs—Treatment of gastric hyper-secretion by alkalies—Medicine and biological science—Necessity for experimental investigation—Experimental pharmacology a branch of physiology—A science of experimental therapeutics required—Laboratory and other needs of experimental medicine.

GENTLEMEN,—I invite your attention to-day to matters bearing upon the intimate relationships which exist between the various branches of the science of medicine.

The animals employed in our investigations, 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 observation. At first such accidents perturbed 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 upon the organism of an unusual condition, or, more correctly, an ordinary condition unusually intensified? Suppose one receives a mechanical shock or becomes exposed to the effects of great cold or heat, or to an attack of pathogenic micro-organisms, 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, exist within it, and share in the maintenance of the general equilibrium of the whole living organism. The means of defence are, consequently, worthy objects for physiological investigation. But physiology learns of them only through illness; at other times their work is not seen. The struggle in question leads either to a repulse of the enemy, when the defence ceases, or to a conquest, which brings as a result the injury or destruction of one or other part of the body. But if an organ be destroyed, its function naturally ceases. Have we not here, therefore, 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 technique? 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 to discover functions previously hidden. If, however, the injury be not limited to a single organ, but spreads wider owing to functional relationships with other 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 the value of such methods of investigation, and to logically apply them to the study of vital phenomena. The Physiologist is here, therefore, in his appropriate place.

The method of experiment 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 data which appear to me 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 observed, but is invaluable in the analysis of a pathological condition. When pathogenic agencies (such as great heat or cold, strong chemical reagents of various kinds, &c.) were applied to 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 produced by 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 else continued its ordinary course in the remainder 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, since it is always empty, no stimulant takes origin in it which reacts either on the large stomach or on the intestine. An exception is to be made, however, of the short interval when the abnormal 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, on the other hand, the large stomach is attacked by noxious agencies we are able not only to see the reflex effects in the small cavity, but also to observe the disturbance provoked by a general disorder of digestive activity. In this way it is possible to investigate separately 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 potent reagents 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 copious, indeed, in many cases an enormous secretion of mucus. (*Experiments of Dr. Savriev.*) One might think that this indicated a serious pathological condition, an acute mucous catarrh. But is it at all 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 repeat, is it a morbid state? Often, after the lapse of an hour or two, a moderate secretion of mucus, which immediately appeared upon the application of the irritating substance, had wholly exhausted itself; or, again, an enormous flow, which on the day of the experiment completely suppressed the normal secretion of gastric juice, may, to one's utter astonishment, have disappeared next day without leaving a trace behind. The contrast between the intensity of the phenomenon and its short duration is really striking. One cannot help thinking that in these cases a morbid condition had not as yet been established, but rather that the pathogenic influences had been successfully encountered and conquered before one's 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 expels it 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 in question stimulate therefore the one kind of epithelium only, leaving the other unaffected. We have already seen an analogous differentiation of stimulating effect 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, as it appears to me, an unusually weighty fact before us—namely, that extraordinary stimuli which come in as pathogenic agencies, serve at the same time as specific excitants of the protective mechanisms of the organism—namely, of those which are adapted to overcome injurious effects. I believe that this applies to all diseases, and that it gives a general indication of the adaptive mechanisms by which the animal body is enabled to encounter pathogenic influences. Indeed, the intricate process of normal life, with all its power of adaptation, is unceasingly dependent upon the specific excitability of one or other apparatus.

Naturally the effects of the substances named, if of sufficient strength, may also involve 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, varying greatly in its details, according to the nature of the pathogenic cause, but which for the most part assumes a phasic character. By such means we succeeded in establishing different pathological conditions in the peptic glands, and, at the same time, obtained 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 weakness and irritability of the peptic glands. (*Expmts. of Dr. Savriev.*) 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 of flesh (150 grms.).

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 a special and unusual character. The quantity for the first hour markedly exceeded the normal ; but in the second hour, an exceptionally steep decline to an unusually low value 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 is at once clear. Obviously it cannot be regarded as merely a specific 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 was first established by experiment in my laboratory, notwithstanding the infinity of cases where it might previously have been observed in the hospital. It is a striking confirmation of the belief that, in the analysis of morbid phenomena, clinical observation has to contend with much greater difficulties than 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-cells have become much more inert, more difficult to set in motion, and more tardy in action when they first begin, but once set fully going, they do more work for the same amount of stimulation than under normal conditions. We have, therefore, in all probability, two typical conditions of the living substances when thrown out of equilibrium, 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. Volkovitch.*) 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. Khizhin. The normal secretion after bread is characterised by a copious flow during the first hour, then a great fall in the second, to about half the initial value. As in previous investigations further inquiry revealed that there were two different periods of secretion sharply separated from each other, namely, a period of free psychic flow centrally excited, and one of much weaker secretion chemically excited by peripheral reflex. 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 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 of peripheral origin, it must be taken to prove that the augmented excitability of the secretory apparatus at this stage, has originated in the mucous membrane, possibly either in the centripetal nerves or in their nerve-endings. Here, then, are indications pointing to the special seat of origin of the disorder, which, so far as I know, have not hitherto been discovered or defined in the clinical investigation of the disease.

In the occasional illnesses of our experiment animals we have frequently observed an augmented or a diminished activity of the digestive glands as contrasted with the normal. It has often occurred to us that these converse conditions represented different phases of one and the same affection. But which 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 appears to be of a reflex nervous nature. It is due to the influence of the inhibitory nervous system which is thrown into activity by the unusual degree of stimulation. When, for instance, ice-cold water, or a solution of nitrate of silver, is poured into the large stomach (*experiments of Dr. Soborov*), the secretion subsequently produced by the effect of 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 at no time come into direct contact with the injurious substance. The thought suggested itself that, as soon as the stomach encounters a violent stimulus, the activity of the peptic glands is at once inhibited by means of a special reflex, the object of which is to protect the deep-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 to pour from the small cavity. Conversely, by acting on the small, alcohol is able to set up an abundant secretion in the large. (*Experiments of Dr. Savriev.*)

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. Soborov.*) 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 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, is 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 became 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 secretion 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 into 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 secretion from both cavities, which, in such cases continues for some time. Or lastly, towards the end of 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 two 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 that we have mastered, in point of fact, the whole problem under investigation. Thus the necessity for an EXPERIMENTAL THERAPEUTICS spontaneously arises, apart from the question of 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 illustration 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 is due to modern bacteriology of having, by the experimental method, united the whole of medicine. 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 capabilities, 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 practical knowledge, and therefore in every way 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, after the sudden cutting-out of this most important secretory and motor nerve, almost every trace of digestive action disappears from the stomach 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. I. P. Pavlov and Dr. P. E. Katshkovski.*)

We may return once more to digestion. In a series of dogs with well-marked hypersecretion, arising from illness occurring spontaneously, or produced intentionally, we have used alkalies (a ½ per cent. solution of sodium bicarbonate) as a form 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 hospital. In all the cases observed by us (*Prof. I. P. Pavlov* and *Dr. J. C. Soborov*) 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, 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.

We have already taken up the question of how the individual kinds

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

of food effect the condition of hypersecretion (*Dr. Soborov*). These experiments are now being carefully pushed forward. Judging from the material at 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 hyper-secretion.

We have further endeavoured to come to the aid of an enfeebled 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. Savriev.*) We based this upon earlier facts (*experiments of Prof. I. P. Pavlov*), 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 the secretory cells abstracting water from the blood. In certain circumstances the blood opposes a considerable resistance to this abstraction. If sufficient water be not present, the cells cannot 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, endeavours on the contrary to expel. Our experiments have confirmed this hypothesis, but they are not as yet concluded.

Let us now turn to MEDICINE. In spite of the extraordinary complexity of biological processes when compared with other natural phenomena, in spite of the difficulty of bringing them under control by determining their proper causal relationships, MEDICINE from the beginning has been destined by the inevitable ordinances of Life to achieve mastery over biological things, and this even before such things became matters for scientific investigation.

Moreover, Medicine has, in large measure, accomplished what was expected of her. Her task seemed endlessly large and hopelessly complex, but yet it is in no small part accomplished. From amongst the countless number of possible solutions of problems set to her, she has fortunately arrived at many correct ones. This unexpected result has only been made possible by the co-operation of two conditions. These are, that man from the earliest times has constantly and passionately striven to maintain life and health; and, secondly, that in this search for health numerous individuals—indeed, I might say all mankind—have taken part. But if the present achievements of medicine seem remarkable, it cannot be doubted that they are only very small in comparison with what must ultimately be accomplished. These future advances will not be attained, however, by merely calling in the results of increased knowledge in different branches of natural science to assist in 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 thereby imposed, she is limited in the majority of cases to one method of investigation, namely, *observation;* while the other method, *experiment*, dare not be employed by her except with great precaution, and within relatively narrow limits. Observation is a means, however, which only suffices for the investigation of simpler phenomena. The more complicated they 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 different phenomena occurring side by side in the animal organism, between which there is in one case an essential connection, in another only an accidental association. The true character of this connection can only be *guessed* by the investigator who observes: he has to choose between a number of possible hypotheses. Experiment, on the contrary, grapples with the problem, and searches for the solution; permits now one condition, now another, to come into play, thus learning, by artificial but simplified combinations, what the real explanation is. In other words, observation collects what is offered by nature; experiment wrests from nature what is sought. The power of biological research is immense. It has created in the short space of seventy or eighty years almost the whole of what must be described as the very comprehensive subject of the physiology of the animal body. If an educated man, not otherwise intimately acquainted with biological science, were to attend an ordinary, carefully conducted course of experiments in animal physiology, such as is carried out by medical students, he could not fail to be astounded at the mastery which modern science has acquired in regard to a knowledge of the complicated animal organism. And his astonishment would further increase were he to learn that this power has been acquired not in thousands or hundreds of years, but in a few decades.

The method of experiment likewise extends its triumphant influence into the subject of pathology, and also into that of therapeutics. There is no reason why this influence should become less. To me it appears that the most remarkable advance of modern medicine lies in the fact that it has been made possible to submit all its important fields to experimental research. This revolution has, for the most part, been accomplished by bacteriology. Although for some time before the evolution of the latter subject, pathology had come into the laboratory, yet the investigation of the subject was greatly restricted for want of knowledge of such important factors 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. It is now possible to investigate experimentally almost every pathological phenomenon in the laboratory.

Although clinical medicine had clearly distinguished the different types of diseases, and had given an almost perfect morphology of pathological conditions, while at the same time macroscopic and microscopic anatomy (associated with clinical investigation), had collected an enormous amount of information concerning the subtler processes of disease, and still continues to do so, yet the possibility of a complete analysis of the whole course of a malady from its inception to its cure —of a thorough knowledge of all its processes—was first attained by the method of experiment. Pathological anatomy provided 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 can distinguish in the organism the defensive and reparative or compensatory arrangements from the lesion itself. It is laboratory experiment alone that can unravel the connection between them and settle which is the primary and which the secondary lesion arising from it. It is by such knowledge only that appropriate and effective assistance can be rendered to the diseased organism. Then, and not till then, will our interference be attended by no evil results, but on the contrary always bring help.

Again, it is only by experiment that we can ultimately discover the remote cause of disease and estimate its importance, since in it we always begin with a causal factor intentionally set in operation. 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 intelligently combat the etiological factor when the cause is known. On the other hand, and what is still more important, it is only by virtue of this knowledge that one can forestall the cause of disease, and render it harmless before it has effected an entry 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 help 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 studies, it usually appears, either as an appendix to pathological anatomy, or is lost in the subject of general pathology. But the methods of pathological anatomy and of experimental pathology are too different from each other to be combined under one representative, and in one laboratory, at least in a manner 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 subject to which we now 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 mode of statement. 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.

To turn now to Experimental Pharmacology: one can readily conceive himself in the difficult position of the physician who, in his efforts to combat disease, or in his use of one or other remedy against a particular symptom, often does not know how the remedy acts in the organism, or how it aids in any given case. How insecure, therefore, and indefinite must be his interposition, and how much room for all sorts of chance occurrences! Hence, the endeavours of the clinician to understand the mode of action of his remedies are easily 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 own purely theoretical aims. Against this in itself no objection can be raised. The connection, however, between 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 design of Pharmacology, and even still finds expression in the name of the science, yet in many cases it has grown very lax and almost nominal. Thus in the ordinary text-book, after the author has dealt with the physiological action of a particular 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 dissatisfied with modern pharmacology. In the mutual interests of both the experimenter and the practical physician, pharmacology should be supplemented by an experimental *therapeutics.* It would then deal not alone with the healthy, but also with the diseased animal body. It would then study not alone the action in general of the different remedies, but also their healing influence on the diseased organism. It would then in its own interests expand and deepen our knowledge of the reaction of the organism to chemical agencies, and also, at the same time, our knowledge of the organism itself. In the interests of the practical physician, it would 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 hitherto in the difficulty of procuring the requisite diseased animals in the laboratory. This difficulty is now, in 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 delusion about drugs 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, or perhaps could not be, carried out in the right way, owing to the animals being healthy. In the teaching plan of experimental therapeutics the experimental investigation of remedial measures, other than the mere administration of chemically active substances, should also find a place. At present, in the comprehensive programme of medical studies, they obtain no proper recognition.

One may hope, not without reason, that we shall 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 rest assured that the experimenter can 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 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 just as little subjected to experiment as elsewhere. Further, special clinical pharmacology would have no claim to pre-eminence in the systematic and effective use of therapeutic remedies, since the highest competence is aimed at by every clinical teacher. Thus without any special good to the science itself, either the experimenter would be lost in the clinician, or the clinician in the experimenter. A lasting and stable combination of these separate activities is scarcely to be obtained 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 compass a conscious and purposive healing art. In proof of this we have an example 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.

How far I have succeeded in convincing you of the extreme importance of experiment for practical medicine, and in stimulating you to real activity, is a question which creates profound emotion in my mind. 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 a very 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 well 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 in the laboratory the problems 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. That is a matter greatly to their 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 the worker to devote all his 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 method and conception nothing else than branches of physiology) should be given the most favourable conditions and the most independent positions 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 from the fostering care which science requires: 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 those who in life are called upon to bear a truly excessive burden, and to solve problems which often 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 average of mankind, and this, after all, is what must engage our attention. Think of one who mentally grasps the unfathomable depths of the problem before him, and inwardly nurses a bitter feeling of impotence. Give him everything within your power, and it will not be too much.

And yet, gentlemen, our beautiful hospital buildings are but tributes which we pay to human suffering and helplessness. How much more, then, may the science in which man finds his dignity and pride aspire to palaces, wherein he can cultivate his powers and develop the forces of his genius. Such palaces are 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, the same cannot by any means be said of our laboratories, with one well-known exception, the Institute for Experimental Medicine, which owes its existence to the noble ideas and enlightened benevolence of Prince Alexander of Oldenburg. In many other scientific institutes a great want of accommodation is felt, which is strikingly accentuated by the extraordinary increase in the number of problems biological experiment has to solve. In addition to series of special rooms for the different experiments, a number of sufficiently large and suitably furnished compartments are now absolutely necessary for the different animals under experiment. I have at present, in the laboratory of the Institute for Experimental Medicine, about thirty dogs on which the physiology of digestion has been or is being studied, all of 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 reliability 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 encourages the undertaking and favours the solution of new problems. But if 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 at first no intention of instituting conditions of disease; I operated solely for physiological purposes, and kept my animals alive for months or years. But how many, and what far-reaching pathological processes have, under these circumstances, developed before my eyes! I have seen, in connection with disturbance of the functions of the liver, an enormous ascites develop; at another time an ascending paralysis of the central nervous system; in another case, a general fragility of the blood vessels, and so on.

Biological experiment, to come back to it, requires, therefore, institutes, costing hundreds of thousands of roubles. With us, however, this form of experiment has often been most bitterly opposed. Private individuals and public authorities willingly subscribe 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 projects. Experiments on animals are often depicted in the most malicious way as animal torture. The lofty idea underlying them is confused with the regrettable but unavoidable outward appearance. Investigators themselves, who pass their whole time in the laboratory, and have no regular intercourse with the outside world, cannot influence public opinion on the question of 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 the people, and come into contact with the highest and lowest in the land. You are linked with them by the most intimate ties. You actively share in their greatest joys, and their keenest sorrows. When you speak in defence of a science which devotes itself to the life and health of mankind, your words will be listened to. It lies, therefore, with you to teach the public, that experiments upon animals are unavoidably necessary for the advancement of medicine, and of the greatest conceivable advantage to it. You must make it understood that the greater the precision attained by experiments upon animals, the more certainly will patients be cured, and the less frequently will they have to submit to a trial of remedies, with possibly serious consequences. Take, for example, the following instance. If more had been learned of the functions of the thyroid body by experiment upon animals, the early unhappy results of its removal from patients, the subjects of goitre, would not have occurred. There followed, as you know, an incurable condition of cretinism.

Let it be known to the public that modern medicine has passed the stage of the gruesome experiment upon man himself. It is admitted that medicine in its choice of therapeutic remedies, drew largely upon experience acquired by their popular application. But such 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 entirely to out-of-the-way villages) patients succumb to the revolting torture of inappropriate healing experiments carried out by some quack. And yet do 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 if large and specially equipped apartments are required for experiments, these are naturally performed not only in the interests of scientific research, but also for 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, is three and a half times greater than the income of the physiological laboratory of such a colossal medical institute as the Military Medical Academy of St. Petersburg. But it only approximates the average for the corresponding institutes of the German

Universities. How is it possible, therefore, in view of present-day requirements, for an experimental department to develop an adequately 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 its students a course of practical physiology? And yet a direct acquaintance with the materials of physiology, and a training in physiological thought, are 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, 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 research 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, under the ægis of a great name, the name of the clinician whose memory we celebrate, the work of our laboratory, its fundamental idea, and my own views with regard to the relationship of experiment to medicine. Had I a right to do this? I should not have done so had I not been convinced of that right. I had the honour of being associated for ten years with the work of the departed clinician so far as it concerned his laboratory. More than ten other years have now fled since the death of S. P. Botkin, and yet his memory lives with us all. If he was anything he was a clinician who astonished us all by his rare gift of recognising a disease, and of finding the best remedy for it. On the patients his personality produced a really magic influence; a word from him, or even the mere fact of his visit often had an effect. How frequently have I heard it confessed by his clinical pupils, that the same prescription which had worked wonders in the hands of the master had been, in apparently identical cases, without effect in their own. 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 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 value of experiment by the 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 imparted will no doubt be welcomed by the practical physician. He will often find in our physiological facts an explanation of pathological phenomena, and by knowing the true state of affairs will be led to employ effective remedial measures. Physicians will, however, secure further advantage to themselves if they impart to the physiologist how, in their opinion, the explanations may need readjustment; and still more if they call attention to new phenomena in the subject of digestion which may have already appeared in the wide field of clinical observation, but which have not yet come into the view of the physiologist. I am convinced that it is by frequent 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 safely reached.

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