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Physiology of Digestion

It is not accidental that all phenomena of human life are dominated by the search for daily bread - the oldest link connecting all living things, man included, with the surrounding nature. Food finding its way into the organism where it undergoes certain changes - is decomposed, enters into new combinations and again dissociates - represents the process of life in all its fullness, from such elementary physical properties of the organism as weight, inertia, etc., all the way to the highest manifestations of human nature. Precise knowledge of what happens to the food entering the organism must be the subject of ideal physiology, the physiology of the future. Present-day physiology can but engage in the continuous accumulation of material for the achievement of this distant aim.

The first stage through which the food substances introduced from without must pass, is the digestive canal; the first vital action on these substances, or to be more exact and objective, their first participation in life, in its process, constitutes what we call the *digestion*.

The digestive canal represents a tube passing through the entire organism and communicating with the external world, i.e. as it were the external surface of the body, but turned inwards and thus hidden in the organism.

The physiologist who succeeds in penetrating deeper and deeper into the digestive canal becomes convinced that it consists of a number of chemical laboratories equipped with various mechanical devices.

The mechanical apparatuses are formed by muscular tissue that is a constituent part of the wall of the digestive canal. They either take care of the passage of the components of food from one laboratory to another, or detain them for a certain time in a given laboratory or, finally, expel them when they prove harmful to the organism; moreover, they participate in the mechanical processing of the food, aiding the chemical action on it by thorough mixing, etc.

A special, so-called glandular tissue which is either also a constituent part of the wall of the digestive canal, or lies beyond it in the shape of separate masses and communicates with it by means of tubes, produces chemical reagents, the so-called digestive juices that flow into separate segments of the digestive tract. The reagents are, on the one hand, aqueous solutions of such well-known chemical substances as hydrochloric acid, soda, etc., on the other hand, however, substances which are found only in a living organism and which break up the main components of food (proteins, carbohydrates, and fats) with such ease (so rapidly, at such a low temperature, and in such small quantities) as no other chemically well-studied substance could perform. These substances which act in vitro just as well as in the digestive canal, and which, therefore, are objects of chemical investigation entirely subject to laws, have so far, however, defied chemical analysis. As is known, they are called ferments.

From this general description of the digestive process I shall turn to facts relating to this process established by me and by the laboratory of which I am in charge. In doing so I deem it my duty to recall with profound gratitude my numerous laboratory co-workers.

It is perfectly clear that successful study of the digestive process, as of any other function of the organism, depends to a considerable degree on whether we succeed in finding the nearest and most convenient point of view on the process under observation and in removing all intervening processes between the phenomena under observation and the observer.

In order to investigate the production of secretion in the big digestive glands, that communicate with the digestive canal only by means of tubes, we cut from the wall of the digestive canal small pieces, in the centre of which were the normal openings of the secretory ducts; we then closed the opening in the wall of the canal by stitching, and the excised pieces were sutured to the corresponding site on the surface of the skin with the openings of the secretory ducts to the outside. Thanks to this procedure the juice was diverted from the digestive canal and could be collected in special vessels. In order to collect the juice produced by those microscopic glands that are located directly in the wall of the digestive canal, already since a long time large pieces were cut out from the wall of the digestive canal and artificial pouches with openings to the outside were made; the defect in the digestive canal, of course, was closed by stitching. In the case of the stomach, however, the nerves of the glandular cells were always severed when constructing an artificially isolated pouch and this, naturally, affected the normal work of the stomach. Taking into account the more delicate anatomical relations, we modified the operation in such a way that the normal nervous paths were left fully intact when making the isolated stomach-wall pouch.

Finally, as the digestive canal is a complex system, a series of separate chemical laboratories, I cut the connections between them in order to investigate the course of phenomena in each particular laboratory; thus I resolved the digestive canal into several separate parts. This, of course, necessitated laying short and convenient passage-ways from the outside into each separate laboratory. For this purpose metal tubes have long been in use; these coalesce with the skin in artificial body openings, and during the intervals between the experiments they can be sealed by means of plugs.

In this way we often had to perform very minute operations, sometimes several of them on one and the same animal. It goes without saying that the desire to accomplish the task with more confidence, to avoid wasting time and labour, and to spare our experimental animals as much as possible, made us strictly observe all the precautions taken by surgeons in respect to their patients. Here, too, we had to apply appropriate anaesthesia, observe scrupulous cleanliness during the operation, provide clean dwellings after the operation, and take thorough care of the wounds. But these measures did not suffice. After remaking the animal's organism in accordance with our design, which naturally caused more or less damage to the experimental animal, we had to find a modus vivendi for it that would ensure an absolutely normal and long life. Only by observing this condition would the results of our work be regarded as fully conclusive and as having elucidated the normal course of the phenomena. We succeeded thanks to our correct appraisal of the changes evoked in the organism, and thanks to the expedient measures taken by us; our healthy and happy animals did their laboratory work with real gusto; they always eagerly moved from their cages to the laboratory and readily jumped onto the tables where our experiments and observations were conducted. Believe me, I am not exaggerating. Thanks to our present surgical methods in physiology we can demonstrate at any time almost all phenomena of digestion without the loss of even a single drop of blood, without a single scream from the animal undergoing the experiment. At the same time this is an extremely important practical application of the power of human knowledge, which may also be of immediate use to man, who, due to the implacable fortuities of life, is often mutilated in similar, though more varied ways.

In our observations on dogs, we soon noticed the following fundamental fact: the kind of substances getting into the digestive canal from the external world, i.e. whether edible or inedible, dry or liquid, as well as the composition of the food determined on the onset or else absence of the work of the digestive glands, the peculiarities of their functioning in the former case, the amount of reagents produced by them, and their condition. This can be shown by a number of examples. Take, for instance, the production of saliva by the mucous salivary glands. With each meal, when edible substances find their way into the oral cavity, thick and viscous saliva containing much mucus flows out of these glands. With the introduction into the animal's mouth of substances that it finds repugnant, such as salt, acid, mustard, etc., the saliva may flow in the same quantity as in the first case, but now its quality is quite different - it is fluid and watery. If the dog is given now meat, then ordinary bread, other conditions being equal, the secretion of saliva in the second case will be more abundant than in the first. Similarly, of the substances for which the animal has a distaste some, for example chemical irritants like acid, alkali, etc., evoke a more profuse secretion of saliva than other, chemically indifferent substances, like bitters; consequently here, too, different activity of the salivary glands is observed. The gastric glands react in the same way; they secrete their juice now in larger, now in smaller quantities, now of a higher and now of a lower acidity and content of protein-dissolving ferment, so-called pepsin. Bread evokes the secretion of gastric juice with the highest ferment content, but of lowest acidity; milk evokes the minimum ferment content, while meat evokes the maximum acid content. For a certain quantity of protein if provided in the form of bread, the glands produce from two to four times as much as when provided in the form of meat or milk.

However, the diversity of the work of the gastric glands is not confined to the above-mentioned phenomena; it is manifested also in peculiar fluctuations in the quantity and quality of the reagent during the period of the functioning of the glands following the introduction of one or another food substance.

But that will suffice. I should only abuse your attention by giving an exposition of all the facts collected by us in this field. I shall merely mention that we observed similar correlations in relation to the other glands of the digestive tract.

Now it may further be asked: what does this changeability in the work of the glands signify? In reply we shall revert to the phenomenon of salivary secretion. Edible substances evoke the secretion of thick, concentrated saliva. Why? The answer, obviously, is that this enables the mass of food to pass smoothly through the tube leading from the mouth into the stomach. Under the action of certain substances disagreeable to the dog the same glands secrete fluid saliva. What purpose does the saliva serve in such cases? Apparently, either to dilute these substances and thereby weaken their chemically irritating action, or, as we know from our own experience, to cleanse the mouth from such substances. In this case exclusively water, not mucus, is required, and water is actually secreted.

As we have seen, bread, and especially dry bread, evokes secretion of considerably larger quantities of saliva than meat. This, too, is perfectly understandable: the eating of dry bread requires saliva, firstly, to dissolve the components of the bread and so make it possible to recognize its taste (something utterly inedible might have gotten into the mouth), and secondly, to soften the hard and dry bread, otherwise it would go down with difficulty and could even cause injury to the walls of the oesophagus while moving from the mouth into the stomach.

The relations inside the stomach are exactly the same. The bread protein induces secretion of more protein ferment than the protein of milk or meat, and a corresponding phenomenon is observed in the test tube: protein of meat and milk is broken up more easily by the protein ferment than vegetable protein.

Here again I could cite numerous additional examples of similar purposeful relationships between the work of the digestive glands and the properties of the substances entering the digestive tract (but this I shall do on a future occasion). There is nothing surprising at all in this phenomenon; and other relations would not be expected. It is clear to all that the animal organism is a highly complex system consisting of an almost infinite series of parts connected both with one another and, as a total complex, with the surrounding world, with which it is in a state of equilibrium. The equilibrium of this system, as of any other system, is a condition for its existence. And if in certain cases we are unable to disclose the purposeful relations in this system, the reason is that we lack knowledge; it does not mean at all that these relations are absent in the system during its continual existence.

Now we shall pass to a further question which arises from what has been said above: how is this equilibrium effected? Why is it that the glands produce and secrete in the digestive tract the very reagents needed for the successful treatment of the respective object? Apparently, it should be assumed that in some way certain properties of the object act on the gland, evoke in it a specific reaction and cause its specific activity. Analysis of this influence on the gland is an extremely intricate matter and one that requires much time. The main thing is to reveal in the object those properties which, in this particular case, act as stimuli on the glands in question. An investigation of this kind is not at all so easy as it looks at first sight. Here are some facts to prove this. By means of the previously mentioned metal tube, we introduce meat into the empty and inactive stomach of the dog, without the animal noticing it. In a few minutes the gastric reagent, an acid solution of the gastric protein ferment, begins to exude from the walls of the stomach. Which property of the meat lump has acted as the stimulus on the gastric glands? The simplest way would be to assume that this action has been caused by its mechanical properties-pressure, or friction against the walls of the stomach. But such an assumption would be absolutely wrong. Mechanical influences are completely ineffective with regard to the gastric glands. We can mechanically influence the wall of the stomach in any way - strongly or feebly, continuously or with interruptions, on limited areas or in a diffused way - but without obtaining a single drop of gastric juice. Actually, it is the components of meat soluble in water that are the stimulating substances. However, as yet we lack exact knowledge of these substances since the extractable substances of meat form a large group that still awaits investigation in full measure.

Here is one more example. A few minutes after the thyme finds its way into the next section of the digestive canal - into the duodenum - one of the glands of this section comes into action; this is the *pancreas*, a large organ located at the side of the digestive tract and connected with it by an excretory duct. But which of the properties of the thyme advancing in the intestine acts as a stimulating agent on this gland? Contrary to our expectations, it turned out that this action was exerted not by the properties of the juice which joined it in the stomach, namely, by its acid content. If we pour into the stomach or directly into the intestine pure gastric juice, or simply the acid which it contains, or even some other acid, our gland will begin to function just as vigorously, or even more vigorously, than in the case of the normal thyme passing from the stomach into the intestine. The profound significance of this unexpected fact is quite clear.

The gastric laboratory uses its protein ferment under an acid reaction. Different intestinal ferments, and among them, naturally, pancreatic ferments, cannot develop their activity in an acid medium. Hence, it is clear that the first task of the laboratory is to provide the neutral or alkaline reaction necessary for its successful activity. These circumstances are effected by the above-mentioned interrelations, since the acid content of the stomach, as already stated, induces secretion of alkaline pancreatic juice (and the higher the acid content, the greater the secretion). Thus, the pancreatic juice acts above all as a solution of soda.

One more example. It has been known for a long time that the pancreatic juice contains all the three ferments which act on the major food substances - a protein ferment, which is different from the gastric ferment, a starch ferment and a fat ferment. As proved by our experiments, the protein ferment in the pancreatic juice is, constantly or at times, entirely or partly (this is still a matter of argument), in an inactive, latent form. This may be justified by the fact that the active protein ferment might endanger the other two pancreatic ferments and destroy them. Simultaneously we established that the walls of the upper section of the intestine secrete a special fermentative substance the action of which is to transform the inactive pancreatic protein ferment into an active one. The active ferment, upon coming into contact with the protein substances of the food in the intestine, loses its harmful action with regard to the other ferments. *The secretion of the above-mentioned special intestinal ferment by the wall of the intestine is solely due to the stimulating action of the pancreatic protein ferment.*

Thus, the purposeful relationship of phenomena is based on the *specificity of the stimuli*, that correspond to similarly specific reactions. But this by no means exhausts the subject. Now the following question should be raised: how does the given property of the object, the given stimulant, reach the glandular tissue itself, its cellular elements? The system of the organism, of its countless parts, is united into a single entity in two ways: by means of a specific tissue which exists solely for the purpose of maintaining interrelations, that is, the nervous tissue, and by means of body fluids bathing all body elements. These same intermediaries transmit our stimuli to the glandular tissue. We have thoroughly studied the first kind of these interrelations.

Long before us it was established that the work of the salivary glands is regulated by a complex nervous apparatus. The endings of the centripetal sensory nerves are stimulated in the oral cavity by different stimuli; these are transmitted via these nerves to the central nervous system and thence, with the help of special centrifugal, secretory nerve fibres directly connected with the glandular cells, they reach the secretory elements and induce them to certain activity. As is known, this process, as a whole, is designated as a *reflex* or a reflex stimulation.

We have asserted, and also proven experimentally, that normally this reflex is always of a specific nature, i.e. that the endings of the centripetal nerves receiving the stimulation are different, each bringing about a reflex only when there are very defined external stimuli. Accordingly, the stimuli reaching the glandular cell must also be a special, peculiar one. This is the fundamental mechanism of the work of the organs purposefully depending on external influences, a relationship that is accomplished by the nervous system.

As was to be expected, the discovery of the nervous apparatus of the salivary glands immediately impelled physiologists to seek a similar apparatus in other glands lying deeper in the digestive canal. Despite great efforts no positive results could be achieved in this respect for a long time. Apparently, the new objects of investigation had essential properties that made their elucidation difficult for investigators using the earlier methods.

Taking into account these special relations, we were able, fortunately, to achieve what for such a long time had been a pium desiderium. Physiology has, at last, gained control over the nerves which stimulate the gastric glands and the pancreas. Our success was mainly due to the fact that we stimulated the nerves of animals that easily stood on their own feet and were not subjected to any painful stimulus either during or immediately before stimulation of their nerves.

Our experiments not only proved the existence of a nervous apparatus in the above-mentioned glands, but also disclosed some facts clearly showing the participation of these nerves in normal activity. Here is a striking example.

On dogs we performed two simple operations they very easily endure and after which, if taken good care of, they live for many years like very healthy and normal animals. These operations are the following: (1) Severing the tube leading from the mouth into the stomach and suturing both ends separately to the skin of the throat in such a way that food cannot pass from the mouth into the stomach of the animal but falls out through the upper opening of the tube; (2) the operation mentioned already earlier and used since a long time, in which a metal tube is introduced into the stomach through the abdominal wall. These animals have to be fed, of course, by putting the food directly into the stomach through this metal tube. When, after a fast of several hours and after the empty stomach of the dog has been thoroughly washed, the animal is fed in the natural way (whereby the food, as already mentioned, falls out of the oesophagus before reaching the stomach) then in a few minutes pure gastric juice begins to trickle out of the empty stomach. This secretion lasts as long as the animal is given food and persists some time (in a few cases even a long time) after the so-called sham feeding is discontinued. The secretion of juice is very abundant; one can obtain many hundreds of cubic centimetres of gastric juice in this way. In our laboratory we perform this operation on many dogs and the gastric juice thus obtained not only serves the purpose of research, but also as a good remedy in treating patients suffering from insufficiency of the gastric glands. Our animals living many years (more than 7-8 years) without ever showing any deviation from normal health thus donate a part of their vital supplies to the benefit of man.

From the described experiment it is clear that the mere act of eating, the food even not reaching the stomach, determines the stimulation of the gastric glands. If the so-called vagus nerves are severed at the neck of these dogs the sham feeding will no longer cause any secretion of gastric juice, no matter how long the dog stays alive and in spite of the fact that it feels excellent. So the stimulation effected by the act of eating reaches the gastric glands by means of the nerve fibres that are contained in the vagus nerves.

Now I shall allow myself to leave my main theme for a moment. Cutting of the vagus nerves in animals has been performed already for a long time and presented an absolutely fatal operation. In the course of the 19th century physiologists learned about numerous influences exerted by the vagus nerves on the different organs and their respective investigations revealed at least four disorders in the organism occurring after severing these nerves, each of which being lethal by itself. In our dogs we took appropriate measures against each of these disorders, one of which concerns the digestive system, and due to this procedure the animals whose vagus nerves were cut enjoyed a healthy and happy life. Thus, four simultaneously acting lethal causes were deliberately eliminated. A striking proof of the power of science that regards the organism as a machine!

Some ten years ago the great man to whom the annual science festival in Stockholm owes its existence honoured me and my friend, the late Professor Nencki, with a letter enclosing a considerable donation for the benefit of the laboratories under our direction. In that letter Alfred Nobel expressed his keen interest in physiological experiments and proposed that we should try several highly instructive projects concerning the supreme tasks of physiology, the problem of the organisms ageing and dying off. Indeed physiology is qualified to hope for significant victories in this field; it is as yet impossible to delimitate here the boundaries of the power of physiology. This power of physiology, however, can only be secured in the future if we continue deepening our knowledge of the organism as a very complicated mechanism. Above I have provided a small example supporting this.

I shall now return to the subject of my lecture. One kind of stimulators of the digestive glands - it quite unexpectedly came to the fore during our investigations - has not yet been mentioned. It has long been known for sure that the sight of tasty food makes a hungry man's mouth water; also lack of appetite has always been regarded as an undesirable phenomenon, from which one might conclude that appetite is essentially linked with the process of digestion. In physiology too psychical stimulation of both the salivary and the gastric glands has been reported. It is remarkable that nevertheless psychical stimulation of the gastric glands is far from being generally admitted and the outstanding role of psychical influences on the mechanism of the processing of food in the digestive tract has not at all met with proper acknowledgement. Our investigations led us to bringing these influences to the fore. Appetite, craving for food, is a constant and powerful stimulator of the gastric glands. There is not a dog in which skilful teasing with food does not evoke a more or less considerable secretion of juice from the empty and hitherto inactive stomach. At the mere sight of food nervous and excitable animals secrete several hundred, sedate and quiet animals only a few cubic centimetres of gastric juice. By modifying the experiment in a certain way an extremely profuse secretion of juice takes place in all animals without exception; I have in mind the experimental sham feeding mentioned previously in which the food cannot reach the stomach from the mouth. An exact and frequently repeated analysis of this experiment convinced us that in this case the secretion of juice cannot be regarded as being the result of a simple reflex stimulation of the mouth and throat by the food swallowed. Any given chemical irritant can be brought into the mouth of a dog thus operated upon, without even a single drop of gastric juice flowing upon this stimulation. One can still assume that the oral surface is stimulated not by arbitrary chemical substances but only by specific ones contained in the food consumed. Further observations, however, do not confirm this supposition. One and the same food acts differently as a gland stimulator depending on whether the food was consumed by the dog eagerly or unwillingly, by order. Generally the following invariable phenomenon is observed: each kind of food ingested by the dog during this experiment acts as a strong stimulus only when it suits the dog's taste. We must admit that in the act of eating the craving for food, the appetite - and therefore a psychical phenomenon - serves as a powerful and constant stimulus. The physiological significance of this juice, which we termed *appetite juice,* proved outstandingly great. When we introduce bread into the dog's stomach through the metal tube so as to prevent the dog from noticing it, i.e., without arousing its appetite, the bread may remain in the stomach unchanged for a whole hour, without evoking even the slightest secretion of juice, since it lacks the substances that would stimulate the gastric glands. However, when the same bread is consumed by the animal, the gastric juice secreted thereupon, the appetite juice, acts chemically on the protein substances of the bread, or, in other, more usual words, digests it. Amongst the substances resulting from the protein thus changed are some that in turn act on the gastric glands as independent stimuli. They carry on the work which is started by the first stimulus, the appetite, that naturally is diminishing by then. Already while studying the action of the gastric glands it could be discovered that appetite not only generally acts as a stimulus on these glands, but also that it excites them *in a varying degree* according to its direction. For the salivary glands the rule holds that all variations in their activity observed in physiological experiments are exactly duplicated in experiments using psychical stimulation, i.e. in which a given object is not brought into direct contact with the mucous membrane of the mouth, but arouses the animal's attention from some distance. For example, the sight of dry bread evokes a stronger secretion of saliva than the sight of meat, although the latter, judging from the animal's movements, may arouse a considerably keener interest. On teasing the dog with meat or any other edible substance a highly concentrated saliva flows from the submaxillary glands; the sight of distasteful substances, on the other hand, conditions the secretion of a very fluid saliva from the same glands. In short, the experiments with psychical stimulation represent an exact but reduced copy of those with physiological stimulation of the glands using the same substances. With regard to the action of the salivary glands psychology has thus taken its place besides physiology. Even more than that! At first sight the psychological aspect of this action seems to be even more indisputable than the physiological. When an object attracting the dog's attention at a distance brings about secretion of saliva, it is fully justified, of course, to assume that this is a psychical phenomenon and not a physiological one.

When, however, the dog consumes something or when a substance is forcibly poured into its mouth and saliva thereupon flows, it still has to be proved that indeed there is something physiological in this phenomenon and that it is not purely psychical but in dimensions reinforced due to special accompanying conditions. These considerations would all the more be in accordance with reality, since most substances entering the mouth while eating or artificially, strangely enough, activate the salivary glands after severing of all sensory nerves of the tongue in a very similar way as before this operation. One would have to go further, resort to more radical measures such as poisoning the animal or taking away higher parts of the central nervous system, in order to become convinced that between objects stimulating the oral cavity and the salivary glands not only a psychical but also a physiological connection exists. We are thus confronted with two series of apparently entirely different phenomena. What now is the physiologist to do with the psychical phenomena? Disregarding them is impossible since in the action of the salivary glands, in which we are interested, they are closely connected with the purely physiological phenomena. If, nevertheless, the physiologist wants to study them, he finds himself faced with the question: How?

Since we used the studies of the lowly organized representatives of the animal kingdom as an example, and, naturally, wanted to remain physiologists instead of becoming psychologists, we decided to take an entirely objective point of view also towards the psychical phenomena in our experiments with animals. Above all, we tried to discipline sternly our way of thinking and our words and ignored completely the mental state of the animal; we restricted our work to careful observation and exact formulation of the influence exerted by distant objects on the secretion of the salivary glands. The results were according to our expectations: the observable relations between external phenomena and variations in the activity of glands could be systematically analysed; they appeared to be determined by laws, because they could be reproduced at will. We were pleased to find that our experiments proved to be right and fruitful. I shall give some examples here illustrating the results obtained with the new method in our field of interest.

When the dog is repeatedly teased with the sight of objects inducing salivary secretion from a distance, the reaction of the salivary glands grows weaker and weaker and finally drops to zero. The shorter the intervals between repeated stimulations the quicker the reaction reaches zero, and vice versa. These rules apply fully only when the conditions of the experiment are kept unchanged. The identity of the conditions, however, need to be only of a relative character; it may be restricted only to those phenomena in the external world that were previously associated with the act of eating or with the compulsory introduction of the substances in question into the animal's mouth; the variation of the remaining phenomena is of no significance. This relative identity mentioned above can be very easily attained by the experimenter so that an experiment in which a stimulus repeatedly applied from a distance gradually loses its effect, can be readily demonstrated even in the course of one lecture. When in a repeated stimulation from a distance a certain substance becomes ineffective, the action of another substance is not at all eliminated. For example, when milk ceases to produce an effect, the action of bread is very strong. When bread too has lost its effect due to repetition of the stimulation experiment, acid or other substances is still highly effective. These relations also explain the real meaning of the above-mentioned identity of experimental conditions; every detail of the surrounding objects appears to be a new stimulus. If a certain stimulus has lost its influence, it can recover the latter only after a long resting that has to last several hours.

The lost action, however, can also be restored with certainty at any time by special measures.

When repeatedly showing of bread no longer stimulates the dog's salivary glands one needs only to let the animal eat bread to attain full restoration of the action of bread at a distance. The same result is achieved when the dog is given some other food. Even stronger: If something inducing salivary secretion, such as acid, is brought into the animal's mouth, the original action of the sight of bread is also restored. Generally, everything that stimulates the activity of the salivary gland retrieves the lost reaction: the greater the activity the more fully the reaction is restored.

Also according to rules our reaction can be inhibited by certain interferences, for instance, affecting the dog, its eye or its ear by an extraordinary stimulus and thereby evoking a strong motor reaction in the animal such as trembling of the entire body.

Since my time is limited I shall content myself with what I have said and pass on to the theoretical consideration of the experiments just mentioned. The given facts fit readily in our physiological way of thinking. Our stimuli working from a distance may rightly be termed and regarded as reflexes. When observing carefully it appears that the activity of the salivary gland is always excited by some external phenomenon, i.e. that it is induced by external stimuli like the usual physiological salivary reflex; only the second is evoked from the oral surface, the first, however, from the eye or from the nose, etc. The difference between the two reflexes is firstly that our old physiological reflex is constant, unconditioned, while the new reflex continually fluctuates and, hence, is *conditioned*. Examining the phenomena more closely the following essential differences between the two reflexes can be observed: in the unconditioned reflex those properties of the object act as stimuli with which the saliva is confronted physiologically e.g. hardness, dryness, certain chemical properties; in the conditioned reflex, however, those properties of the object act as stimuli that in themselves have no direct relation at all with the physiological role of the saliva, e.g. colour, etc. These last properties appear here in some way as signals for the first. One is bound to regard their stimulating action as a further, more delicate adaptation of the salivary glands to the phenomena in the external world. Here is an example: We intend to pour acid into the dog's mouth; to protect the oral mucous membrane it is apparently very desirable that saliva accumulates before the acid enters the mouth; on the one hand the saliva prevents direct contact of the acid with the mucous membrane and, on the other hand, it immediately dilutes the acid thus generally weakening its injurious chemical action. However, essentially the signals have only a conditional significance: they change readily and also, the signalized object cannot come into contact with the oral mucous membrane. Consequently the finer adaptation would have to consist in the fact that the properties of the object serving as a signal sometimes do and at other times do not stimulate the salivary glands. This is what we see in reality. Any phenomenon in the external world can be made a temporary signal of an object stimulating the salivary glands, if the stimulation of the oral mucous membrane by this object has been associated repeatedly once or several times with the action of the given external phenomenon on other sensitive body surfaces. In our laboratory we are trying at present to apply many such highly paradoxical combinations, and with success. On the other hand promptly active signals can lose their stimulating effect if repeated over a long period without bringing the object concerned into contact with the oral mucous membrane. When the most usual kinds of food are shown to the dog for days and weeks, without letting him eat it, the sight of the food will finally cease to evoke salivary secretion. The mechanism of stimulating the salivary glands through the signalling characteristics of the objects, i.e. the mechanism of "conditioned stimulation" can be easily conceived from the physiological point of view as a function of the nervous system. As we have just seen, each conditioned reflex, i.e. stimulation through the signalling characteristics of the objects is based on an unconditioned reflex, that is, a stimulation through the essential characteristics of the object. So it must be assumed that the point of the central nervous system that is being stimulated strongly during an unconditioned reflex diverts to itself the weaker stimuli exerted by the external world on other points of the central nervous system, i.e. that due to the unconditioned reflex a temporary, incidental path is created for all the other external stimuli towards the central point of this reflex. The conditions influencing the opening and closing of this path, its being in use or in disuse, constitute the internal mechanism of the signalling characteristics of external objects being effective or ineffective, the physiological basis of the finest reactivity of the living matter, the most delicate adaptive capability of the animal organism.

I wish to express here my deep conviction that in this direction, along the broad lines I have sketched, physiological research can advance greatly and successfully.

Essentially only one thing in life interests us: our psychical constitution, the mechanism of which was and is wrapped in darkness. All human resources, art, religion, literature, philosophy and historical sciences, all of them join in bringing light in this darkness. But man has still another powerful resource: natural science with its strictly objective methods. This science, as we all know, is making huge progress every day. The facts and considerations which I have placed before you at the end of my lecture are one out of numerous attempts to employ a *consistent*, purely scientific method of thinking in the study of the mechanism of the highest manifestations of life in the dog, the representative of the animal kingdom that is man's best friend.

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