An Address

ON

THE INVESTIGATION OF THE HIGHER NERVOUS FUNCTIONS.

GIVEN AT THE CLOSING MEETING OF THE INTERNATIONAL CONGRESS OF PHYSIOLOGISTS AT GRONINGEN ON SEPTEMBER 5TH, 1913.

By PROFESSOR I. PAWLOW,

ST. PETERSBURG.

(Adapted into English by C. LOVATT EVANS, D.Sc., *Institute of Physiology, University College, London.*)

THE work of Hitzig and Fritsch in the year 1870 marks an important epoch in the physiology of the central nervous system, and formed the starting point of a great number of important investigations of the functions of the cerebral hemispheres, which have proved most fruitful in their clinical applications. Why was this? To my mind it was because investigators were dealing with pure physiological facts, all of which lay within the scope of experimental investigation.

It is important that emphasis be laid on this fact, which physiologists would do well to take as a guiding principle in their further researches on the functions of the cerebral hemispheres. We are now on the fringe of such advances. Although the work which has been done concerning the so-called motor areas of the cerebral cortex must be regarded by physiologists as a very satisfactory achievement, it remains quite an isolated chapter in the physiology of the cerebral hemispheres. Work on the so-called sensory centres has only so far resulted in general indications of the nature of the problem which calls for solution, and none of us can doubt that the investigation of the chief functions of the cerebrum still presents a vast and almost untouched field for the physiologist. Sooner or later we shall find ourselves compelled to undertake the investigation and analysis of the functions of this part of the central nervous system working as an integrated structure whose total activities seem almost boundless. But up to the present, with the exception of the facts discovered by Fritsch and Hitzig, and some general information concerning the sensory centres, these activities of the brain have been grouped with the so-called psychic phenomena which form the subject-matter of sciences other than physiology. It is chiefly for this reason that the physiology of the higher parts of the central nervous system has not made that progress which might have been desired in view of its deep interest and the breadth of the various problems which it presents. For physiology to borrow knowledge from a science more exact than itself is one thing, but it is quite a different thing for physiology to take information from a subject which it must be admitted has not yet arrived at the condition of an exact science, from a subject whose followers are not yet agreed concerning the general postulates, the general tasks, and the method of investigation which it is best to follow.

The physiologist who proposes to occupy himself with the investigation of the functions of the cerebral hemispheres is therefore faced with a dilemma. Either, on the one hand, he must wait until psychology has developed into a modern exact science, with its province and its place among the other sciences exactly defined—only then could the physiologist apply the teachings of psychology with any profit to his complex undertaking. It is, in any case, difficult to see in what way the conceptions of present-day psychology could be related or brought into line with our knowledge of the material construction of the brain. Or, on the other hand, the physiologist must work out a path for himself quite independent of psychology, and must himself investigate and systematize the fundamental mechanisms of the higher nervous functions—in a word, he must remain a pure physiologist.

To my mind, there can be no question of choice in this dilemma. If we choose the first alternative we should be postponing for an indefinite time the investigation of the most interesting phenomena of the animal organism. Thus, only the second choice lies open to us, and I venture to suggest that at the present time there are real and

sufficient reasons for believing that this path is the normal and rational one—that is, that its fruitfulness is assured.

We all know what a wealth of material, and what an insight into the phenomena of the central nervous system, has been rendered to physiology by the study of the primitive function which we denote as reflex action. The conception of the simple reflex has removed much of the mystery from the province of neural phenomena, and has brought many aspects of these phenomena within the scope of direct scientific investigation. These investigations have shown with what regularity the animal organism responds, by means of its central nervous system, to various events occurring in itself and in the surrounding world.

It is now time for physiologists to extend their views of reflex action, and to recognize that the nervous system, besides the primitive function of reproducing innate reflexes, possesses another prime function—namely, the formation of new reflexes. Since in machines constructed by human ingenuity we often have examples of the establishment of new relations of the various parts under certain conditions, it is difficult to deny this capability of adaptation to the central nervous system, that complex regulator of an intricate structural entity.

Although these facts and their explanation on these lines do not introduce anything essentially new in our conception of the central nervous system, yet it is highly desirable that they should be systematically investigated, and constantly kept in view in working in this field. It is a generally recognized property of living matter to adapt itself, or, as I prefer to say, to preserve a condition of equilibrium with the world around it. This is equivalent, in this particular case, to saying that new relations are established under new conditions, to the advantage of the living complex; or again, that the living thing is enabled to respond, by definite and suitable activities, to agencies to which it was formerly indifferent.

This establishment of new paths in the central nervous system as a result of the presentation of new external conditions is most clearly seen in the higher animals; their life is one long story of continual evolution and ingrainings of these new connexions. Natural factors which at one time are indifferent for the animal's activities can develop in a very short time into powerful stimuli for the most important vital functions.

With the help of my various collaborators I have studied the feeding of the dog, or the introduction of acid into its mouth, together with the simultaneous application of various external stimuli. In the course of time these stimuli develop into infallible excitants of salivary secretion, and thus become indissolubly connected with the reaction of the animal to food or to the introduction of acid into the mouth. We are here undoubtedly dealing with a response, through the agency of the central nervous system, to a special condition in the outer world—it is in fact a reflex; but it is not a stereotyped reflex, it is one which has been constructed under our observation. If we take the word "reflex" as meaning not merely a response to a stimulus brought about by the intermediation of the central nervous system, but add the conception of the regularity and constancy of the phenomena, then it is only necessary to assume—and such an assumption is quite legitimate and scientific—that the newly developed reflex is no accidental occurrence, but is in accordance with fixed principles, in order to see that the word "reflex" is quite in its place when used in connexion with this phenomenon.

Is there any legitimate obstacle to the acceptance of such new self-constructed reflexes in physiological theory? It seems to me that there can be but one. By deliberate or by involuntary comparison with our own subjective world we may feel inclined, by reason of the fundamental nature and adequacy of the new reaction, to reject a deterministic view of the situation. From our own experiences we may be tempted to imagine that the establishment of such new connexions represents a highly complex process, if not, indeed, the intervention of special forces. But have we the right to do this in the case we are considering? In the lower, as in the higher, animals we have innumerable instances which render it quite clear that the new stimulus for the reflex exerts its action just as directly as did the old one. In our experiments with the new feeding reflex we often observed that when the

accompanying stimulus was a visual one the animal, after the reflex had been fully established, exerted the same grasping movements towards the stimulating visual object as towards the food itself. We have found no evidence of such hypothetical complexity in these cases, but rather the contrary. From the fact that the new reflexes can always be produced in a short time under suitable conditions, we may conclude that their production is a simple and easy matter. The inhibition of the reflexes, however, presents quite a different case, for this represents a highly complex process, and quite a number of stimuli of various kinds continually exert a powerful action on the reflex. So that the complexity of the phenomena which claim our attention does not depend on the complex nature of the newly-formed reflex itself, for this is in essence simple, but rather upon the extraordinary dependence of this reflex on events taking place in the outer world, and also in the organism itself.

We will now pass on to the consideration of the second fundamental mechanism which the higher parts of the central nervous system exhibit. A living animal responds by activity to only particular phenomena of the external world, so that it must analyse these and pick out from them certain special components. The higher an animal is in the zoological scale the greater the number of factors which the world represents for him, and therefore the functions of the animal are conditioned by a proportionally large number of factors. A very lowly creature is itself a single receptor, and also a proportionately simple one. In higher animals, with highly developed nervous systems, an important part of this system is devoted to the task of special receptors, for analysis by physical or chemical mechanisms. Highly specialized and delicate analysis is a fundamental function of the higher parts of the central nervous system. As a result of my experimental work, I propose to regard the analysors as specialized parts of the central nervous system, in each of which we must include the peripheral end-organ of the so-called sense organs, the nerve fibre belonging to it, and its termination in the cells of the cerebral hemispheres. It is better to consider the whole analyser in this way as one structure, since we do not at present know exactly what part the peripheral and central portions respectively play in the analytic process. We do know, however, that the analysis lies in very close relationship to the formation of the new reflexes. The mechanism which is responsible for the origin of the new reflexes can only bring into relation with the functional activity of the organism such physical events as are analysed for it. Conversely, there can be no doubt that any phenomenon of the outer world, however insignificant it may seem, when it has been isolated by the analysors of a given animal, can, and in fact does, become a special stimulus for this or that functional activity on the part of the animal. For this reason the investigation of the new reflexes gives us the fullest possibility for an exact study of the functions of the analysors. But the activity of the analysors in the higher animals is as incessant as is the mechanism by which new reflexes arise, and in the present insufficient state of our knowledge of these activities we can scarcely as yet see how far-reaching these functions are in the life of the animal. Probably at present we often ascribe to metaphysical processes what are really only due to fine and accurate neural analytical mechanisms. There is great need for the systematic investigation of the mode of action of the analysors; we need to be able to determine in a given animal what components its analysors are able to distinguish in the presentations of the external world; we need to know all the qualities of the stimulus, their intensities, their limits, and all their interrelations. At the same time we need to investigate the fundamental laws which are concerned with the process of analysis. Partial destruction of the peripheral or cerebral ends of the analysors can only teach us a little about their detailed activity. And the combined activity of all these various parts must eventually give us a clear insight into the total powers of analysis of sensations of which a given animal is capable.

We have now devoted twelve years of hard work to the investigation of these two fundamental mechanisms—to the investigation of the mechanism of the formation of new reflexes, and the mechanism of the analysors. It is my object now to try to give the outlines of our work as viewed from the standpoint of our most recent results;

the review must of necessity be a very rapid one, and I shall only be able to refer with great brevity to those results that in my opinion are the most important.

"CONDITIONAL REFLEXES."

As a preface to this short summary, I may state that I have called these reflexes of recent formation "conditional reflexes," in order to distinguish them from the ordinary reflexes, to which I have given the name "unconditional reflexes." The name "conditional" is merely used in order to denote an important property which these reflexes exhibit—namely, their very great dependence on a multitude of conditions. There are, of course, many other words which might be used in place of these, such, for example, as innate and acquired, or fixed and plastic, or permanent and transitory, and so forth. As already stated, my colleagues and I have almost exclusively used the salivary glands as the object of our studies of the conditional reflex. Our reason for this is briefly that the salivary glands are in direct communication with the outer world, having, therefore, quite simple internal relations, and that they can work alone, and do not represent parts of a complicated system, as is the case with the skeletal muscles.

We may now pass on to the consideration of some of our facts. As already mentioned, a fundamental condition for the formation of a conditional reflex is that whatever indifferent stimulus is chosen for the purpose of the reflex which it is desired to build up is given at the same time as the food or acid is introduced into the mouth. After a few such sittings it will be found that this formerly indifferent stimulus alone is now capable of calling forth a secretion of saliva. The conditional reflex has been formed; the formerly indifferent stimulus has now found a path to the requisite parts of the central nervous system. The reflex arc now has a different afferent neuron.

Conditional reflexes can be formed not merely from indifferent stimuli, but also from a stimulus which is more or less closely connected with some special centre in the brain. A good example of this is seen in the experiments with noxious stimuli, which in common terminology are called painful stimuli; the usual result of such a stimulus is that the animal does its best to defend itself against the stimulus, and to get away from it if possible, or to attack the source of the painful stimulus. But it is possible without any great trouble to modify this response by systematically accompanying each feeding of the animal (that is to say the stimulation of its feeding centres, for there are as good reasons for the existence of the feeding centres as for that of the respiratory centre) by strong electrical stimuli applied to the skin. We now find that even the strongest electrical stimuli applied to the skin give rise merely to the feeding reaction, that is, to secretion of saliva, and to no symptoms of fright or pain at all. The skin of the dog can now be subjected to cutting, pinching, or burning, and the only result we shall obtain will be the manifestation of what, judging from our own experience, we should call the symptoms of the keenest appetite; the animal follows the experimenter about, licks himself, and saliva flows in abundance. This fact has been demonstrated very frequently to large audiences, and to many of my friends privately, and the result can invariably be obtained. Its significance seems to me to be quite clear, for what other explanation is more appropriate than that the nervous impulse resulting from the stimulus, which formerly went to a particular region of the nervous system, is now directed to a different one? In this way we have been able to divert the impulse from one path to another, according to the conditions, and we cannot avoid the conclusion that this represents one of the most important functions of the highest parts of the central nervous system.

Apparently the same factors are at work when a conditional reflex is formed from any indifferent stimuli. The presence of certain special conditions (the administration simultaneously with the unconditional reflex, or with a previously established conditional reflex) causes the indifferent stimulus, which otherwise would be dispersed in the higher centres, to be directed to a particular focus, and eventually to lay down for itself a path to that part.

The question which now arises is—What conditions will determine the direction of the nervous impulse along special channels? Judging from our results it seems to

be a question of the relative functional power of the various centres or of their degree of irritability. The following case can be explained in this way. We have already shown that it is easy to train a feeding reflex with nocuous skin stimuli as the conditional stimulus. All our efforts have been in vain, however, in the special case where the stimuli have been applied to areas of skin which lie directly over bone—in other words, when we have used nocuous stimuli applied to bone. We have also been unable to make nocuous skin stimuli the conditional stimulus for the reaction of the gland to acid (0.5 per cent. HCl introduced into the mouth at the time of the stimulus), in spite of all efforts. To express the thing somewhat crudely, we may say that the centre connected with the painful stimulation of bone is physiologically stronger than the centres connected with the feeding reflex, and that in like manner the feeding reflex is prepotent as compared with the reaction of the gland to acid. For these and similar reasons we say that the stimulus is directed to the centre which is physiologically the more powerful.

There are many subsidiary conditions which play a part in the formation of conditional reflexes, and of these I wish to call special attention to the particularly advantageous conditions of experiment which obtain when the conditional stimulus slightly precedes, in point of time, the unconditional stimulus (feeding or acid) with whose help the reflex is to be built up. If we try to carry out the experiment by feeding the dog, or introducing acid into its mouth, and then even only five seconds afterwards apply the indifferent stimulus with which we wish to build up the conditional reflex, we shall be introducing a condition which will present a remarkable obstacle to the formation of the reflex. This can be explained in the same way as many other well-known inhibitions; the unconditional stimulus creates a focus in a special centre of the cerebrum, and this results in relative depression of the excitability of other centres of the brain, so that stimuli arriving at those parts are now below the threshold value, or else suffer some block to further propagation to other parts of the cerebrum. It seems that the new stimuli are only efficient and can only effect the proper connexion with other stronger and subsequent stimuli when the centres are in a more or less indifferent condition to begin with.

It is naturally of much importance that the stimuli from which the new reflex is to be worked out shall be rigidly isolated. If, in addition to the stimulus which has been chosen for the experiment in hand, another stimulus regularly obtrudes without the operator perhaps being aware of its existence, and if this extraneous stimulus happens to be absolutely or relatively of greater physiological strength than the intended one, then the reflex will be formed not from the desired stimulus at all, but from the incidental one. It has happened in many cases that at the commencement of an investigation, and sometimes throughout the work, the reflex has been dependent upon some peculiarity of the experimenter, upon some odour or movement (or even, it is thought, a change in the mode of breathing on the part of the operator), which has preceded or accompanied the feeding of the dog or the administration of the acid. It was partly on this account that in some of the experiments made by my colleagues in my old laboratory all applications of stimuli and all observations were carried out by mechanical devices from another room. In our new special laboratory we now obtain complete isolation of the animals not merely from the incidental stimuli which may proceed from the person carrying out the experiment, but also from all sudden and variable stimuli. Lack of time will not allow of the description of the other less important conditions which operate in the formation of conditional reflexes, nor of the description of the numerous types of reflex which we have studied, since we must now go on to the consideration of another important aspect of the physiology of these reflexes.

INHIBITION OF CONDITIONAL REFLEXES.

Fully formed conditional reflexes, as already mentioned, exhibit great sensitivity to all sorts of conditions, and on this account they are subject, in circumstances of everyday life, to continual variation, and often, indeed, to complete inhibition. This sensitiveness is, however, of value, since it serves as a useful means of checking our methods in any particular experiment.

Spontaneous Inhibition.

We have devoted a great deal of attention to the inhibitory phenomena which are so often encountered, and our experimental material has led us to recognize three distinct types of inhibition. The first type is that which is seen when the animal becomes drowsy, or when it falls asleep; this is seen as a fading and final vanishing of the conditional reflex, and presents many interesting features.

External Inhibition.

The second kind of inhibition we call also "external inhibition," and it corresponds completely with the process of inhibition which has been so much studied in the spinal reflexes. This mode of inhibition is obtained as a result of the arrival at the higher centres of stimuli, either from without or from other parts of the central nervous system, which give rise to other reflexes. There are also various subtypes which can be distinguished.

Internal Inhibition.

A third highly characteristic and especially interesting form of inhibition is that which we have designated as "internal inhibition." This kind of inhibition is developed as the result of particular relations between the conditional stimulus and the unconditional stimulus, with the help of which the reflex has been prepared. Whenever the conditional stimulus, in a fully formed reflex, is occasionally (or, under certain conditions, regularly) not followed by the particular unconditional stimulus (feeding or acid), it becomes converted into an inhibition. We have investigated several types of such inhibition. Thus, if with the fully developed reflex the conditional stimulus is given alone for a few times without being followed, or, as we say, "confirmed," by the unconditional one, the type of inhibition which results is called "extinction." When in working out a new reflex the unconditional stimulus is only allowed to follow some time (from one half to three minutes) after the conditional stimulus, the intervening inhibition is called "retardation."

Conditional Inhibition.

"Conditional inhibition" is seen when the conditional stimulus is accompanied by some indifferent stimulus, and is then not followed by the unconditional stimulus; and, lastly, "differential inhibition" is seen in the fact that stimuli approaching closely to the conditional stimulus in location or quality, and which are at first effective, gradually lose their efficiency as the reflex is developed. That all these phenomena are in reality due to inhibition can be shown by the fact that under appropriate conditions the inhibition may be removed, and the reflex restored—a phenomenon which we have called "escape" of the conditional reflex (*Losshemmung*). Such an effect can be obtained by giving any stimulus of moderate strength which shall evoke an orienting reaction on the part of the animal, and also by some other stimuli. By the observation of various aspects of this phenomena we have been able to study the relation between different varieties of the same types of inhibition and also to study the differences between different types.

Latent After-effect.

In order to cover all contingencies, it is necessary to reckon with the important phenomena of latent after-effect. Many factors co-operate to influence the duration of this after-effect. We have found that it can vary from a few seconds to several days, according to the stimulus and to the special conditions of each experiment.

PROPAGATION OF NERVOUS INFLUENCES IN THE CEREBRUM.

We must now return to the question of the propagation of the nervous impulses in the cerebral hemispheres. In addition to the phenomena of the focussing of an impulse in a particular direction, there are many facts which indicate that an impulse can be more or less dispersed or distributed in all directions. The following may be taken as an example in illustration of this. We have a dog which is evidently a watch dog; that is to say, he has developed the reflex of flying at a strange person—an attacking reflex—and, in addition, he is readily roused. When no person except the one who generally experiments with the dog is in the room the animal is quite quiet, and various conditional reflexes and inhibitions can be worked out with ease with him. But if any strange person

enters the room the dog commences at once to bark violently, and if this person makes threatening gestures, or especially if he strikes the dog, the aggressive reaction reaches its climax. Now if the newcomer takes the place of the experimenter, and remains alone to continue the experiment, a very interesting phenomenon is observed. In spite of the fact that the dog continues to bark angrily, the conditional reflex, contrary to all expectation, not merely does not give less effect than usual, but it gives a much *greater* one; saliva flows in great abundance, and the food is taken with hasty snatchy movements from the hand of the experimenter, the object of the aggressive reflex. Now if the new experimenter remains as still as is possible, only applying the conditional stimulus and the subsequent feeding from time to time, the dog finally ceases to bark, although he follows the person closely with the eye the whole time. Now, strangely enough, it will be found that the conditional stimulus is without any effect as judged by the salivary secretion, and the dog only takes food five to ten seconds after it is offered to him, and this is not eaten with relish. But it is only necessary for the visitor to get up and move about in order to restore the hostile demonstration once more, and with this also the heightened conditional reflex to food.

The mechanism of this reaction is, I think, somewhat as follows: The conditional reflex towards the stranger when brought to its climax by the movements of the man acting as a special stimulus, incites the food reflex also. As its intensity diminishes, the excitatory process is confined to its own special centres in the brain, so that the excitability of the food centres is now lowered. When taken in connexion with analogous experiments on the mutual effect of different feeding reflexes on each other, on the effect of heat and cold reflexes on each other, and with other observations, and also with the fact, known since 1870, that general epileptiform convulsions can be evoked by the stimulation of quite small points in the motor cortex of the cerebrum, these facts make the idea that an impulse can spread very widely in the higher centres quite incontestable. Besides the phenomenon of dispersal of the impulse, we see also the converse phenomenon, the focusing and concentration of the excitatory process as the second phase of the whole process.

The same principle can be conclusively demonstrated with the phenomenon which we have called internal inhibition. Although I have recently published an account of this case in the French language, still it will bear repetition here for the sake of rendering the present account more complete. Suppose that we arrange serially several apparatus for effecting cutaneous stimulation along the hind leg of the dog, and that these stimuli have been worked up as conditional stimuli for the feeding reaction, with the exception of the lowest one of all, which has been differentiated so as to be inactive; with such an arrangement it is easy to show that when the lowest piece of apparatus is put in action the resulting inhibition spreads to all the areas above it, and then fades away in strict sequence, to concentrate itself again at its point of origin.

PHYSIOLOGY OF SLEEP AND HYPNOSIS.

In the course of the investigations on the conditional reflexes the question of the physiology of sleep and hypnosis has forced itself on our attention. The following unexpected facts can now be demonstrated regularly with all the dogs, although at first they were only obtained occasionally. When the conditional stimulus commences half a minute, or one or more minutes, before the unconditional one, a retardation of the effect is developed, as already mentioned; this latter gets nearer and nearer to the point when the unconditional reflex is introduced. The time which intervenes between the conditional stimulus and the response is occupied by the internal inhibitory process. But this is not all. By degrees the effect quite disappears from the period immediately preceding the unconditional reflex, and experiments show that it only persists during the time when the unconditional stimulus is acting. But finally the effect disappears also from this period, and the conditional reflex becomes quite inactive. At the same time the animal enters into a kind of cataleptic condition; inert to stimuli, the animal assumes a particular pose and thus remains rigid, finally falling into a deep sleep, from which

it can only with difficulty be aroused. This curious phenomenon develops with different speeds and attains different degrees of intensity, according to certain conditions. The intensity of the conditional stimulus, the length of time which intervenes between the conditional and unconditional stimuli, and the number of repetitions of the subdued reflex, are all conditions which have an influence on the result. The animals also exhibit considerable individual differences. The phenomenon just described disappears rather quickly when the conditional stimulus is given almost simultaneously with the unconditional—that is, when it precedes it by only three to five seconds. It is difficult to avoid the conclusion that these effects are closely connected with the phenomena of sleep and hypnosis, and we shall have to return to a consideration of them presently when we deal with the experiments in which portions of the cerebral cortex have been removed. In conclusion of the part of this lecture dealing with conditional reflexes, I would remark that time is for us also a real conditional stimulus, which might be subjected to investigation with regard to differentiation, inhibition, and escape. At all events, I have the certain knowledge that by means of exact experiments on the lines here described the problem of time, which has concerned and still concerns philosophers so much, may be definitely solved.

THE FUNCTIONS OF THE ANALYSING MECHANISMS.

Now we will briefly review the chief results which we have obtained in our experiments on the functions of the analysing mechanisms. We have attempted to investigate still further those qualities and intensities of stimulus which could be isolated by the analysors of the animal.

As we have accumulated more and more experimental material, it has become increasingly clear that the principles on which the discriminative process works are quite general. When any stimulus is used as a conditional stimulus, extensive and less specialized parts of the discriminating mechanism are at first involved, and it is only later on, after frequent repetition of the conditional reflex, that the conditional stimulus becomes more and more specialized and restricted, so as to correspond finally with a very small part of the analyser. Concerning the degree of sensitiveness and the limits of accuracy of these analysers, we are unfortunately unable to state anything, since the limits were determined in the cases investigated by the incompleteness of the apparatus at our disposal.

We have especially studied those inhibitory processes by the help of which the differentiation of the stimulus is brought about; neighbouring and similar stimuli which at the commencement are as effective as the special conditional stimulus gradually become inoperative as the reflex is worked out. This process of differential inhibition can readily be investigated in the form of inhibitory after-effects—that is, the inhibited condition which lingers in the higher parts of the nervous system after the application of the differentiated inactive stimuli. The higher the grade of the differentiation in any case the more clearly are the inhibitory after-effects seen. A new differentiation gives a more powerful inhibitory effect than one fully worked out. The more strongly the differentiation is worked out the shorter the duration of the inhibitory after-effect. If in the course of one and the same experiment the stimulus which has been rendered inactive by differentiation be repeated several times running, the after-inhibition which it produces is intensified by a sort of summation. The phenomenon of escape from inhibition can also be seen with the differentiated stimulus.

Since we have seen that the higher nervous activities can be regarded as the work of two mechanisms—that of the conditional reflex and that of the analysers—we will now see what are the effects of injury or destruction of those structures which are believed to be concerned in the carrying out of these functions. Only a few examples can be given.

The experiments on conditional reflexes with skin stimuli are especially striking. Since at the commencement all conditional reflexes are generalized, it is easy to render mechanical stimuli of each of several large skin areas a conditional stimulus for the feeding reflex. If now certain parts of the frontal lobes of the brain be extirpated in such an animal, it will be found that the conditional reflex cannot now be obtained at all from a particular

and sharply delimited area of skin; in all other parts, however, it can be obtained in the normal manner. It is a fact of some importance, also, that on stimulation of the inactive skin areas one obtains a strong *inhibition* of the effect got by the stimulation of the active areas; and that, further, such stimulation of inactive areas leads very quickly to drowsiness and sleep. The conditional reflexes return again in time, but definite injury to the differentiation persists at these places; the analysis is either less accurate or else it presents certain abnormalities. The following effects are permanent, even for years, at the affected areas; the conditional reflex can only be obtained under complete synchronism of the two stimuli, conditional and unconditional; if the unconditional stimulus be removed ever so little from the conditional, the reflex rapidly vanishes and the animal becomes drowsy. At the neighbouring skin areas the conditional reflex remains quite normal. In this way the phenomenon which is seen in the normal animal, and which appears to me to have such an important connexion with the problems of sleep and hypnosis, is evidently much intensified by the operation of partial extirpation. The skin receptors seem to me to be especially well adapted for the investigation of the functions of the cerebral cortex.

Conditional reflexes can also be obtained from stimuli from the locomotor apparatus—for example, from the joints, when the latter have been differentiated from the skin stimuli. The proof that such differentiation is attained is furnished by the extirpation of parts of the frontal lobes. When one part is extirpated the reflex is obtained from the flexion of the joint, but not from the skin; if a different part be removed, we can get the skin reflex, but not the reflex from the joint.

In one case we extirpated the greater portion of the posterior part of the brain, and the dog lived for several years afterwards in complete health; in the later years it was found easily possible to obtain a conditional reflex from various intensities of illumination, yet we could not succeed in getting a reflex for individual visual objects. It was also possible to obtain conditional reflexes for sound in the same dog, and we could even get a fine differentiation of tones. Yet the auditory discrimination of this dog differed greatly from that of a normal animal. Whereas the normal dog can easily distinguish when the same tones follow each other in a different sequence, this was not attained in the present case, in spite of much trouble, and it seemed to lie outside the range of possibilities for this animal. Thus it appears that the limits of accuracy of the analysors are, to some extent at all events, determined by the cerebral apparatus, and that partial destruction of the central end of the analysors leads quite definitely to some special limitation of the activity of the analysors.

The ideal conditions for the investigation of this question would, it seems to me, be obtained in a case in which we had an animal with such numerous differentiations worked out that the slightest interference with the cerebral cortex would be at once rendered evident by a change in this system of differentiations.

Another of our experiments on ablation of part of the brain is especially interesting. In this dog the anterior half of the brain was taken away and all the reflexes which had been worked out on this animal disappeared. The animal appears to be completely helpless and to have lost all its normal relations with the outer world; it cannot take food which is placed before it, it recognizes no objects, persons, or animals, and when it attempts to walk it encounters every obstacle and gets into all kinds of difficulties. And yet even in such an animal there can be found a link with the normal complicated nervous reactions; we can train it to give that response of the salivary glands which we have called the "water reflex." In a normal dog, when water is poured into the mouth, there is usually no secretion of saliva, or at most a few drops. But, if first of all an irritating substance—for example, a little acid—be introduced into the mouth, the subsequent administration of water will provoke an abundant secretion of saliva.

Apparently the various stimuli which accompany the forcible introduction of acid into the mouth, and which also accompany the reflex secretion which follows upon this, become converted into conditional stimuli for the reaction to acid; as such they would also come into play

in the administration of water. This secretion of saliva in response to water has all the characters of a conditional reflex. In the animal which I have just mentioned it is also possible to work out the conditional reflex to water in all its normal details. This result has also been confirmed in another animal in which the centre for smell had been spared, but which in other respects resembled the previous one. In this animal it was possible to train smell reflexes also. These animals, speaking psychologically, were uneducatable idiots when judged by their locomotor systems, but as judged by their salivary apparatus they were rational beings enough.

CONCLUSIONS.

As my time is so limited, I will only mention two of the conclusions which may be drawn from the experiments which have just been described. The advantage of using the salivary glands and not the skeletal muscles as indicators of the higher functions of the brain is clear enough. If we judged by the muscles, the important fact that these complicated nervous relations still remain after the extirpation of the anterior half of the brain would be concealed. These experiments deal a severe blow to the psychological classification of subjective states; a psychological explanation here would encounter insuperable obstacles and a quite incomprehensible series of phenomena.

In an animal from which the cerebral hemispheres have been completely removed it is impossible to form any conditional reflexes at all. It appears, therefore, that the cerebrum is the organ for the analysis of sensations, and for the construction of new reflexes and new connexions. It represents that part of the animal organism which is specialized for the purpose of retaining the animal always in a state of equilibrium with the outer world; in other words, it is an organ for direct and appropriate adjustment to the most varied combinations and changes in the phenomena of the surroundings; it is the organ which is above all others necessary for the unimpeded evolution of the organism.

It is perhaps not rash to think that some of the newly-formed conditional reflexes can be transmitted hereditarily and become unconditional thereby.

Finally, I can assert from my own experience that the various facts which have been described here are all of them easily and faithfully reproducible. My colleagues and I, to whom I take this opportunity of expressing my best thanks, have demonstrated these facts in the two courses of lectures on the conditional reflexes which I have given, and they have also been shown at various scientific societies and to many visitors in my laboratory.

During our many years of work we have never been able with advantage to turn to psychological conceptions for help, or to utilize explanations founded on these conceptions. I must confess that formerly, when I have found myself in difficulties, I have, perhaps in my anxiety, turned in some cases to these explanations, as to conceptions which have been long regarded as established. But in the long run I have recognized how badly they have served me. It was when I was in difficulties that I did not perceive the natural sequence of phenomena. Such help as psychology gives consists only in words; the animal has remembered, he has desired, he has thought—in other words, these were merely examples of undetermined thought. The methods for the investigation of the higher nervous functions of animals which arise from psychological conceptions, the extrication from labyrinths, the disproving of certain hypotheses, and so forth, naturally yield a scientific material; but this is merely fragmentary, and teaches us absolutely nothing of the fundamental principles of the higher neural processes, since it needs itself to be first of all analysed and explained. For an exact and continuous scientific investigation of the functions of the higher nerve centres, it is necessary that the fundamental and guiding principles be purely physiological ones. On the groundwork which I have just outlined it will be possible to work. The results in the hands of other investigators will show whether my premises are correct and whether they are sufficient.

Gentlemen, I feel that I can reckon on your sympathy with what I have described to you of my work, since it must all be accounted in general, if not in detail, immeasurably more your work than my own. I have not felt that it was necessary for me to mention the names of

those of you who have worked at the central nervous system, and especially at the complicated relations of the animal to the exterior, and who have stimulated me with observations and conclusions to undertake the detailed study of the subject which I have in hand. In these studies we have always felt to what an extent we were dependent upon the work of others, rather than upon our own initiative.

I desire to express my best thanks to our distinguished president for having given me the opportunity of speaking to such a distinguished gathering of my professional brethren on a subject to which I have devoted a good third of my scientific life; and you, gentlemen, I must also thank for your attention, which I have so long abused.

"STRUMA" AN IMPORTANT FACTOR IN DISEASE OF THE EYES.*

By T. HARRISON BUTLER, M.D. OXON.,

HONORARY OPHTHALMIC SURGEON TO THE COVENTRY AND WARWICK-
SHIRE AND TO THE WARNEFORD, LEAMINGTON, AND SOUTH
WARWICKSHIRE GENERAL HOSPITALS.

THE older school of ophthalmologists recognized "struma" or "scrophula" as an important factor in many ocular affections, but when Koch showed conclusively that struma and tuberculosis were identical the term was more or less dropped and their successors ceased to employ it. The logical sequence of thought would have been—certain affections of the eye were once regarded as strumous; struma is only another name for attenuated tuberculosis, therefore these diseases are due to attenuated tuberculosis. This reasoning, however, failed to arrest the attention of ophthalmic surgeons, and consequently many of them have even now failed to appreciate the fact that attenuated tubercle plays an important rôle in many of the diseases of the eye, diseases as common and simple as phlyctenular conjunctivitis and keratitis. Dr. Koller, of New York, in a paper on recurrent tuberculous choroiditis, says that the prominent part played by tuberculosis in the causation of eye diseases was not recognized until the beginning of the present century. I would go further and say that even to-day the most recent textbooks pay little or no attention to it. Von Michel was the first to point out, many years ago, that about 50 per cent. of all diseases of the uveal tract were tuberculous in nature. His work received little notice, although Sydney Stephenson and Carpenter amply confirmed his views, mainly on clinical grounds. Dr. Windbiel, writing in *Ophthalmology* (vol. vii, 1910, which also contains Koller's paper), says that tuberculosis of the eye is a relatively frequent disease, although up to within two or three years ago it was believed that the eye was immune to the tubercle bacillus. He goes on to state that in his clinic at Amsterdam, New York, about one half of all the eye diseases were due to tuberculosis and occurred chiefly in childhood and middle life. I think this high percentage must have been associated with some peculiar local conditions. Mackay, of Edinburgh, read an interesting paper at the annual meeting of the British Medical Association in Liverpool, 1912, which showed that the activities of the *Bacillus tuberculosis* were responsible for a large number of diseases of the eye. His paper was copiously illustrated by a series of excellent lantern slides, and was founded upon a laborious and painstaking research. Many other prominent ophthalmic surgeons, both in England and abroad, are fully alive to the importance of tubercle, but others are still content to talk of diatheses and dyscrasias, and to them the word "rheumatic" is a veritable shibboleth.

Before considering the various parts of the eye and their liability to affection with tuberculosis it will be well to consider the grounds for regarding this etiology as probable or certain in any case under consideration. The most important diagnostic agent we possess is tuberculin used by subcutaneous injection. I reject Calmette's procedure at once as utterly fallacious and very dangerous. I have myself proved it to be harmful to normal eyes, but were the eye actually infected with tubercle it might quite easily lead to its total loss. It is unnecessary

to go further into this question, it is one upon which all ophthalmologists, including the originators of the test, are agreed. Von Pirquet's reaction is far too delicate; it gives a positive answer in about 90 per cent. of all adults and in a high percentage of children. A negative result would be far more valuable than a positive, especially if the test were repeated and remained negative. The subcutaneous test is made by injecting old tuberculin into the subcutaneous tissues between the shoulder-blades or into the arm. The patient should be kept in bed for a few days before the test is made, and his temperature taken four-hourly. I always commence with a dose of 0.001 of a cubic centimetre of Allen and Hanburys' old tuberculin. It is uncommon to get a reaction to this first injection. After three or four days I repeat the injection, giving 0.002 c.cm. If no reaction be noted I give a third injection of 0.004 c.cm. The test is not very delicate. It is uncommon for a reaction to follow the first injection, but this sensitizes the body, and the second or the third injection should cause a reaction in a tuberculous individual. It is not essential to increase the dose. In my last case my new house-surgeon misunderstood my directions and gave three successive doses of 0.001 c.cm. Reaction followed the third dose. It has been suggested that this sensitizing action may allow a normal non-tuberculous individual to react. This is not the case; several of my patients have failed to react, even to the third injection. Reactions are far more common after the third than after the previous injections. There are three kinds of reaction: the local, the general, and the focal. The focal reaction is by far the most important in eye work. I have not paid much attention to the local reaction; it seems to me too capricious in its action. It consists of swelling and redness at the site of injection, and may be the only reaction obtained. At present I disregard it as a sign of tuberculosis. In this I may be wrong. The general reaction consists of a rise of temperature occurring at from twelve to twenty-four hours after the injection, accompanied in some cases by general malaise and headache. I take it to signify that somewhere in the body there is a tuberculous focus. The focal reaction consists of increased injection of the eye, pain, lacrymation, and sometimes in the appearance of definite choroidal tubercles of a transient nature, or of nodules in a case of scleritis. I have also noted alterations in pigmentation in cases of tuberculous choroiditis. Up to the present I have never seen any harm done to the eye by a focal reaction to old tuberculin, and in many instances reaction has heralded a rapid recovery. I regard a focal reaction as an absolute indication of the actual presence of bacilli in the eye. Here again I may be in error. Perhaps it is given by an inflammation due to a tuberculous toxæmia.

The second great indication of ocular tuberculosis is the presence of definite tuberculous deposits elsewhere in the body. The most important are enlarged glands in the neck and abdomen, and tuberculous joints and bone disease. I have never so far detected pulmonary complications or pleural disease. In fact, as Straub points out, the chronic attenuated tuberculosis which causes secondary disease, either definitely bacillary or toxæmic, has immunized the organisms to the bacillus, and so serious tuberculosis is rarely seen.

I attach great importance to a family history of phthisis and other tuberculous affections. I obtain it in the majority of my cases. Finally, the actual appearance of the eye will often lead to a correct diagnosis of tuberculosis when the observer has become accustomed to this class of case.

In this paper I am dealing with struma of the eye, attenuated tuberculosis, but it is often impossible to draw a hard and fast line between this class of case and classical florid tuberculous processes, such as, for example, a tuberculous iritis with massive tubercles in the anterior chamber.

It is often difficult or impossible to differentiate between a definite infection where the eye actually contains bacilli and a tuberculo-toxæmia, and in most cases it is unnecessary to make this distinction.

Phlyctenular Ophthalmia.

I shall now after these general remarks consider in detail some of the common diseases of the eye in which

* A paper read before the Birmingham Branch of the British Medical Association.