A British Medical Association Lecture ON SPECIFIC SENSITIVENESS AND ANAPHYLAXIS.*

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You have honoured me with an invitation to lecture to you on some pharmacological subject. I have never felt able to attribute a rigid significance to those divisions which, for our own convenience, we make in the body of medical science, and I shall venture to assume that the form of your invitation merely indicated that you were good enough to desire that I should speak on some subject in which my own work has given me a direct interest. I propose to devote my remarks to a subject which seems, at the moment, to have a great and growing interest for workers in clinical medicine—namely, the group of specific idiosyncrasies, which definitely includes hay-fever, many cases of spasmodic asthma, and specific urticaria, and seems destined to extend its boundaries to include many cases of eczema, and, in the view of some enthusiasts, epilepsy, and various other conditions. The clinical study of these conditions, for which most general practitioners have daily opportunities, I can only approach as an interested outsider. Fortunately there are several recent and readily available publications dealing comprehensively with this side of the question. Dr. John Freeman lectured on the subject to the Royal Society of Medicine, Mr. Frank Coke to a meeting analogous to this, and at the annual meeting of the British Medical Association last July illuminating discussions were opened by Sir Humphry Rolleston and Dr. Harold Barber. The clinical investigation of these conditions made rapid strides in the United States of America during the war, and the publications of Chandler Walker, Ramirez, and others abound in interesting detail. My object is to endeavour to put before you the conception as to the meaning of those phenomena to which experimental evidence seems definitely to point.

For the experimental basis of any conception which we may form of these manifestations of specific sensitiveness or idiosyncrasy we must look to the investigation during the past fifteen years of the phenomenon known as anaphylaxis. I shall make no attempt at a review of the confused and well-nigh overwhelming mass of literature which has accumulated round this phenomenon. I shall not even try to put before you the various theories as to its meaning, with the points of evidence for and against them. I shall, quite frankly, put before you, and commend to your acceptance, the theory which alone seems to me adequate, secure in the conviction that it is the only one that can enable you to bring the facts of clinical experience into coherent relation with those of laboratory experiment. It is fair that I should state that there are still many who do not accept the view which I shall put forward; but I believe I shall do you a greater service by presenting one clear and consistent scheme, than I should by introducing a confusion of rival theories.

The First Recognition of Anaphylaxis.

The first recognition of anaphylaxis as a definite phenomenon was due to Richet. He was working on the substance to which sea-anemones owe their stinging properties—a subject which might seem almost peculiarly remote from the problems of general pathology and practical medicine, though you will note that the effect of the poison, in common experience, was to produce a reaction of an urticarial type, where locally inoculated by the thread-cells of the animal. Richet determined the toxic dose of a preparation for dogs, and, having given a subtoxic injection to a dog, he gave the same animal a second similar injection a few weeks later, with the object of producing an immunity to the poison. The result, on the contrary, was an immediate and violent reaction, with flushing and irritation of the skin, vomiting, purging, haemorrhage from the intestine, and profound collapse. As he was working with a substance which, in larger doses, produced a reaction of somewhat similar though less rapid type in the normal dog, Richet naturally supposed that the condition

which he had accidentally produced was an artificially lowered resistance to the natural poison, the direct opposite of immunity or prophylaxis, and he named the condition "anaphylaxis."

The True Meaning of the Phenomena.

The name "anaphylaxis" has persisted and has passed into general use in medical literature, though it soon became clear that the conception which gave rise to it was not altogether correct. Evidence quickly accumulated which showed that any perfectly harmless protein, provided that it came from a species other than that of the animal into which it was injected, also behaved as an acute poison when it was injected a second time into an animal which, some weeks previously, had received an injection of the same substance. This phenomenon, indeed, had been observed and incidentally recorded by Magendie as long ago as 1839, and by several observers in the intervening period. Only after Richet's work, however, was it systematically studied and recognized as a regularly occurring phenomenon. The symptoms produced by reinjection into an anaphylactic animal were found to be the same, whatever the protein to which it exhibited this abnormal sensitiveness, though they differed according to the species of animal used for the experiment. The guinea-pig, in which the phenomenon was practically rediscovered in America, was found to exhibit the condition with great regularity, and has been the subject of a large proportion of the experimental investigations.

Anaphylaxis, then, is not to be regarded as a weakened resistance to a natural poison; it is rather a condition produced by previous introduction into the system of a foreign protein, in which the same protein, but not any other, acts on subsequent injection as an acute poison, whether it has normally any poisonous properties or not.

The Relation of Anaphylaxis to Immunity.

Anaphylaxis, though superficially so different, soon proved to have many points in common with immunity. The condition, we may say with certainty, is due to the formation of some kind of antibody. In the guinea-pig the specific sensitiveness can be transferred to a fresh animal by injecting the blood or serum of one which has been made actively sensitive; there is a "passive anaphylaxis," due to the transfer of ready-formed antibody, and corresponding to passive immunity. But there are features of this passive anaphylaxis which seem, at first sight, paradoxical. It does not appear immediately, even when the serum containing the antibody is injected directly into the circulation. It is not perceptible until some six hours have elapsed, and not completely developed for twenty-four hours. We can understand why, after a first injection of a protein, a period of ten days or a fortnight must elapse before the animal becomes sensitive; as in the better known reactions of immunity, time is needed for the response leading to the formation of antibody. But when the antibody is ready formed, one would expect the condition which it produced to appear immediately after its injection into the blood, and to be then at a maximum.

There is another paradox. Not only the serum of an anaphylactic animal will convey anaphylaxis; that from an animal immunized against a foreign protein, by a series of properly spaced injections, will convey this passive anaphylaxis even more efficiently—that is, in a much smaller dose. If we take a rabbit and give it a series of injections of, say, egg albumen, its serum develops a precipitin—that is to say, it acquires the property of forming an obvious precipitate when mixed with egg albumen in very high dilutions. Now a very small dose of the serum of such a rabbit, injected into a normal guinea-pig, will make the latter within twenty-four hours acutely anaphylactic to the normally innocuous egg albumen. There are strong reasons for identifying the so-called precipitin with the anaphylactic antibody; yet the serum of a guinea-pig made actively sensitive to a protein forms no visible precipitate with that protein, while the animal whose serum has acquired a high precipitating quality for a protein is not anaphylactic to it, but immune.

As so often happens, these seeming contradictions probably provide the real clue to the nature of the phenomenon with which we are dealing. Weil studied the fate of the precipitating antibody, injected into a normal guinea-pig, during the twenty-four hours which elapsed before the animal became fully sensitive. He found that it rapidly disappeared from the blood, and that when sensitiveness was fully developed the antibody had nearly all vanished. If the

* The substance of a lecture delivered to the Sheffield Division of the British Medical Association.

animal, which had thus become acutely sensitive to a foreign protein, received a further large injection of the serum containing precipitin for that protein, the immediate effect was not to enhance but to suppress the sensitiveness. Antibody freely circulating in the blood was therefore not sensitizing, but protective in action; the antibody must be somehow changed, or must be differently located, before it could render the animal sensitive.

A satisfactory interpretation of these facts would be provided by the supposition that the antibody must get out of the blood and into the living cells of the tissues before it can render the animal sensitive. On this supposition the occurrence in the living cell protoplasm of an aggregation of

FIG. 1.—Shows the specificity of the reaction. The plain muscle was taken from a guinea-pig rendered sensitive to horse serum by an injection of 0.0025 c.cm., given fourteen days previously. The doses added to the bath were in each case 0.1 c.cm., making a concentration of 1 in 2,500 of A sheep serum, B cat serum, C rabbit serum, D dog serum, E human serum, F egg white, and finally at G horse serum. (From the *Journ. of Pharm. and Exp. Therap.*, iv, p. 214.)

favour, I must give some further details as to the nature of the poisonous action.

The Nature of the Symptoms.

I have said that, whatever the protein producing the condition, the picture of the anaphylactic poisoning is practically constant in the same species. In the different species the symptoms are superficially very dissimilar. When the protein is injected intravenously, the guinea-pig which is anaphylactic

FIG. 2.—A similar experiment, the guinea-pig being made sensitive to egg white by an injection of 0.1 c.cm. twelve days previously. At A 0.5 c.cm. horse serum, at B 0.1 c.cm. egg white. (From the *Journ. of Pharm. and Exp. Therap.*, iv, p. 180.)

to it dies in a few minutes, and in an extraordinarily dramatic manner, the cause of death being a tense contraction of the plain muscle surrounding the bronchioles, which in this species are small in diameter and provided with a rich and folded mucous membrane. The rabbit dies of right-sided heart failure, due to excessive resistance developed in the branches of the pulmonary artery. In the dog the central feature of the effect is a collapse of the circulation, with accumulation of a large part of the blood in the enormously distended liver. Certain changes in the blood are present, though in varying degrees, in all the species—leucopenia and delayed coagulation, changes which are associated with the action of any poison injuring the vascular endothelium. In all, recovery from an attack is associated with eosinophilia. Superficially, the general aspect of the shock is very different in these three species, but when we come to analyse the effects we find in all cases a complex, of which the essential features are an intense stimulation of plain muscle and a

poisoning of the endothelial wall of the blood capillaries. One or other of these effects predominates, and is locally prominent, according to the special conformation or liability of the tissues in the different species; but fundamentally the action is of the same kind in all. The view that we are dealing with one common type of poisoning, as exhibited by these different species, is confirmed by the observation that there is a whole group of natural poisons, partial cleavage products of proteins, formed by bacterial or other ferments, which produce these same pictures of intoxication, with the same striking differences, in the different species. Among such bodies I may mention the base known as histamine, a base easily derived from the amino-acid histidine, which is a constituent of almost all proteins.

Laidlaw and I some ten years ago described the intense activity of histamine, and drew attention to the fact that in each species it produced a picture of intoxication resembling that seen in the anaphylactic shock. This has led some observers to suggest that histamine

is actually formed in the anaphylactic animal, when the protein to which it has been sensitized is again injected. A suggestion of the part played by histamine in such phenomena appears again, as we shall see, in connexion with current views as to the nature of asthma. I have never been able to accept such a view of the events in the anaphylactic shock, or any other which attributes the symptoms to the formation of a poisonous product in the blood, and the action of this as the directly toxic agent. All such views are, for me, excluded by the simple fact that simultaneous injection of the antigen and the antibody concerned in the anaphylactic reaction, so that they meet in the blood, has no perceptible effect of any kind. So far as I am able to judge, the simple view that the anaphylactic condition is due to location of the antibody in the cells of the vital tissues, where its reaction with the antigen is the cause of the symptoms, suffices to account for all the phenomena which can with certainty be regarded as anaphylactic.

Direct Evidence of Cellular Sensitization.

Returning to a consideration of this simple conception, we have seen that a characteristic feature of the anaphylactic reaction, in the guinea-pig especially, is stimulation of plain muscle. If the effect is due to antibody fixed in the cells, we ought to find that the plain muscle of an actively anaphylactic guinea-pig, removed from the body and freed from all blood, will respond by contraction to application of the protein to which the guinea-pig was sensitive, but not to any other. We ought to find that plain muscle from a guinea-pig rendered passively sensitive behaves in the same way. We ought further to find that the same antibody as conferred the sensitiveness, if present in excess in the fluid surrounding the plain muscle, will protect it from the protein to which it has been made sensitive, so that it no longer responds. In other words, we should be able to make *in vitro* artificial combinations corresponding to the conditions of active and passive anaphylaxis and of true immunity.

There is another condition, which we ought to be able to illustrate in such experiments, and which I want clearly to differentiate from immunity—namely, the condition which

FIG. 3.—Shows that the reaction discriminates between the pure egg albumen of the hen and the duck. Guinea-pig sensitized with 1 mg. of pure hen albumen twenty-one days previously. No response to duck albumen. After the first effective dose of hen albumen the plain muscle is desensitized, and no longer responds to this substance, even in a ten-fold dose. (From the *Biochemical Journal*, xiii, p. 253.)

FIG. 4.—Shows that the reaction discriminates between individual proteins of the same serum. The guinea-pig was sensitized with 1 mg. of the euglobulin of horse serum thirteen days previously. At A and B 1 mg. and 10 mg. of the pseudoglobulin of horse serum were added to the bath without effect; at C 10 mg. of the euglobulin of the same serum were added. (From the *Biochemical Journal*, x, p. 422.)

has somewhat clumsily been called "antianaphylaxis," and which I should prefer to call "desensitization." When a sensitive guinea-pig is given a sufficient dose of the antigen to cause symptoms, but not death, especially if the antigen is slowly introduced, so that the dose can be relatively large without killing the animal, it is found on recovery to have lost its sensitiveness, and to remain normally insensitive for a week or so. The antibody which its cells contained has been used up; more must be formed and fixed to the cells before the guinea-pig is again anaphylactic. Contrast this with the condition which I have called "true immunity," in which plenty of antibody is present, but in such excess in the body fluids as to catch the antigen and put it out of action before it can reach the sensitive cells.

Now it is very simple to demonstrate all these phenomena on a slip of plain muscle taken from the guinea-pig after death. This is carefully freed from all traces of blood or serum by perfusing Ringer's solution through its vessels, and it is then suspended in a small volume—100 c.cm. or so—of clean Ringer's solution, kept at body temperature, and saturated with oxygen. To this bath the antigen can be added, and the response of the strip of plain muscle recorded by fixing one end and attaching the other to a light lever, writing on a slowly revolving drum. The tracings show the ease with which the various phenomena can be demonstrated; they are taken from a series of papers which I have published since 1913.² (See Figs. 1 to 5.)

You will agree, I hope, that these figures give direct support to the conception that anaphylaxis is due to sensitization of the cells by the presence in them of the precipitating antibody, excess of which in the surrounding fluid protects the sensitive cells and constitutes an immunity.

Non-specific Sensitiveness and Non-specific Desensitization.

So far we have been dealing with the experimental phenomenon of anaphylaxis as seen in the laboratory, and, before leaving it, there is one other point which I want to make clear, as it has some bearing on our further discussion. We have seen that the anaphylactic sensitiveness is highly specific, discriminating between similar proteins from different species, and even between different proteins from the same species. But the animal which is highly anaphylactic, whatever the protein to which it has been made sensitive, shows also some degree of enhanced sensitiveness to naturally poisonous substances, having a type of action resembling that seen in the true anaphylactic response. The upholders of the alternative theory, which supposes that the anaphylactic shock depends on the formation of a poison in the blood, have shown that normal guinea-pig's serum, when treated with various colloids and suspensions, acquires a toxicity of such a kind that it kills a normal guinea-pig with symptoms more or less closely resembling those of the anaphylactic shock. To such a toxic serum the anaphylactic guinea-pig usually exhibits an abnormal sensitiveness, so that the cell protoplasm would appear to have acquired a more general instability, an increased liability to this kind of toxic disturbance, in addition to its highly specific idiosyncrasy of reaction to one, normally harmless, protein in particular.

In this connexion also mention should be made of another point of contact between true anaphylaxis and non-specific intoxications. We have seen that the anaphylactic guinea-pig, which recovers from the effects of reinjection, is desensitized for a week or so. An anaphylactic guinea-pig, which recovers from a non-fatal dose of one of the natural poisons producing similar symptoms, is found to be less sensitive to its specific antigen than another, similarly sensitized, but not treated with the non-specific poison. The full sensitiveness is, in this instance, recovered in twenty-four hours or so, and there is no evidence as to whether the

temporary loss of sensitiveness is due to detachment of antibody from the cells, or to formation of some substance which inhibits aggregation in the protoplasm. The phenomenon is worthy of note, as having its parallel in a certain method of treatment, as we shall see later.

Anaphylaxis in Man.

Turning now to a more practical aspect of our problem, we have to inquire what bearing these phenomena, exhibited by guinea-pigs and other animals in the laboratory, have upon conditions seen in man. The first and most obvious application is to the effects of injecting horse serum into human patients. You will be familiar with the fact that a certain proportion of patients, as the result of a first injection of horse serum, exhibit, after an interval of some ten days, a reaction which has many features suggesting that we may be dealing with an anaphylactic phenomenon. The commonest symptoms point clearly to an injury of capillary endothelium, leading to urticaria, swelling or pain in the joints, and sometimes facial oedema, accompanied by constitutional disturbance. The latent period of some eight to ten days is highly suggestive; it is the interval needed in the guinea-pig for the appearance of the anaphylactic condition. We are led to suspect that in this interval an antibody has been produced and located in the tissue cells the sensitiveness of which gradually rises, till reaction with some remnant of the original dose of horse-serum protein causes the outbreak of

symptoms. The suspicion is strengthened when we consider the result of a further injection into such a patient, at an interval of months or even years. The phenomena have, fortunately, not that certainty of production to which we are accustomed in the guinea-pig, but a certain number of patients receiving such a second injection give a reaction of a much more clearly anaphylactic type. The onset is almost immediate in the neighbourhood of the hypodermic injection, and within a short time a general dermal and constitutional reaction of much greater than normal severity appears. Oedema of the glottis may occur, and, of course, be a dangerous feature of the condition. In a number of cases where such a second injection has been made intravenously the result has been rapidly fatal. Here we have quite obviously the conditions which, in other animals, have been found to produce a typical anaphylaxis, and there can be little doubt as to the nature of the phenomena with which we are dealing. Fortunately it is

clear that the anaphylactic condition is produced in man with nothing like the fatal regularity with which it appears in some of the animals used in the laboratory. If there is reason to suspect its presence, a small hypodermic injection of the serum should reveal it without dangerous symptoms, and at the same time begin the desensitizing process, which must be completed by carefully graded intravenous doses before a large intravenous injection can be undertaken with safety. When we bear in mind that, after the first year of the late war, practically every wounded man in our armies received an injection of antitetanic horse serum, and that a large number must subsequently have received treatment by an immune horse serum of one kind or another, the paucity, in relation to the total number, of reports of dangerous or fatal anaphylactic shock seems to indicate that such sensitization in man is the exception rather than the rule.

Indeed, of the total number of fatalities recorded as the result of injecting horse serum into man, a surprisingly large proportion have occurred after injections into patients who have never received serum before—into patients, that is to say, who had a natural sensitiveness to horse serum of an intensity but seldom appearing as the result of a preliminary injection. A large proportion of such cases, again, has occurred in subjects of asthma: but I am not aware of any data which would entitle us to connect them definitely with an asthma due to horse sensitiveness. It would certainly not be surprising to find such a connexion established. This leads us to another part of our subject, but before

FIG. 5.—Plain muscle from a guinea-pig which has been rendered immune to horse serum, showing that, when washed free from the protective excess of antibody in the blood, it is sensitive, like that from the anaphylactic animal. At A 0.5 c.cm. of horse serum was added to the bath; at B, 0.5 c.cm. of sheep serum. (From the *Journ. of Pharm. and Exp. Therap.*, iv, p. 191.)

* Records were also exhibited, which will be published shortly by Dale and Kellaway, showing that the anaphylactic plain muscle can be protected from the effect of the antigen by adding to the saline bath an excess of the antibody which was used to sensitize it passively.

leaving the question of serum sickness I should like to mention one further point of some theoretical interest. There are numerous records of more than one rash following a single injection of horse serum, the rashes following one another with an interval of a few days. I have searched and inquired, but have found no record of more than three such distinct rashes in one patient following a single injection. Now, there are three distinct proteins in horse serum, and it is possible in the guinea-pig to produce a separate sensitiveness to each; and these do not develop simultaneously, but at different intervals from the primary injection.

Naturally Occurring Specific Sensitiveness ("Toxic Idiopathies").

Turning now to the question of the different types of specific sensitiveness, which appear to be inborn or to develop spontaneously in some human subjects, the case of hay fever or hay asthma seems fairly clear. It is common ground that we have, in this case, a cellular sensitiveness to the proteins of certain pollens which are easily borne on the wind. In this country grass pollens are chiefly responsible; in the United States they have a second outbreak of a similar condition in the autumn, due to the pollen of a composite, the ragweed, which is very abundant there. The work of Noon, Freeman, and others has shown that the sensitiveness is not restricted to the conjunctiva and respiratory mucosa; the reaction occurs in these regions especially, because the proteins of the pollen can there easily reach the sensitive cells. A typical urticarial wheal is formed on the skin, however, if the pollen is applied to a lightly scarified area; and Freeman, by getting a subject of hay fever to ingest grass pollen, produced in him a vigorous diarrhoea. The skin test can be used to discover the species of pollen to which the sensitiveness and the attacks are due.

Very much on the same footing are the numerous cases of asthma which, by investigations in recent years, have been proved to be excited by the inhalation of minute quantities of material originating from some particular species of animal—horse, cat, or dog being, apparently, the commonest culprits. The substances exciting reactions of this type are mostly particles of epidermal origin—hair or scurf from the skin—and the patients give a specific skin reaction to proteins extracted from the material responsible and applied to a minute, very superficial cut. Usually, but not always, the patient sensitive to the epidermal structures shows also a sensitiveness to the blood serum of the same species. It is hardly a matter for surprise, therefore, that there are cases on record in which asthmatic patients have exhibited a fatal sensitiveness to horse serum, injected with a therapeutic or prophylactic aim. Many cases have been brought to light in which asthma, coming on at night, was associated with a sensitiveness to chicken feathers, and disappeared when a pillow stuffed with horsehair or vegetable fibre was substituted for a feather pillow.

Now, cases of this kind present many points of close similarity to the condition of artificial sensitiveness or experimental anaphylaxis. An objection to their identification has been raised on the ground that the so-called natural idiosyncrasies cannot be passively transmitted. I admit that such an objection would be fatal if we were to adopt the humoral theory of anaphylaxis, attributing the condition to the presence of an antibody in the blood, with which the antigen there reacts. But on the theory which I have commended to you, which attributes sensitiveness to an antibody present in the cells, the objection has little weight. It is true that anaphylaxis can be transferred from the anaphylactic to a normal guinea-pig, at a time when the anaphylactic condition is newly developed. But after an interval of months from the primary injection, though the sensitiveness is still acute, passive transfer often fails; the antibody has practically disappeared from the blood. We have only to regard these cases of human sensitiveness as extreme examples of this condition—and the sensitiveness is, indeed, often of an extreme order—in which the antibody, if it ever was in the blood, has usually become located exclusively in the cells, to bring the two kinds of phenomena fully into line. There are, moreover, a few cases on record in which the blood was by no means free from antibody. Ramirez records a case in which, after receiving a transfusion of blood from a fellow patient, who happened to be a subject of horse-sensitiveness, a patient was seized with asthma, for the first time in his life, on going for a drive in a horse-drawn carriage during his convalescence.

When attacks of asthma or urticaria, or both, are excited

by the ingestion of certain articles of animal or vegetable food, another difficulty of explanation presents itself. The cases present similar phenomena of specificity, and respond as well to the diagnostic skin reaction as the former class. But it is contrary to experience in experiments on anaphylaxis that the symptoms should be excited when the protein is swallowed, and, therefore, has to run the gauntlet of the digestive juices before absorption. I believe the fact to be that we do not, by experimental procedures, succeed in producing such extreme sensitiveness as that which appears in certain human patients. Even the minute traces of unbroken protein which pass the alimentary mucosa, possibly owing to some fault of digestion or absorption, seem sufficient, if they are of the specific kind responsible for the condition, to cause an outbreak of urticaria or an attack of asthma. Sensitiveness to the proteins of certain molluscs and crustaceans, or of certain fruits, such as the strawberry, is not uncommon. They cause little trouble, since the patient learns that he cannot tolerate these foods, and avoids them. When the sensitiveness is directed to a protein occurring in some common article of diet, such as wheat, egg, potato, or milk, the cause of the condition is often not identified by the patient, and requires a skin test for its detection. Even when the diagnosis is complete, treatment by elimination of the offending protein from the diet may present great practical difficulty.

Other Features Concerned in Asthma and Similar Conditions.

Time alone can show what proportion of the cases of spasmodic asthma and urticaria will ultimately be referable to this type. At present the tendency is for the proportion to increase, as investigators gain experience in the application of the specific tests, and have a growing range of animal and vegetable proteins under suspicion and available for use. There are other factors, however, which are generally credited with importance, and which are often regarded as incompatible with the conception of the condition as due to sensitiveness to a foreign protein.

One such factor is heredity; but it is clear, from some interesting family trees published by Freeman, that the inheritance is not of sensitiveness to a particular protein, or even of a certain type of reaction, but of the tendency to acquire some kind of idiosyncrasy for foreign proteins. A father subject to hay fever may have among his children one suffering from horse-asthma and another from some idiosyncrasy to a particular food, and so on. If the inheritance is simply of the tendency to respond, by forming cellular antibody, to some chance parenteral introduction of a trace of foreign protein, the hereditary tendency is in no way inconsistent with the conception which we have been discussing.

Another factor in the causation of asthma or hay fever which has also been regarded as inconsistent with the theory of sensitization by foreign protein is that of neurosis. Many cases are on record in which the sight, or even the mental image of the supposed source of the sensitizing protein, without any possibility of its actual presence, has been sufficient to induce an attack—the sight of an artificial rose, a film at the picture palace representing hay-making, or, in a case recorded by Freeman, a vivid description of a field of mustard in flower. I have already disclaimed any experience of clinical matters, but as an experimental worker, who has read something of Pavlov's more recent work, I find it difficult to believe that any real incompatibility exists between such phenomena and the view that the condition has its origin in specific sensitization to foreign protein. We know from Pavlov's work that in a dog, an animal of relatively simple psychological development, it is possible, by daily association of a sound or a skin stimulus with food or acid in the mouth, to produce a new psychological reflex, so that the sounding of the note or the stimulation of the prescribed skin area now suffices by itself to evoke a secretion of saliva. I do not think it is difficult along such lines to suppose that a man who has become sensitive to rose pollen, and has had repeated experience of an association between the presence of roses and suffocating constriction of his bronchial tubes, might ultimately develop a new reflex, connecting the visual image of roses with the nervous control of the bronchioles, so that the sight of an artificial rose would eventually suffice to excite an attack of asthma.

There are, I gather, other cases of asthma in which the attacks seem to be excited by some non-specific chemical stimulus—in which, for example, a digestive disturbance,

a mild enteritis, however produced, is sufficient to produce an attack. It would appear that in such cases the absorption of poisonous cleavage-products of proteins may be the exciting cause, and even histamine has been held by some writers to be responsible. If you have in mind what I stated, in dealing with experimental anaphylaxis, concerning the generally enhanced sensitiveness of the anaphylactic animal to poisons of this type, you will find no difficulty in reconciling the occurrence of such attacks with a specific, anaphylactic origin of the asthmatic condition, in the patient in whom they occur. Nor should the evidence brought forward by Auld and others, as to the improvement of such patients under treatment with small injections of poisonous protein derivatives, such as Witte's peptone, present much difficulty of interpretation, if you remember my statement that the anaphylactic guinea-pig can be partially desensitized by a similar non-specific intoxication.

I am by no means suggesting that every case of so called asthma is of the anaphylactic type. Even if the so-called cardiac asthma and renal dyspnoea are excluded, I imagine that there are many cases in which the symptoms are asthmatic, but which have a different origin altogether. When the question is raised of sensitization to the proteins of infecting organisms, the distinction between a primary toxic action of their products and an anaphylactic reaction to their proteins becomes difficult to draw. Especially is this the case with an infection of the respiratory passages themselves. There seem to be some clear cases; however, of infection at a distant site, causing, not a local trouble, but a genuine general anaphylactic reaction. But the discussion of the relation of anaphylaxis to bacterial proteins, full of suggestion though it is for a rational conception of the genesis of certain chronic morbid conditions, would lead us into such inadequately charted waters that I shall not attempt the rôle of pilot. My object has been to provide, from the experimental side, a more definite conception of the nature of those conditions in which sensitization to foreign proteins is clearly established; such a conception as may help to focus ideas, to stimulate observation, and even to rationalize treatment.

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A British Medical Association Lecture

ON THE

DIAGNOSIS AND TREATMENT OF INTRATHECAL TUMOURS OF THE SPINAL CORD.*

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In this lecture I shall not endeavour to advance any original ideas, but will present certain aspects of an important topic which, although they are familiar to the neurologist, are, I fear, not so well known as they ought to be to the general body of the profession. The subject is important because we have in the treatment of intrathecal tumours of the spinal cord one of the most, if not the most, reliable developments of the surgery of the nervous system, and yet I am convinced that in this country many cases which could be readily and almost dramatically cured are allowed to pass without recognition or radical treatment and to run unaided their inevitable course to death.

I propose to illustrate my remarks by showing two patients, both operated upon sufficiently long ago to demonstrate what may reasonably be called "end results." The first will serve to illustrate all the salient points of an intrathecal tumour; the second is one of a more obscure condition liable to be confused therewith.

H. H., a motor driver, aged 43, came under my observation in the Manchester Royal Infirmary in March, 1920, when I was asked to see him by my colleague, Dr. Ramsbottom, and the first point which I must note is that, as these cases rarely come directly before the surgeon, it will quite properly lie with the general

practitioner and the physician to make the preliminary diagnosis, without which nothing further can be done.

The patient, whose complaint may be briefly described as "paraplegia," gave a clinical history of the utmost importance. About the end of 1918, while in an army hospital with an attack alleged to be one of influenza, he noticed what is described as an indefinite pain about and just below the left costal margin. At first this pain was felt only in the morning, and it passed away throughout the day, but it tended gradually to become more constant. In March of 1919, when demobilized, he had no great amount of pain, but suffered a little from what he and his advisers called lumbago. He was, however, able to return to civil work and to continue thereat until October. During this period he noticed a gradually increasing weakness of the left lower limb, which at first used occasionally to "give" a little, and which later began to "drag." In the autumn of 1919 the right leg also began to show similar symptoms, and he then had to give up his work, although still able to walk about with the aid of a stick. In the month of January, 1920, he became rapidly weaker, and in the first days of February he was entirely confined to bed. From that time until I saw him in March he was in hospital and only growing feebler.

I have dwelt in detail upon this clinical history for reasons to which I shall return directly, but we may now turn to his condition as first seen.

He could not stand or walk unless supported. The right leg was very weak; the left could not be moved in the bed. When assisted he attempted to walk, but did so with an extremely spastic gait, more marked on the left side. There was no marked atrophy of the limbs, but the left was thinner than the right. As regards anaesthesia, he presented fairly good appreciation and localization of contact throughout, although there was a little delay in response. The appreciation of heat and cold and the sense of pain were lost in both lower limbs, and thence upwards to a level of about 2 in. above the umbilicus. Knee-jerks were exaggerated on both sides, and he had marked ankle clonus, especially on the left; the plantar reaction was extensor; the lower abdominal skin reflexes and the cremasteric reflexes were very sluggish. Bladder and rectum showed no abnormality. Pain was of the girdle type, running round immediately above the umbilicus, although in the early stages it had been assigned to a higher level; it was sufficiently severe to require a nightly dose of opium.

So far, then, we have a sufficiently typical case of a transverse lesion of the spinal cord more advanced on the left side, but on a very slight consideration of the symptoms and onset, we can go much further and recognize with almost absolute certainty an intrathecal tumour which may readily and most hopefully be removed—a diagnosis founded on both negative and positive indications.

About traumatic lesions we need not trouble. I have seen several cases of haemorrhage into the lower dorsal region of the cord, generally occurring in boys or young men and often after bathing in cold water, but in such, as in trauma, the onset is acute. Tuberculous disease of the spine is excluded by the absence of any evidence of bone disease either clinical or radiographic, and by the very slow onset; in this connexion I may say that local tenderness on tapping the spinous processes, and even local kyphosis may be present in the case of intradural growths, and that such symptoms must not be taken as excluding the presence of such growths, but here this possible source of error had not arisen. For similar reasons it is not at all probable that we have a growth—generally malignant—of the vertebrae themselves; the pain is not the intense pain of "paraplegia dolorosa" met with in such cases, and, while vertebral growths are generally secondary, there is here no indication of any primary growth elsewhere. Syphilis is excluded; so far as exclusion is possible, by the total absence of any indication of that disease, and by the fact that the cerebro-spinal fluid gave a negative Wassermann reaction. Growths, tuberculous masses, and cysts within the cord itself are all comparatively rare, especially in the lower dorsal region, and are not as a rule accompanied by pain. Cysts, such as hydatid cysts, in the meninges would, of course, produce the same symptoms as true tumours, but their treatment is identical. Of a remaining possible source of error I shall speak in connexion with our second case.

So much may be said for the negative side of our diagnosis. On the positive side we have a very strong argument. The essential feature of the clinical history was, as we have seen, pain long precedent to the paraplegia, of varying intensity and associated with remissions, while it was not localized in the back, but extended vaguely along one or more spinal segments. Such pains are almost invariably present as an early symptom of intrathecal tumours; I have traced back their history to as long as two years before any paraplegic phenomena were noted, and I have known them to be in abeyance for many months. They may or may not be associated with paraesthesiae or with a certain amount of anaesthesia. They may be bilateral or, as in the early stages of

* Delivered to the Birmingham Branch, November 17th, 1921.