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ALLERGY OR ANAPHYLAXIS IN EXPERIMENT AND DISEASE*

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It is a general idea that when an animal previously injected with an antigenic substance is injected again with that substance, the immunity induced by the first injection is reenforced. Under certain circumstances, however, that would not seem to be the case, because violent, even fatal symptoms as well as other manifestations may set in after the second injection. This aspect of immunization has been studied very actively of late and results are being obtained that seem to place important pathologic processes in a new and clearer light.

In 1892, von Behring described an increased susceptibility in animals to diphtheria and tetanus toxins, even when they were immunized so that the blood contained antitoxin, and this condition he termed "hypersusceptibility." A few years later, Richet and Héricourt found that dogs, on reinjection with eel serum, which is primarily toxic, seemed to become increasingly susceptible rather than immune. And when Richet found that reinjection of extracts of actinia, in place of causing immunity, might give rise to acute symptoms that would differ from those ordinarily caused by the toxic constituents of the extract, he coined the word "anaphylaxis" to designate this peculiar condition as the reverse of prophylaxis. In 1905, von Pirquet, and Schiek published their classical studies of serum disease and in this, and in other publications by von Pirquet, is developed with great clearness, the conception that it concerns a change in the reactive powers of the body to the introduction of foreign substances, to designate which von Pirquet introduced the word "allergy" (*ergeia*, "reactivity" and *allos*, "altered"). In 1906, Theobald Smith's phenomenon became known; this name has been given to the violent and convulsive symptoms that may arise when guinea-pigs injected previously with mixtures of diphtheria toxin and antitoxin are reinjected with horse-serum.

This observation gave rise to a series of important researches by Rosenau and Anderson, Otto, and many others, and it has become established that when foreign protein is introduced into the tissues and blood of the body, there develops a condition which may manifest itself in acute symptoms, often fatal, and in other special ways, when that protein is introduced again under proper circumstances. This condition is transferable to normal animals by means of the blood and organs of prepared or sensitized animals, and animals passively

prepared in this way present the characteristic symptoms, soon to be described, when injected with the protein in question.¹

HYPERSUSCEPTIBILITY TO TOXINS

At first hypersusceptibility to toxins (Behring) and anaphylaxis were regarded as describing the same things, but now it seems that the toxin-hypersusceptibility may differ in important respects. Thus the symptoms of immediate anaphylaxis are essentially the same in the same species, no matter what the foreign protein, whereas toxin-hypersusceptibility is said to present the symptoms of intoxication caused by the toxin used for immunization. And then hypersusceptibility to toxins does not seem to be transmissible to normal animals, whereas in anaphylaxis the condition is so transferable, hence toxin-hypersusceptibility is excluded from further consideration at this time.

THE ANAPHYLACTIC EXPERIMENT

The typical experiment involves the first or sensitizing injection (or injections), the period of incubation and the reinjection. The exact quantitative relations have been determined best in the case of the guinea-pig, the animal used the most in this work because the most sensitive. It has been found that 0.001 c.c. of horse-serum, for instance, so changes a guinea-pig, sensitizes it, that a violent and fatal reaction occurs on reinjection of horse-serum (Rosenau and Anderson); in the case of beef-serum, 0.01-0.001 c.c. and even less leads to acute death when 0.2 c.c. of beef-serum are injected intravenously at the end of the incubation period (Dörr and Russ); 0.1 c.c. of a 10 per cent. suspension of red corpuscles induces anaphylaxis with respect to the corresponding hemoglobin (H. Pfeiffer and Mita); of pure egg-albumin one-millionth of a gram suffices to set up a fatal reaction on intravenous reinjection of one-tenth to one-twentieth of a milligram, and as little as one twenty-millionth of a gram makes a guinea-pig distinctly anaphylactic (Wells). With respect to bacterial and other proteins the quantitative relations have not been worked out so exactly. The first injection may be given subcutaneously, intraperitoneally, or intravascularly. From observations in connection with serum disease we know that human beings may be sensitized by a single injection of horse-serum. Rabbits and dogs do not respond nearly so easily as guinea-pigs, and several preliminary injections at intervals of a few days may be necessary. Guinea-pigs may be sensitized by the introduction of horse-serum and egg-white into the

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1. I omit all references to the literature on allergy or anaphylaxis, which I shall use as synonymous terms, because complete bibliographies are given by von Pirquet in his fine article on "Allergy," *Arch. Int. Med.*, 1911, vii, 259; by Friedemann, "Anaphylaxie," *Jahresh. B. d. Ergebn. d. Immunitätsforschung*, 1911, vi, 31, and by Schittenhelm, "Ueber Anaphylaxie vom Standpunkt der pathologischen Physiologie und der Klinik," *ibid.*, p. 115.

stomach and the large intestine, and even by the inhalation of a fine spray of foreign serum. It is believed, also, that in man foreign proteins may enter the blood from the digestive tract, but probably only under pathologic conditions. The allergic reaction has been obtained in goats, sheep, horses, mice, chickens and pigeons, and is a phenomenon of general biologic significance.

In guinea-pigs injected with serum the period of incubation lasts about from six to eight days; when very small or very large quantities are injected it may last longer. In serum disease there is an incubation period of about the same length. At the end of the incubation the reinjection of the same protein as injected or of a closely related substance brings on the symptoms of allergy. Here the intravenous injection is the most effective, and the quantity injected must be several times that of the first injection (guinea-pig). The duration of the sensitive, allergic or anaphylactic state varies; facts obtained from various sources indicate that in some cases it may last for months and even years; in guinea-pigs the maximum sensitiveness occurs between the tenth to twenty-first days after the first injection.

In its various phases the allergic state recalls the course described by antibodies in the blood on introduction of antigens—there is the same latency, followed by a period of maximum intensity of development, and then a gradual fall. This correspondence becomes better understood when we consider that the allergic state is dependent, if I may anticipate, on the formation of specific antibodies.

SYMPTOMATOLOGY

Generally speaking the severe, general symptoms produced by different proteins are quite uniform and characteristic in the same species, while in different species the symptoms may vary because the same organs are not involved to the same degree, even when the reaction is produced by the same antigen. We are most familiar with the symptoms as they appear in the guinea-pig, dog, rabbit and man.

Guinea-Pig.—This animal gives the most constant and most intense symptoms, being, according to one statement, four hundred times as sensitive an anaphylactic reagent as the rabbit. On intravenous reinjection, the symptoms may be explosive and death may result in a few moments with dyspnea and convulsions. The symptoms develop somewhat slower on intraperitoneal and subcutaneous reinjections, and some minutes may elapse before the animal begins to scratch its nose and body. It becomes restless, seems to choke; convulsive movements occur about the mouth and throat; there is retching, discharge of urine and feces, and then convulsions, respiratory arrest and death may ensue. In the so-called paralytic form weakness with flaccidity of the muscles is characteristic; there may be combinations of the convulsive and paralytic forms. If recovery takes place there follows loss of weight. The most striking change observed after death is permanent distention of the lungs—the Auer-Lewis phenomenon. The lungs fill the chest cavity completely; the alveoli are distended, the walls may be ruptured; and the walls of the bronchi (secondary and tertiary, Schultz and Jordan) are contracted, owing, it has been found, to peripheral action, the death in reality resulting from asphyxia due to folding of the bronchial mucosa by the contraction of the smooth muscle in the bronchi, and not, as Besredka and others have asserted, from central

causation. Multiple hemorrhages occur in the lungs and elsewhere associated with fatty changes.

H. Pfeiffer has shown that depression of the temperature is constant in the severer forms of anaphylaxis in the guinea-pig. In fatal cases this fall may be as much as from 7° to 13° C. In all cases in which the animal survives there is a close relation between the severity of the symptoms and the extent of the fall of the temperature—the severer the symptoms the deeper the fall and the longer the time required for the animal to reach its normal temperature again. These two factors, the extent and duration of the fall, are used to obtain accurate measurements of the degree of shock. It is important to note that the reinjection of very minute quantities of antigen may raise the temperature.

Leukopenia and a temporary loss of complement in the blood also occur in instances not immediately fatal.

Dogs.—In this animal the symptoms are not so violent as in the guinea-pigs, and deaths are infrequent. On intravenous reinjection there is great restlessness often with screaming; soon the animal becomes very weak, falls over, and it may be still perhaps for hours; feces and urine are usually discharged; dyspnea is not marked, but there is a rapid fall of blood-pressure, sometimes to the extent of 80-100 mm. and it has been found that this is due to peripheral action on the splanchnics. When the pressure begins to rise, the other symptoms begin to disappear. In some cases blood is discharged from the intestines and there may develop a condition of hemorrhagic inflammation, in both the large and the small intestine, which Schittenhelm and Weichardt have termed "enteritis anaphylactica." There is leukopenia with loss of mononuclears, and the coagulability of the blood is reduced.

Rabbits.—Arthus noted that in rabbits subcutaneous reinjection of horse-serum may cause local edema and even necrosis—Arthus' phenomenon: (similar phenomena may occur in other species). In addition, non-fatal anaphylaxis is associated with respiratory disturbances, marked prostration, fall of blood-pressure, increased peristalsis. In rabbits highly sensitized to horse-serum by repeated injections and then given 5 c.c. of fresh serum intravenously, Auer observed a short clonic convulsion, weakness or absence of the heart-beat, and death: in this case death is due to a change in the heart-muscle, a chemical rigor, which is most pronounced in the right ventricle. Blood coagulation is delayed.

Man.—In human beings the injection of therapeutic serums may give rise to a variety of allergic phenomena. A few instances of alarming collapse and even of death, the immediate symptoms being not unlike those of immediate anaphylaxis in guinea-pigs, have occurred after the first injection of antidiphtheria serum, and in such cases it is not clear how sensitization has been produced. The suggestion has been made that, in some cases, sensitization has resulted from the oral introduction of horse-meat or closely related substances.

It is possible that under very special circumstances the poisonous substances causing the symptoms may develop through autolytic processes in the serum itself, or from the action of the serum on the proteins of the patient. In most cases we probably shall have to rest content with the assumption that for reasons not now understood, the persons so affected harbor in their blood an unusually large amount of the antibodies concerned in the reaction. Schultz and Jordan suggest that the occasional severe serum phenomena in man are due to an abnormal development of the bronchial mucous mem-

brane whereby asphyxia is produced on contraction of the bronchial muscle.

The more familiar, typical serum disease, concerning the allergic nature of which there is no question, is peculiar in that the symptoms may appear after only one injection of serum, usually in from eight to twelve days. In this case part of the antigen, that is, the horse-serum, is assumed to remain unchanged, or incompletely changed, possibly in the skin at the point of injection and elsewhere, until enough of the substances required to cause a sharp reaction has been produced by the body. If serum is reinjected some days after the first injection, there may develop an immediate reaction, with marked local changes even in case of small doses of serum, and sometime with severe symptoms and collapse. In this case the conditions and general results of the anaphylactic experiment are reproduced quite accurately. Or the reaction after reinjection may be accelerated, that is, develop after a short period of latency (from five to seven days). Here also the manifestations may be severe. The ordinary symptoms of serum disease are so familiar that it is only necessary to mention them: urticarial and erythematous eruptions, local and general edema, swelling of lymph-nodes, pains in the joints, headache, weakness, fever and leukopenia. In some cases there may be a bloody diarrhea.

In by far the larger per cent. of cases the first injection of antidiphtheria serum as now used—concentrated and properly aged—does not produce any symptoms of serum disease; here we can assume that the foreign proteins are disposed of so gradually and in such a way that sufficient toxic substances are not formed at any one time to cause symptoms. Other forms of allergic manifestations in man are discussed later.

From this consideration of the functional and other disturbances in anaphylaxis it is clear that the criteria and standards of measurement are more or less peculiar to each species.

THE ANAPHYLACTOGENIC OR ALLERGENIC SUBSTANCES

The anaphylactic reaction is obtainable with a variety of substances such as serum, milk, egg-white, cells (animal, vegetable, bacterial) and more or less pure proteins. These are substances that have the power to induce in suitable animals the formation of antibodies, i. e., they are antigens.

Now, the bodies that take part in the anaphylactic reaction follow the same laws of specific action as the antigens and antibodies, with the action of which *in vitro* we are familiar. In both cases, species-specificity obtains with respect to most antigens, that is to say, in the case of anaphylaxis, the reaction that has been discussed is obtainable only by means of the protein used to sensitize the animal, or from some closely related species; and usually best by means of the very same protein as that used for sensitization. Dörr and Russ found that guinea-pigs of the same weight, passively sensitized in the same way with the same quantity of antishoop-serum, reacted on reinjection of the serums about to be mentioned in the following minimal doses:

Sheep-serum	0.004 c.c.
Goat-serum	0.004 c.c.
Beef-serum	0.01 c.c.
Swine-serum	0.6 c.c.
Human serum	1.0 c.c.
Horse-serum	2.0 c.c.
Chicken-serum	No reaction.

This illustrates species-specificity in anaphylaxis. This specificity is well marked in case of bacteria.

In strongly immunized or sensitized animals the scope of the reaction becomes extended so that it reaches over to more or less closely related species. It is said that in the case of fish protein the specific limitations are not so precise as in birds and mammals. Human and ape, horse and ass, sheep and goat, rat and mouse serum-proteins are not distinguishable by the anaphylactic reaction; rabbit and hare proteins are.

Some animal proteins appear to possess a specificity of their own, in addition to the specificity of species: Thus hemoglobin and blood-serum are limited in their reactions by species at the same time as they seem to be in some degree distinct the one from the other. In certain cases at least, milk is different from blood-serum. It is highly interesting, indeed, that certain animal proteins have no species-specificity. This is illustrated by the crystalline lens. Uhlenhuth found that the lens of one species is not distinguishable from those of other species by means of the precipitin reaction, and this seems to be the case, also, with respect to the anaphylactic reaction: Guinea-pigs injected with extracts of beef-lens react not only to these extracts, but also to lens-extracts of widely separated species and even of the guinea-pig itself, but not to the corresponding serum-proteins. We may say that the lens-proteins are strictly organ-specific and without species-specificity. Results are recorded that indicate that the tissues of the uveal tract, the sexual cells, especially of the male, and cells of malignant tumors contain substances with organ-specific characteristics, but further investigation is necessary before any final conclusions are indicated.

Here may be mentioned that fetal tissue, placenta and amniotic fluid in experiment may cause anaphylaxis in their own species—observations of great significance in connection with the problem of eclampsia.

In order to determine accurately questions of specificity it is necessary to work with pure materials. This is not yet possible with many protein substances of animal origin, but the results obtained with vegetable proteins and recrystallized ovalbumin are of much interest and indicate that the specificity of the anaphylactic reaction is intimately connected with the structure of the protein (Wells and Osborne), and that this reaction can be used to determine the relation of one protein to another, when these are so nearly alike that differences between them cannot be recognized by careful comparison of their chemical and physical properties. To quote Osborne (Harvey Lectures, 1910-11):

Preparations of globulin from the seeds of hemp, flax, squash, and castor-oil plant are obtained which are so nearly alike in ultimate composition, crystalline form, solubility and physical properties that only the most minute examination reveals any differences between them. While these proteins showed a strong anaphylaxis reaction, only those from the flax-seed and castor-bean showed any tendency whatever to react with each other, and between these the reaction was of a doubtful character. On the other hand, gliadin from rye reacts strongly with gliadin from wheat, a result in accord with the fact that by chemical and physical means no differences have been detected which were sufficient to indicate that these gliadins were different substances. Likewise legumin from the pea reacts with the apparently identical legumin from the vetch. No reactions were obtained between proteins of distinctly different structure nor between those from seeds botanically unrelated.

From these facts it is evident that structural differences exist between very similar proteins of different origin and it is interesting to note that chemically identical proteins apparently do not occur in animals and plants of different species, unless they are biologically very closely related. In this

respect the proteins are in marked contrast to the other constituents of plants and animals, for not only do the same sugars and fats occur in many species of plants and animals, but many of these are common to both forms of life. The morphologic differences between species find their counterpart in the protein constituents of their tissues.

ARE SENSITIZATION AND THE REACTION CAUSED BY THE SAME SUBSTANCES?

On heating horse serum, Besredka found that it would no longer cause reaction in sensitized guinea-pigs and yet would sensitize normal pigs; hence, he concluded that in serum anaphylaxis are concerned two substances in the foreign serum—a thermolabile intoxicating substance and a thermostable sensitizing substance. Since it requires only one-hundredth as much serum to sensitize as to cause the symptoms of the reaction, it becomes necessary to use exact quantitative methods in experiments of this kind and, on using such methods, Dörr and Russ have found that heating apparently affects both qualities of the serum equally, indicating that it concerns only one substance.

From their work on egg-white and certain bacterial proteins, Vaughan and his co-workers also conclude that the reaction depends on two substances, because on heating the proteins in question in hot alcohol with 2 per cent. sodium hydroxid they obtained two substances, one of which in normal guinea-pigs causes typical symptoms of the immediate anaphylactic reaction, including respiratory arrest and fall of temperature, while the other one, at least so far as the one that is derived from egg-white is concerned, sensitizes guinea-pigs to whole egg-white, but not to itself.

Using the purest protein obtainable, namely, crystalline egg-albumin, Wells found that one-twenty-millionth of a gram produced a distinctly sensitizing effect while one-millionth of a gram would prepare for a fatal reaction, the minimum second dose being one-twentieth of a milligram intravenously. This result would seem to indicate that sensitization and intoxication are caused by the same substance. At present the general opinion seems to be that the two effects are induced by the protein molecule itself and the fact that the purer the egg-albumin is made by recrystallization, the smaller the quantity necessary to sensitize, points in this direction.

Because gelatin, which is poor in aromatic radicles, does not sensitize and because it does not yield any toxic substances when injected into animals, it has been suggested that the anaphylactic reaction of proteins may depend on the aromatic radicles.

As protein substances that are not coagulated (like casein) when heated, may be heated to 100 C. without losing their allergenic characters, it would seem as if the physical change on coagulation suspends the sensitizing effect. As sensitization by the mouth must be exceptional, it would seem also as if the antigenic powers of proteins are destroyed by digestion, and Wells found that tryptic digestion gradually destroys the sensitizing power which runs parallel with the remnants of coagulable protein.

In all cases in which lipoids have been assumed to act as anaphylactogenic substances, the possibility that proteins were present in the alcohol or ether extracts used cannot be excluded.

PASSIVE ANAPHYLAXIS

Passive anaphylaxis is produced by injection of normal animals with the blood or serum of animals or persons already sensitized. It is the analogue of passive immunization and is specific for the antigen with which the

donor is sensitized. Guinea-pigs have been used almost exclusively for the study of this phenomenon, which plays an important rôle in the explanations of anaphylaxis, but it is not essential that the animal furnishing the blood or serum be of the same species as that injected. In guinea-pigs passive sensitization may last for fourteen days and longer. At this point may be mentioned that the young of sensitized guinea-pigs may be born sensitive, and remain so for a longer or shorter time. Passive anaphylaxis was described first by Otto on the basis of experiments illustrated by the following: A guinea-pig was injected in the peritoneal cavity with 0.1 c.c. of horse-serum; twenty-one days later it was bled and the serum injected in a healthy guinea-pig, which twenty-four hours later on injection of horse-serum responded with a typical anaphylactic reaction. First it was believed that a certain period must elapse between the injection of the serum of the sensitized animal, that is the antiserum, and of the antigen; this interval was assumed to be necessary in order that the active element or antibody in the serum might become anchored in the proper way to the cells, especially of the nervous system, of the animal injected. This assumption is no longer necessary because Dörr and Russ and others have shown that when the optimal quantitative relations are obtained, an immediate passive anaphylaxis may be produced. By simultaneous intravenous injection of antiserum and antigen after adjustment of the quantitative relations, Friedmann obtained immediate passive anaphylaxis in rabbits also. At the same time, it is true that this period of latency observed in so many of the experiments in passive anaphylaxis has not been explained altogether satisfactorily.

ANTI-ANAPHYLAXIS OR ANERGY

This condition succeeds the anaphylactic reaction from which the animal recovers and is complete insensibility to further reinjection of the antigen. The animal behaves as if it never had been sensitized; after three weeks or longer it gradually becomes sensitive again. This refractory state may be demonstrable within one hour after the reaction. In the case described by de Besehe, of severe acute symptoms with collapse, following injection of antidiphtheria serum, the patient became insensitive to odors and other emanations from horses which previously incited attacks of asthma; the former sensitiveness returned after about six months. Whether the refractoriness to tuberculin that develops in certain cases of tuberculosis is anti-anaphylaxis is not known. In addition to being produced by a non-fatal intoxication refractoriness may be induced also by a large dose of the antigen in the latter stages of the incubation. Reinjection of refractory animals with large doses of antigen is said to prolong the state of refractoriness. It is usually stated that this state is specific, that is to say, producible only by the protein used for sensitization, but this is not altogether clear as there are contradictory observations. In the dog and guinea-pig, it is claimed that it may be set up by intoxication with Witte peptone.

Several explanations have been advanced in regard to anti-anaphylaxis. At first it was thought that it concerned an antitoxic immunity, but the condition does not correspond to the induced immunity with which we are familiar, because there is no incubation period, and the serum of refractory animals, instead of being protective as would be expected from the point of view of this hypothesis, actually confers passive sensitization.

According to Friedberger, the refractory state results from the antibody in the serum being neutralized by

the antigen; in other words, that we are dealing with a negative phase in antibody formation; but this does not cover the facts, first because the serum from refractory animals confers allergy and, in the second place, because the refractory state may develop after a passive anaphylaxis, that is to say, after the injection of antibody antigen mixtures. Among other possibilities we have the disappearance of the complement, but this is merely transitory whereas the refractory state may last for some time. At present this condition must be viewed as an unexplained suspended or reduced susceptibility to anaphylactic poisons.

THE MECHANISMS OF ANAPHYLAXIS

The earlier observations were made on man, on dogs and on rabbits, and the relationships of the anaphylactic phenomenon to antibody formation seemed to be so clean-cut that it was regarded as an antibody reaction *in vivo*. It was believed that on the first injection an antibody was formed which, on meeting the antigen on reinjection, set free the poison (Weichardt, Richet, von Pirquet, Wolff-Eisner). Von Pirquet expresses this conception most clearly in his discussion of serum disease, the period of incubation of from eight to ten days being the period necessary for the formation of the antibody, while the immediate reaction and the accelerated reaction correspond to the shortening of the incubation in previously sensitized or immunized animals.

Richet advanced a hypothesis similar to this. He used a primarily toxic antigen and did not consider the possibility of the origin of the anaphylactic poison from non-toxic proteins. Consequently he assumed the development of an antibody which he called "toxogenin," which, acting on the toxin that he introduced, split off a new toxic substance, "apotoxin." Weichardt and Wolff-Eisner extended Pfeiffer's endotoxin hypothesis to anaphylaxis and regarded the toxic substance as pre-formed in the antigens and as set free by the action of the antibody on the antigen. Friedemann and Isaac observed that when foreign proteins are introduced parenterally they are reduced gradually to urea in normal animals, but in animals treated with protein the reinjection of that protein was followed by the manifestations of anaphylaxis and evidences of rapid protein splitting. Hence they concluded that the first injection resulted in the formation of antibodies which caused rapid splitting of the protein when this was reinjected, with the formation of toxic intermediary products. Similar hypotheses were advanced by others as, for instance, Nicolle.

Then came 1906, with the intense work on serum anaphylaxis, especially in guinea-pigs, that followed when Theobald Smith's phenomenon became known. The minuteness of the sensitizing dose, the duration of the sensitive state, the refractoriness following large reinjections and the failure to find in the guinea-pig any antibodies, the action of which *in vitro* was known, served to push aside the older view in place of which came various hypotheses of a cellular nature.

These conceptions were overthrown when Otto and others found that guinea-pigs might be rendered sensitive by the transfer of the serum of sensitized animals. As the transfer of anaphylaxis, however, seemed to succeed only when the serum was introduced twenty-four hours or so before the injection of the antigen, it still was insisted that the active substance in the serum must first be bound to the cells of the nervous system. The immediate inactivity of the antigen-antiserum mixture seemed to make it necessary

to assign an active part to the cells. But this stumbling-block in the way of the humoral hypothesis was removed when it was found that mixtures of antibody and antigen in proper quantitative relations may cause an immediate passive anaphylaxis. At present the prevailing idea is that allergy both to protein in cells and to dissolve proteins is essentially a humoral process, and it is unquestionably true that the return to the general view expressed by Friedemann and others several years ago has pointed the road for further progress by presenting problems susceptible of attack.

On analyzing the circumstances under which an immediate passive anaphylaxis is obtainable it was found, first, that complement is necessary; second, that the specific element in the antiserum or sensitive serum is thermostable and that in case of anaphylaxis with respect to red corpuscles, it is bound by the corpuscles, hence, acts as an amboceptor. In serum anaphylaxis the binding of the complement also pointed to an amboceptor-like mechanism. It was found, further, that complement in the blood is diminished in anaphylaxis and that the reaction is preventable by the injection of hypertonic salt solution, which, as is known from other experiments, prevents the complement from acting.

The general conception at present is, then, that on sensitization, immunization with proteins, substances of the general nature of amboceptors are formed; these are specific and their union with the antigen in cooperation with complement results in the formation of substances that produce the anaphylactic symptoms and lesions. The action is regarded as one of protein digestion, first, because the toxic effect closely resembles that of substances in Witte peptone, i. e., substances obtained in the course of protein splitting, and second, because evidence of actual protein splitting in mixtures of antigen and antiserum may be obtained by chemical means as well as by observations on their rotatory power (Abderhalden's polariscopic method).

At this point it may be recalled that Vaughan, from the similarity of the symptoms of egg-white anaphylaxis and those following the injection of toxic split-products of egg-white, was one of the very first to advance the idea that the anaphylactic intoxication is caused by protein split-products and that there is an increase in the protein-splitting power of the blood of sensitized animals. Vaughan speaks of this power as dependent on a ferment which is present in extracts of organs of sensitized guinea-pigs, these extracts splitting the protein in question, namely egg-white, so that its injection into normal animals causes immediate symptoms. The active element in these extracts is rendered inactive by heating to 56 C., and may be reactivated with normal serum in quantities so small as to be without action by themselves, thus indicating a mechanism which immunologists would regard as dependent on the action of amboceptor and complement.

The production of proteolytic and peptolytic ferments in the blood after the parenteral injection of proteins is now being studied by chemical and physical as well as biologic methods. Abderhalden and Pinkussolm find that in dogs the introduction of gelatin, for instance, leads to the formation of non-specific peptolytic ferments. Dick, on injection of serum and bacterial proteins, obtained evidences of the formation of specific proteolytic substances of the nature of amboceptors, that is, activable by means of complement. Further developments may be anticipated with great interest, as the indications are that the conception of parenteral protein

digestion will play an increasingly important part in our explanations of many of the phenomena of infection and immunity.

THE RELATION OF THE ANAPHYLACTIC ANTIBODIES TO OTHER ANTIBODIES

I have tried to make it plain that in the typical anaphylactic reaction, bodies come into play which are of the nature of amboceptors because they require complement for their action. The relation of these bodies to antibodies whose action is demonstrable *in vitro* is still under discussion. In the case of allergy to red corpuscles, Friedemann finds that there is a close parallelism between the anaphylactic bodies and the hemolytic amboceptors. In rabbits, Dörr and Russ and others find a complete parallelism between the precipitins and the bodies concerned in anaphylaxis. There is no such parallelism, however, in serum disease, and the question whether allergy depends on the action of a distinct and peculiar antibody is still an open one.

THE PRODUCTION OF ANAPHYLACTIC POISONS IN VITRO

Vaughan, Friedberger and others have shown that substances which in guinea-pigs cause symptoms indistinguishable from those of immediate anaphylaxis in sensitized animals may be produced *in vitro*. Various methods employed for this purpose may be divided into specific and non-specific.

By the specific method the antigen, the antibody and the complement are brought together under certain conditions and the question whether any poison is formed is determined by removing the antigen-antibody complex and injecting the clear fluid. In the case of red corpuscles, Friedemann obtained anaphylactic substances in this way, even before lysis occurred. He concluded that the poison is a split product and not a preformed substance because the mere laking of the corpuscles with water does not necessarily set free any poison.

Substances producing the symptoms of typical anaphylaxis have been obtained from a large number of bacteria by the action of antiserum and complement. Even normal guinea-pig serum may suffice, the normal amboceptor present being regarded as the active agent. In experiments of this kind the conditions that must be observed seem to vary in each case.

Friedberger has also obtained anaphylactic poisons from the specific precipitates that form when serum and the corresponding antiserum are mixed; the precipitate is washed and digested with guinea-pig serum. Here also certain quantitative relations must obtain and the digestion must not be continued too long.

R. Pfeiffer long ago obtained poisons in the course of bacteriolysis which he regarded as preformed and termed "endotoxins"; Weichardt obtained poisons from the action of specific antiserum on placenta and Wolff-Eisner in like manner from pollens, and these results were interpreted by them in the light of the endotoxin hypothesis, that is, as due to the setting free of preformed poisons.

Of the non-specific methods I mention the hydrolysis of egg-white and other proteins with hot alcohol, practiced by Vaughan and Wheeler, whereby they obtained an alcohol-soluble substance which in guinea-pigs caused all the typical symptoms of immediate anaphylaxis. Biedl and Kraus have found that in dogs, peptone (Witte) poisoning reproduces the symptoms of anaphylaxis including fall of pressure, incoagulability of the blood, leukopenia and a temporary refractory state not only to peptone, but also to true anaphylactic

intoxication; furthermore, that in antianaphylaxis there is refractoriness to peptone poisoning. Manwaring, however, was not able to confirm the latter observation.

When pneumococci, streptococci, meningococci, gonococci, typhoid bacilli, colon bacilli, and other bacteria are suspended in salt solution for varying periods of time, Rosenow, in The Memorial Institute, finds that toxic substances develop which on intravenous injection give the phenomena of immediate reaction in guinea-pigs. In such suspensions evidences of protein splitting are obtainable by chemical and physical means. Rosenow also finds that intoxication with pneumococcus autolysates gives rise to conditions of refractoriness (anti-anaphylaxis). In man, solutions of this kind cause fever and leukocytosis. Rosenow's work seems to establish then that substances causing the symptoms of acute anaphylaxis may develop in the course of autolysis of bacteria without the presence of serum.

In all these experiments *in vitro* the criteria that it concerns similar substances as those that are at work in true anaphylaxis are the symptoms observed during life and the appearances after death. So far, guinea-pigs have been used, as they are the most sensitive. Objections have been made to the reliability of the conclusion that the same substances are at work in anaphylaxis in the sensitized animal and in intoxication by the substances obtained in the test-tube. It is very important to proceed cautiously in order not to fall into confusion, but it may be emphasized that by the specific test-tube methods the conditions obtained in life are closely imitated, so that it is not unlikely that the actual poisons exciting the symptoms in the sensitized animal are obtainable outside of the body. At all events an interesting field for further study has been entered. There is ground for objection to Friedberger's name of "anaphylotoxin" for all these substances; in the first place, it probably does not concern a single substance, but a variety of more or less closely related substances; in the second place, it does not concern substances of the nature of toxins in the immunologic sense because they do not appear to induce the formation of antitoxins. Further progress depends on obtaining an insight into the true chemical nature of the substances concerned.²

ALLERGIC (UNPUBLISHED) MANIFESTATIONS IN DISEASE

There are various manifestations in infectious and other diseases that point to the occurrence of reactions of the nature of anaphylaxis or allergy. Let us first briefly consider infectious diseases from this point of view.

THE INCUBATION PERIOD

In many infections the incubation period corresponds more or less closely to the period preceding the acme in antibody formation, and on the basis of this fact, von Pirquet has developed the idea that the symptoms are not the exclusive result of the direct and immediate action of the microbe, but in greater or less measure the result of interactions between microbe and host. In many cases it would seem as if the symptoms arise when the antibodies have become concentrated enough to break up the microbe, in other words, when specific proteolysis begins. The fact that the first symptoms of serum disease usually begin in from eight to twelve days after

2. Rosenow seems to have been able to effect a separation of substances in toxic pneumococcus extracts by means of ether, the ether-soluble part causing death by pure bronchial spasm, while the insoluble part does not affect the bronchioles but may cause death in twenty-four hours or so with hemorrhage in various internal organs (unpublished).

the first injection supports this idea. In persons previously injected with serum the incubation period is greatly shortened or practically absent because here the antibodies appear more quickly and attack the protein promptly. It is possible that in many of our common infections the incubation period is shortened on account of sensitization from previous mild attacks. The shortening of the incubation period is illustrated beautifully by von Pirquet's work on vaccinia. After primary vaccination the reaction about the point of inoculation reaches its maximum between the eleventh and fifteenth days, when there is also fever with leukopenia. Now, on revaccination after the lapse of some time, various types of early and accelerated reactions may be observed, and von Pirquet has shown that on daily vaccinations in an unvaccinated person for a fortnight or so, the maximum reaction occurs at the same time about all points of inoculation, namely, at the time it is due about the earliest inoculations. Here we may assume that the antibodies educed by the first vaccination, on reaching the required concentration, act in the same way on the virus deposited in the skin from day to day.

It is possible that in some infections the microbes as they enter the body are broken up by the normal antibodies and also that a spontaneous or autolytic splitting may occur with corresponding irregularities in the period of incubation.

FRIEDBERGER'S ANAPHYLATOXIN VERSUS PFEIFFER'S ENDOTOXIN HYPOTHESIS

Friedberger ventures the explanation that practically all symptoms of infections are caused by anaphylatoxin or substances of that general nature arising from protein splitting, the variations in the symptoms depending on the quantity of the poison set free, on the rate of liberation, and on the differences in localization. This leads to a brief consideration of Pfeiffer's endotoxin hypothesis according to which symptoms of intoxication are due to preformed substances—endotoxins—set free on lysis of the bacteria or protozoa.

All microbes are assumed to contain poisons of this general nature, the infectious microbes being dangerous because they can grow in the body for a time at least and thus furnish large quantities of poison. Immunization with this class of bacteria gives rise to specific lytic and opsonic amboceptors and other antibodies. Now the question is whether this endotoxin hypothesis is to be replaced by the anaphylatoxic. We observe that the mechanisms assumed at work are essentially the same, namely, of amboceptor-complement nature. Hence the question actually narrows down, one might say, to whether Pfeiffer's endotoxins are preformed or simply transitory split products formed in the course of bacteriolysis. Friedberger's view does not account so plausibly for the specific actions of the substances in question as the endotoxin conception. The symptoms and lesions in these infections are characteristic and peculiar in each case and it is hard to believe they can be caused by the same substances. Friedberger's view is also out of harmony with the prevailing idea that in the microbes the toxic and the antigenic substance is one and the same in each case, but different in the different bacteria because the resulting antibodies are specific. The indications therefore seem to be that the fragments of lysis which cause the toxic symptoms retain certain original peculiarities. It has been urged against Friedberger's view that we rarely if ever encounter, so far as we know, intoxication in natural infections resembling those of the typical anaphylactic reaction, but as to this

it may be said that in infections the amount of poison set free at any one time may not be sufficient to produce such intense effects. Even if Friedberger's conception may not succeed in replacing the endotoxin hypothesis, progress in our knowledge of infections and other diseases has resulted. Surely the non-specific and non-antigenic substances produced in the breaking down of foreign proteins may take part in causing general disturbances of temperature, of metabolism, and of the leukocytes.

CUTANEOUS MANIFESTATIONS

Von Pirquet has pointed out the analogy between the eruptions in small-pox, varioloid and vaccinia to the skin lesions of serum disease. In small-pox the eruptions contain the living virus of the disease because this is transferable by means of the contents of the vesicles and pustules. This virus is brought to the skin by the blood, and as the eruption occurs at a period after infection that corresponds to the climax in antibody formation, it seems reasonable to believe that the cutaneous reactions develop as the virus is attacked. Indeed, by complement deviation it has been found that the contents of the pustules do react with the serum. Viewed in the same light varioloid may be regarded as an allergic modification of small-pox, due to reinfection in a sensitive person.³ And it has been suggested that hemorrhagic small-pox may be an expression of a specially intense reaction between antigen and antibody. Of other diseases that present striking relationships of this nature I would mention measles with its definite incubation period, its leukopenia, and its eruption with fever at a time that corresponds nicely to the acme of the antibody curve. The skin, then, offers a series of very interesting phenomena from the point of view of allergy: the cutaneous lesions of serum disease, the eruptions of many infections, reactions like the tuberculin reaction, the urticarias and eczemas and other manifestations of what is coming to be called alimentary anaphylaxis all indicate that the skin has not only a marked affinity for foreign protein substances, but reacts in a striking manner to the various split products.

TUBERCULIN AND SIMILAR REACTIONS

That the tuberculin and similar reactions, like Noguchi's recent luetin reaction, the gonococcus reaction of Irons, etc., are of allergic nature can hardly be ques-

3. The recognition of the importance of allergy is preceded by isolated observations of allergic phenomena, the bearing of which, however, was not understood at the time. As examples, I would mention that long ago while transfusion of lamb's blood was practiced in anemia and other conditions, it was observed that sometimes urticarial eruptions would appear a few days after transfusion. Magendie noted (1839) that in rabbits, repeated intravenous injections of egg albumin may give rise to serious symptoms. But perhaps the most interesting of these early observations on allergy is that of Jenner on the character of the reaction to variolous matter by the skin of persons who had had either small-pox or cow-pox. In his "Inquiry into the Causes and Effects of Variolæ Vaccinæ, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cow-Pox," 1798, he records (page 13, Case 4) that a woman who had had cow-pox thirty-one years before was inoculated with variolous matter, and that "an efflorescence of a palish, red color soon appeared about the parts where the matter was inserted, and spread itself rather extensively, but died away in a few days without producing any variolous symptoms." In a footnote he comments on this phenomenon as follows: "It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the small-pox. Indeed, it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable, too, that whether this change has been effected by the small-pox or the cow-pox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter." This remarkably clear statement probably records the first observation of allergy in an infectious disease.

tioned. The tuberculin reaction, though best developed in the tuberculous, is obtainable after sensitization with various forms of tuberculo-proteins. Typical immediate anaphylaxis has been produced in guinea-pigs with watery extracts of tubercle bacilli by Baldwin; and Friedberger has extracted anaphylactic poisons *in vitro*. The quantitative relations of the reaction are similar to those in repeated vaccination, progressive dilution leading to diminishing intensity. And passive transfer of the reaction has now been accomplished in a number of ways so that at least the general and local reactions are readily explained on a humoral basis. The failure to obtain the reaction in certain conditions of advanced tuberculosis and other states remains to be explained.

SYMPATHETIC OPHTHALMIA, ECLAMPSIA, HAY-FEVER, ASTHMA, IDIOSYNCRASIES

Space does not permit any attempt at discussion of the possible anaphylactic nature of many of the other local reactions and lesions of infectious diseases, many of which may be conceived as the results of the localization of foreign proteins and their destruction by antibodies in the blood and lymph. In passing, mention may be made, however, of the possibility that in infectious diseases proteins of the body itself, especially in the severe lesions, may become so changed or heterologized as to acquire antigenic powers, and on reacting with the antibodies give rise to toxic substances. It has been suggested that certain drug eruptions, notably iodid and bromid eruptions, may rest on some such basis as this.

At this point I would mention that since it has been shown that the lens protein, and possibly also uveal tract protein, may cause antibodies in the animal from which they are obtained, the thought has arisen that sympathetic ophthalmia may be an allergic phenomenon. After partial destruction of one eye and absorption, the uveal tract of the other eye might be affected by the antibodies thus formed. For the present this must be viewed as an interesting suggestion only.

And the hope that puerperal eclampsia may receive adequate explanation from the point of view of anaphylaxis has received new support since it has been announced that animals of the same species may be made anaphylactic not only with the placenta, but also with the amniotic fluid and fetal serum; and, furthermore, that immediate anaphylaxis may be obtained by injecting pregnant guinea-pigs with serum of their young, indicating that sensitization may occur during pregnancy.

The experimental evidence clearly favors the view that hay-fever is an anaphylactic reaction to various pollens which are believed to be split up into poisonous substances in the mucous membranes of the respiratory tract. And the asthmatic symptoms that appear in certain persons when exposed to the odors of horses and of other substances naturally are regarded as expressions of anaphylaxis.

The view that the peculiar idiosyncrasies, so-called, with respect to certain articles of diet — strawberries, cheese, fish, oysters, buckwheat, pork, eggs, cow's milk, etc. — are forms of anaphylactic reactions is steadily growing, and the chapter of alimentary anaphylaxis is already a large one, although in only a very few instances have cases been analyzed carefully from this point of view. Thus, Bruck found that guinea-pigs were made passively sensitive to pork protein by the serum of a person that always reacted violently to pork. Interesting examples of extreme sensitiveness to cow's milk

in infants and to egg-white have been described. In connection with this subject of alimentary anaphylaxis it should be mentioned that the proteins of the intestinal bacteria under certain conditions might give rise to symptoms of sensitization.

This then, must suffice as indications and suggestions of the part that what is called allergy or anaphylaxis may play in guiding us to better explanation of various phenomena in infections and other diseases.

WHAT OF ANAPHYLAXIS AND IMMUNITY?

The conception that introduction of microbes and their products induced distinctly protective reactions is seemingly not in harmony with the fact that an increased susceptibility seems to develop after introduction of all foreign proteins, whether cellular or in other forms. But this contradiction is only apparent. In the first place, there is, in most cases at least, probably no real increase in susceptibility — the actual degree of susceptibility to the same poisons being probably the same in the average normal and average sensitized animal; it is the power of reaction of the latter that is peculiar and for this reason "allergy" is perhaps the best word we have for the condition. Stated in the simplest way, we could say that the sensitized animal splits up a particular protein so rapidly that toxic substances are produced or set free in toxic quantities, while in the normal animal the process proceeds so slowly that no evident intoxication may result. Now in the case of microbes, lysis with splitting is not consistent with continued existence, and when small quantities are introduced as in natural infections, they may be killed in this way before they can multiply so as to furnish toxic doses of poison, and this would be immunity, either natural or acquired. The relations between antibacterial immunity and intoxication remains essentially the same as outlined by Pfeiffer. While he limited himself to the conception of preformed endotoxins, under the newer view we conceive the poisonous substances as being, at least in part, intermediary digestive products and as arising also in part from changes in harmless proteins. There is then no contradiction between immunity and allergy, which is a form of antibody reaction and, so to speak, an incident in the course of immunization.

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THE TREATMENT OF SACCULATED ANEURYSM BY WIRING AND ELECTROLYSIS

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The treatment of sacculated aneurysm by the introduction of various foreign bodies, ranging from nails to strands of silk and horse-hairs, was practiced many years ago. The design was of course to aid or produce clotting in the sac and so to reenforce the weakening aneurysmal wall. These measures failed chiefly because most of the operations were performed before the days of asepsis, or else they caused so much damage to the sac-wall that its continuity was destroyed and the end hastened. It is not my intention in this paper to go into a historical review of these cases, or of the early trials of more recent methods, such as the Moore-Corradi operation, which