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THE

EVOLUTION OF DISEASE

WITH A

DISCUSSION OF THE IMMUNE REACTIONS OCCURRING IN INFECTIOUS AND NON-INFECTIOUS DISEASES

A THEORY OF IMMUNITY, OF ANAPHYLAXIS AND OF ANTIANAPHYLAXIS

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TRANSLATOR'S NOTE.

In translating this work of Professor Danysz from French into English, an attempt has been made to preserve carefully the original meaning. The original work contains much repetition arising from the desire to emphasize and elucidate the author's theories and deductions on the evolution of disease: the translation also contains repetition but the translator has taken the liberty of omitting sentences, paragraphs and, in certain instances, whole sections, in order to present the book to the American profession in a more readable form. In particular, the case reports in the second section of the second part have been greatly shortened and many have been omitted.

In this book Professor Danysz has traced in a clear and logical manner the various stages in the development of acute infectious diseases; and proceeding along the same course, has developed an interesting theory of the evolution of chronic morbid states whose etiology and pathogenicity are today so little understood and whose treatment is therefore as difficult as it is unsatisfactory.

The book should be of interest to those who recognize the importance of a comprehension of the principles underlying the study and treatment of disease.

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F. M. R.

PREFACE.

As the study of physical and biological phenomena, of the constitution of matter and of its manifestations becomes more extended and more precise, it tends to prove that the perpetual changes noticed in all things, consist in an uninterrupted series of decompositions and syntheses; and as the transformations of any one substance have a beginning and an end, it can be said that any substance in process of change undergoes an evolution of which the different successive phases are determined by the physical and chemical properties of its constituent elements.

Decompositions follow, as a rule, a very uniform path and lead to simple elements which may be considered as definite. Synthesis, on the other hand, is itself subject to evolution; it leads step by step to compounds that are more and more complicated, varied and numerous, and it is impossible to predict any end to these changes.

The final result of natural synthesis, the most complicated and the most perfect product known to us, is the chemical species which we may call "albuminoid micelle."[1] Its characteristic is that it rebuilds itself as it wears out, or, in other words, that it is continuously undergoing partial decomposition and at the same time a reconstruction of the

[1] The word "micelle" is used to define the units of albuminoid matter of every colloid in the same sense that the word "molecule" expresses the unit of chemical compounds. The word "particle" is used by many American authors in the same sense.

decomposed elements with simpler elements found in its environment, so that although always in an unstable equilibrium, it constantly retains its initial composition and structure.

It is easy to conceive that if the conditions of this "nutrition" of the "micelle" depend on what is provided by the surrounding matter, the "micelle" may decrease or increase in volume; that is to say, it may decompose faster or slower than it is constructed. When a sufficient quantity of building material is at hand, the increase in volume will predominate; and when its volume will have reached certain limits capable of modifying its conditions of normal nutrition, the "micelle" will split into two equal parts.

It is this *multiplication* which together with *nutrition* constitutes *life*.

The "micelle" develops as an *individual* and as a *species;* in its evolution it must obey the law which obliges every substance to replace in its complexes, the less stable or more soluble compounds by more stable or less soluble compounds.

The "micelle" will "age" because, as its elements become more stable, substitution becomes slower and slower; it will "die" when stabilization will have passed beyond certain limits, because a certain rapidity of exchange, producing a certain amount of heat, in a given time, is an indispensable condition of life.

The individual may die under these conditions; the species likewise, because the child-"micelles" will inherit the degree of stability acquired by the parent-"micelles."

When a cell's "micelles" find in their surrounding medium elements of which they are composed themselves, or other elements for which their own elements have no affinity, they can find nourishment and can develop in a normal manner; but when, on the contrary, they find strange elements,

requiring fixation by their affinities, the nutritive equilibrium will be modified; and when the proportion of "micelles" so affected among the "micelles" composing the plasma of the cell, will have passed beyond certain limits, the cell itself will become diseased and may die.

These are the general ideas which have guided us in the following study of pathological states.

In Part II the *secondary consequences* in the organism of the conditions of immunity and anaphylaxis, which result from recovery in infectious disease, or from an habitual or periodical digestion of antigens are discussed.

The study of these questions has led to the conclusion that all the chronic morbid states with their periods of acute crises alternating with longer or shorter remissions, originate from antigens, and are determined by the state of immunity-anaphylaxis of the organism. The necessary experimental confirmation of this hypothesis has shown in reality that the anti-anaphylactic treatment is of unquestionable efficacy in all those chronic diseases in which we have been able to apply it up to date (except organic mental diseases) and a long series of observations corroborates this.

We have obtained these results by non-specific antigens and in order to explain the curative action of these antigens, we have been obliged to assume the direct and predominating intervention of the nervous centers.

The work is concluded by a general theory of immunity, anaphylaxis, and anti-anaphylaxis, based on the structure, properties and function of the organism, and of the structural and functional units composing it.

J. Danysz.

CONTENTS.

PART I.

CHAPTER I.

CHAPTER II.

CHAPTER III.

Evolution of the Infectious Diseases.

CHAPTER IV.

Mechanism of Infection. Infection or Contagion. Virulence. Immunity. Refractory State.

CHAPTER V.

Immunity and Anaphylaxis.

CHAPTER VI.

Influence of the Central Nervous System on Immunizing Reactions and on Anaphylaxis.

CHAPTER VII.

Therapeutic Measures.

CHAPTER VIII.

Principles of the Classification of Infectious Diseases.

CHAPTER IX.

General Conclusions.

PART II.

CHAPTER X.

EVOLUTION OF THEORIES CONCERNING IMMUNITY, ANAPHYLAXIS AND ANTI-ANAPHYLAXIS.

CHAPTER XI.

PRINCIPLES OF THE ANTI-ANAPHYLACTIC TREATMENT OF CHRONIC DISEASES BY ENTERO-ANTIGENS.

CHAPTER XII.

GENERAL SUMMARY: THEORETICAL DEDUCTIONS.

EVOLUTION OF DISEASE.

PART I.

CHAPTER I.

THEORIES OF IMMUNITY OF METCHNIKOFF AND EHRLICH.

Experimental Researches Inspired by These Theories.

MEDICAL science has for its object to teach us why and how an organism becomes diseased, what constitutes this disease, and how cure is effected. It is only by knowing how to answer these three questions that it is possible to treat disease successfully either by preventing its occurrence or by assisting the organism in recovering from it. Up to the time of Pasteur we knew as pathogenic agents only poisons as such; chemically crystallizable products and venins, all of unknown composition, but which with the crystalloids have this fact in common, that the diseases of which they are the cause are non-contagious.

With the discovery of bacteria we began to know the origin of contagious diseases and it was recognized at about the same time, that if a certain microbe was the primary cause of the disease it could act only by means of its soluble secretions or by products which were allowed to escape at its death; that is to say, by poisons of an unknown composition analogous to the venins. But although we know the cause of disease, we do not know the *mechanism* by which the patho-

logic state is brought about. The symptoms and the anatomical lesions of disease were recognized but it was not known how these symptoms and lesions were produced. It was learned how to "accustom" the organism to certain poisons, to "vaccinate" against certain diseases and to effect cure by certain antidotes. But we have been obliged to recognize that methods, either preventive or curative, applied with success in certain cases, do not give any appreciable result in others.

Thus neither the mechanism of the pathogenicity nor that of the pathologic state nor that of the cure was understood, so that curative measures were necessarily limited to attempts to relieve symptoms and to the treatment of lesions by means found by chance experiments.

In order to throw light on the mechanism of cure, especially in the infectious diseases, Metchnikoff put forth his phagocytic theory, according to which, the leukocytes, the only cells of the organism provided with a membrane which could engulf microbes, digested these microbes and thus destroyed the primary cause of the disease.

However, much before the phagocytic theory, vaccination of the organism against smallpox, anthrax, erysipelas, chicken cholera, carbuncle, had been successful. The first practical results in the curative treatment of an infectious disease, viz., the cure of diphtheria by antitoxic serum, did not result from the conception of immunization by leukocytes.

Vaccination by soluble bacterial secretions had been observed in numerous diseases, as for example: by Chauveau in lambs born of ewes inoculated with anthrax during gestation; by Salmon and Smith in their experiments in hog cholera; by Charrin in pyocyaneous infection and by Roux and Chamberland in symptomatic anthrax and the infection by septic vibrio. Moreover the production of an antitoxin "in excess" for diphtheria and tetanus following injection of toxins filtered from both living and dead organisms was demonstrated; as well as the fact that these bacterial poisons might be fixed to and might act not only on the leukocytes but also on every other cell.

These observations inspired Ehrlich to a more general

conception not only of the mechanism of cure but also that of the pathogenicity. Without denying the possibility of the intervention of leukocytes Ehrlich propounded the idea of indispensable chemical affinities for every reaction between two substances: taking the same point of view for every reaction, whether immunizing or pathogenic, between bacterial poisons and the cells: namely, that some one substance of the cell possesses a chemical affinity for these poisons. Pathologic symptoms are then the result of fixation of poisons by cellular substance and cure is the result of the multiplication of this cellular substance neutralized by poison, which the cell produces in excess. The product of the combination ought necessarily to be neutral.

We shall see further what there is to take or leave in this theory which Ehrlich formulated. It will suffice to note, at the moment, that Ehrlich's theory was no more capable than that of Metchnikoff of explaining the evolution of every disease, and that it could not explain the reaction provoked in the organism by bacterial poisons, or the necessity or possibility of the organism reacting to certain poisons in a way different from that in which it reacts to many other poisons.

But even if the purely biologic theory of Metchnikoff as well as the purely biochemical theory of Ehrlich cannot explain the entire mechanism of pathogenicity and immunity, yet each contains certain truths which have been the basis of countless studies in the domains of biology, biochemistry and biophysics. These studies have made possible the discovery and the definition of a great number of facts concerning the properties of pathogenic agents, the nature and the mechanism of their action on the organism, the reactions which they provoke, the nature and properties of the products of their reactions with the fluids of the organism both *in vitro* and *in vivo*.

Notably so, these studies have allowed us to establish a very fine distinction between these pathogenic agents, which are crystallizable and those which are not: these latter being grouped under the general name of colloids. These studies have permitted us to enlarge the horizon, to clarify and to

better understand the true significance of facts in daily experience and to better group these facts in order to construct a general idea which in its turn will point the way toward new researches. In the discussion which follows we shall try to recall the merits of the two theories of Metchnikoff and Ehrlich and of the experimental researches which these have inspired. We shall try to interpret the results of these researches in the light of new facts and to draw from the total of these studies conclusions which are necessarily logical.

Metchnikoff's theory of immunity attributed the defensive mechanism of the organism against pathogenic germs exclusively to the leukocytes. Leukocytes engulf the germs, digest them and there results an overproduction of a specific digestive ferment which renders this digestion more and more easy and active. When all the microbes are thus destroyed, there is cure and the organism remains immunized against the same germ because the leukocytes which have learned to digest these germs retain this new property for a certain time and transmit it by heredity to their descendants so that they also will be able to attack a small quantity of the same parasites in case the organism again becomes spontaneously infected.

We may easily understand the destruction of the microbes in the interior of the leukocytes. The rôle of these latter in the defense of the organism is certainly very important but we must recall that if the phagocytic theory contains one part of the truth it cannot include the whole problem of pathogenicity and immunity because the struggle between microbes and organism does not take place exclusively in the blood. If we must assume that it is the microbe which is the origin of disease and that its destruction by the white blood corpuscles can lead to cure, it is by no means less certain that it is not only the microbe body but also and often principally the soluble products or poisons which it secretes during its life or which are allowed to diffuse after its death that by acting not only on the leukocytes but also on a large number of other cells, produce the lesions and symptoms characteristic of each disease.

Pathologic manifestations can be only the results of reac-

tions between cells and bacterial poisons. When the cells do not succumb in the struggle they become more resistant to the action of the same poison. But the presence and the destruction of bacteria in the organism may provoke reactions of still another nature. The poisons which they excrete are not the only substances of which the protoplasm and the membrane of the bacterial body are composed. There are albumins which without being poisonous are not harmless for the organism. These albuminous substances themselves must be transformed in order to be assimilated and there may result from them disturbances which we will discuss later when we come to treat of pathologic states provoked by the injection of albumin. It is sufficient to note here provisionally that we have to consider an *intravascular* immunity which may be explained in many cases by the phagocytic theory of Metchnikoff as well as a *cellular* immunity which is not so explained and which is the object of the biochemical theory formulated by Ehrlich.

Ehrlich's theory has for its basis, as we have seen, the general conception that a reaction between two substances is possible and can be determined only by chemical affinities between these substances: and it would seem evident that a body which is insoluble in the fluids of the organism can exercise only a purely mechanical action on the fluids and the tissues. Not being able to form any combination, it cannot produce a reaction or any disturbance in the existing equilibrium.

Ehrlich pictures the process of immunization in the following manner: a toxin is attracted and fixed by a cellular substance which possesses a chemical affinity for it: the toxin neutralizes this substance and is itself neutralized. The neutral product thus formed is expelled from the cell as useless and as the cell cannot be permanently deprived of the substance which the toxin has neutralized and which we will call *normal antibody*, it reproduces not only as much as is lost, but a little more; it is the custom of every living cell to react to any sort of excitation by a multiplication of the substance excited, or, in other words, by a reinforcement of the tissues and of the organs excited in order to be able to support

future excitations with less danger and fatigue. But it often happens that the cell in this process of defense and rehabilitation exceeds the normal reaction: it makes a "normal antibody" in much larger quantity than it can use and then expels the excess, which passes into the blood and the fluids to become *antibody in excess* or *antitoxin*, which is found in the serum of a hyperimmunized animal and which may be used to cure disease in another subject, provided this disease is caused by the same toxin secreted by the same germ.

Antibody-in-excess is then a substance which, according to its definition, does not need to be transformed in order to be assimilated. It is "homologous" for the organism and may be considered as a sort of "substance in reserve" which the organism may resorb according to its need.

Such as it was formulated by Ehrlich the theory of immunity based on the general principles of chemical affinities is applicable in reality to only a small number of special diseases caused exclusively by certain toxins as diphtheria and tetanus and even in these cases Ehrlich was obliged to add purely hypothetical distinctions between certain properties "toxophores" and "haptophores" of each toxin to explain and distinguish their pathogenic and their immunizing action.

As to the mechanism by which a pathologic state could be provoked in an organism by infection; as to the question of knowing why different diseases differed from each other by a special evolution and by a total of symptoms more or less characteristic to each; why in certain cases the processes of immunization are complicated by an inverse process known since the time of Charles Richet as "anaphylaxis"; and finally, why there are certain substances for which the organism makes specific "antibodies" and others for which it does not make them, as well as other questions, neither the one nor the other of the two theories can explain.

Should we conclude that these theories cannot be of any use because they are almost always incomplete and inadequate? Certainly not!

General ideas are always necessary to stimulate the studies of new generations along new lines.

All the works on serum diagnosis by Bordet and Gengou, Besredka, Widal, Wassermann, and others, are the direct emanation from the ideas of Metchnikoff. Modern chemotherapy is a creation of Ehrlich and his pupils. And all these studies which have confirmed in part the theories of these two great savants have had at the same time the result of exposing their faults and discrepancies which it has been necessary to correct with new researches, which in their turn have permitted us to formulate a theory more complete for the actual state of our knowledge.

Today we may conceive of a process of immunity in the most general manner as a necessary reaction of the whole organism against each and every substance which is not a part of the organism and which is introduced into its interior in any way whatsoever. From our present point of view we may divide all these substances into two great groups:

First, those which on injection into the organism provoke the formation of "specific antibodies," that is to say, of substances which appear in the fluids and tissues of the organism, some time after the introduction of the foreign substance and form with these substances products which are neutral or active toward the organism.

Second, those to which the organism may accustom itself in a certain measure but to which "specific antibodies" are not formed. To this last group belong all those substances of a relatively simple and well defined chemical composition such as alkaloids, glucosides, mineral salts, in a word, crystalloids, which from the biophysical point of view, have the common property of traversing dialyzing membranes and of being able to be directly assimilated or eliminated. All these substances if they are poisonous belong to the domain of toxicology and will not be discussed here.

The substances of the first group including albumins of every sort, bacterial secretions, venins, etc., have a composition and physicochemical constitution which is much more complicated and even today imperfectly understood. From the biochemical point of view, they have the common property of not being able to traverse dialyzing membranes and under the ultramicroscope they appear as very fine granules.

To these substances of biologic origin have been added quite recently, several organic compounds obtained synthetically and notably substances of the series of arsenobenzenes, either simple or multimetallic, of which the chemical composition is well defined but of which the constitution is still imperfectly understood.

The ability or lack of ability to traverse dialyzing membranes is the most important distinctive characteristic of these two categories of substances in their reaction on the organism. Those which can traverse membranes rapidly penetrate into the tissues, combining with substances of the organism according to the laws of their chemical affinities and produce immediately or at least very rapidly, effects which are nutritive, exciting, toxic, hypnotic, or anesthetic according to the nature of the products which they form with the cell contents and according to the rôle of the cells in the life of the organism. That part which is not fixed by the tissues is quite rapidly eliminated by the kidneys or the intestines.

On the other hand the colloids, which do not traverse the cell membranes which enclose each cell, cannot be either assimilated or fixed by the tissues or eliminated without being subjected to a special transformation. The characteristic feature which results is the relative delay of the reactions which they provoke in the organism. Furthermore, we must well understand that there are no absolutely sharp distinctions between colloids and crystalloids.

In setting up a series of more or less permeable dialyzing membranes it is recognized that certain colloids traverse certain membranes which others do not traverse, and that the same membranes may allow one part of one colloid to pass without the other. Thus a given membrane may pass diphtheria toxin more easily than antitoxin and the toxin will be only partially eliminated or dialyzed. We must necessarily conclude that all colloids, from the point of view of the size of the granules of which they are composed are not identical, that a colloid is not absolutely homogeneous in all its parts, that it is composed of granules larger or smaller, that is to say, of granules containing a larger or smaller number of molecules.

When a certain quantity of such a product is injected into the blood of an animal it is found at the end of twenty-four hours that one part has been able to penetrate into the tissues and has been fixed in the cells, a second part has been eliminated, while a third part is still found to circulate in the blood. Thus in the case of disodoluargol (the disodium salt of dioxydiaminoarsenobenzene-antimonious-silver-bromide); if 10 cg. are injected into a rabbit's vein, after twenty-four hours there will be found of it about a quarter in the excretions and a quarter in the blood and we ought to conclude that the other two quarters have been absorbed and fixed by the organs and tissues. Three-quarters of the injected product have thus been able to traverse cellular membranes within twenty-four hours while the final quarter composed of larger granules has not been transformed into a dialyzable product.

For each colloid the proportions may be different but for the colloids of biologic origin we are unable to evaluate them accurately because we do not know the chemical constitution. We cannot conceive an idea of their quantity by biologic reactions which are always uncertain. But we do know with certainty that, as in the case of the arsenobenzenes, albumins, like the toxins injected into the blood, are partly fixed by the tissues some hours or some days after the injection; because we see these tissues react with characteristic symptoms and we know that no part of these products circulates for a long time in the blood without being modified. Toxins generally remain longer in circulation than albumins (white of egg, serum, etc.). Thus we may conclude that they are more fluid and less colloidal, than these latter.

We have seen above that all colloidal substances on which experiments have been made up to the present time have, from a biological point of view, another character in common: injected into the blood or under the skin of an animal, they cause, after a variable incubation period, the formation of "antibodies in excess," that is to say, of products which exert certain specific actions on themselves.

For want of a better term all these substances have been grouped as "antigens" precisely because they provoke the

formation of "antibodies" and at the moment they can hardly be called anything else because all we know of them except in the case of arsenobenzene, is that they are reciprocally "anti." When after a preparatory treatment, the intensity and duration of which may vary widely for different antigens and different animals, the prepared animal is bled and the blood serum mixed with the antigen in a test-tube, reactions are seen which are not produced with the serum of a normal animal and which are different according to the nature of the antigen injected.

Toxins (diphtheria, tetanus, botulism), some venins and poisons of certain mushrooms cause the formation of antibodies which neutralize the pathogenic effects of these poisons without visible change. The mixture of the two liquids remains clear and one can determine neutralization of the "antigen" only by injecting the mixture into a susceptible animal. After a sufficient preparation, a relatively very small quantity of the blood serum of the treated animal is able to neutralize a large number of "lethal doses" of the antigen. One cubic centimeter of antitetanic serum may, for example, often neutralize a thousand or even more times the dose of toxin necessary to kill a guineá-pig and it is this property of the antibody discovered by Behring and Kitasato which E. Roux first utilized in the practical serum treatment of diphtheria and in the preventive treatment of tetanus and which Calmette also used in the preparation of antivenomous serum.

Ricin, a vegetable antigen extracted from rice, whose composition is unknown but whose effects on the organism presented many analogies with that of diphtheria toxin, forms with its antibody an insoluble compound. When antiricin serum is added to a solution of ricin a precipitate is formed and if the two solutions have been mixed in suitable proportions the supernatant fluid will contain neither ricin nor free antiricin. We have been able to conclude then that a part if not all the antigen and antibody are combined or fixed one by the other and are contained in the precipitate and this supposition has been confirmed by experiment. By submitting the precipitate to the action of gastric juice which

destroys the antibody and does not destroy the ricin, it is possible to recover the ricin which the precipitate contains.

Ricin presents another peculiarity which permits us to study with a little more precision what it has not been possible to study with diphtheria and with tetanus toxin. Ricin dissolves red blood corpuscles in the test-tube. This peculiarity is very precious because it permits us to make a large number of tests under identical conditions and which are in consequence exactly comparable; for example, to estimate the pathogenic dose of diphtheria toxin or, in other words, to establish a "unit of measure," it is necessary to inject different quantities into a very large number of animals. Each animal can be injected only once and as there are very appreciable individual differences between the animals from the point of view of their sensitiveness to the action of toxin, even when they are of the same age, of the same weight and apparently of the same species, one can obtain units of measure of only an approximate value, sufficiently exact for the practical use of antitoxic serum but insufficient for the study of the mechanism of the reactions.

With ricin the same solution (relatively more stable than that of bacterial toxins) can be made to act in the test-tube on the same blood cells of the same animal and these tests can be multiplied almost indefinitely so that "units of measure" can be much more exactly obtained.

By studying the reaction of ricin and antiricin in the presence of blood cells it has been made possible to discover what one may call the *phenomenon of surcharge*, that is to say, the property of antigens to combine with their antibodies in variable proportions and not according to the immutable law of equivalents established for chemical combinations as such. Thus, for example, when we mix one hundred toxic units of ricin with one hundred antitoxic units, presumably well titrated, a neutral mixture is obtained; but when the hundred toxic units are added in fractions of five or of ten units to one hundred units of antitoxin, a mixture is obtained in which there will be a certain number (five to fifty according to circumstances) of free toxic units. This fact has been verified for other toxins and antitoxins and the conclusion

follows that in mixtures of toxins with their antitoxins or in general, of antigens with their antibodies, there are not produced chemical combinations in the ordinary sense but certain states of equilibrium which are variable for each concentration or proportion of one product in the other; in other words, if in certain proportions, two products can exactly neutralize each other, either of them can fix its "anti" *en surcharge.*

We will see further how this theory which results from facts established by very exact experiments is important in explaining the biologic action of antigens. For the moment, it is necessary to remember that antigens may form with their antibodies compounds which are *soluble* (in the cases of diphtheria toxin, tetanus toxin, or venins) or compounds which are *insoluble* (in the cases of ricin or abrin). We may also say in this last case that the antibody precipitates its antigen and all precipitating antibodies are called "precipitins."

The discovery of antidiphtheritic serum gave birth to the hope that it would be possible to prepare antibodies specific for every infectious disease of which the bacteria were known. Thus after the discovery of anthrax vaccine, it was hoped that man and the domestic animals could be vaccinated against all the contagions. It has been established that not only all the microbes and their secretions are "antigens" but that many other substances have a similar property of causing the formation of specific antibodies. But we have been obliged to remember that processes so simple and so efficacious as vaccination against anthrax and serum therapy in diphtheria cannot be applied to every infection.

The action of antigens on the organism including the reactions which they provoke as well as the properties of antibodies and the compounds which they form with their antigens differ widely among themselves and produce many contrary effects. Thus it is known that the injection of bacteria, killed or living, as well as bacterial secretions provokes in the injected animal the formation of antibodies which agglutinate and precipitate these bacteria *"in vitro";* that in certain cases (cholera) microbes are destroyed by

their antibodies while in others (typhoid) they continue to live and multiply without losing any of their virulence. With rare exceptions, antibacterial sera not only do not cure diseases but are rather more harmful than curative (typhoid, plague cholera, tuberculosis). Thus preventive vaccination, however efficacious and durable in small-pox and anthrax, is usually very precarious and transient in many other diseases.

A series of facts have been discovered which without touching infectious diseases directly have, from the theoretical and practical point of view, given interesting results. Thus it has been recognized (Bordet) that the serum or the blood of an animal of another species provokes on injection the formation of an antibody which can precipitate the serum or dissolve the blood cells and can precipitate the serum of the first animal and these researches, as well as the discovery of bacterial precipitins, have led to the serum diagnosis of a large number of infectious diseases, as well as to the reaction called "complement fixation" (Bordet and Gengou, Wassermann and others).

In order to understand the biologic action of antigens in general, it is necessary to consider at first the characters of the reactions which are common to each of them and then for each antigen to study:

1. Its direct and immediate action on the blood and the tissues; in other words, on the normal antibodies in the blood and cells.

2. Its delayed action, that is to say, its action on the "antibodies in excess" which, after a variable incubation period, will have appeared in the organism.

3. The nature of its compounds with these "antibodies in excess" as well as the reactions which these compounds may call forth in the tissues and in the blood.

It is very difficult to appreciate accurately the direct and immediate action of antigens on the organism because we have no idea of the quantity of actual antigen, that is of the really active substance which is only part of a mixture and which we cannot extract in pure state.

For example, we do know that a cubic centimeter of a broth culture of diphtheria bacilli contains two or three hun-

dred doses, lethal for a guinea-pig, while in the case of typhoid or plague 2 or 3 c.c. of a broth culture are necessary to kill, but we do not know to what quantity of active substance a fatal dose corresponds nor whether typhoid or plague bacilli produce quantities of toxins greater in the organism than in artificial cultures. We cannot then know whether typhoid or plague toxin produces on the organism effects analogous to those of diphtheria toxin even if it were possible to obtain typhoid and plague toxin in very much greater concentration than other more or less poisonous substances in our culture media.

At all events, however much we can judge by the apparent results of present experiments, we may admit that the products of the secretions of certain bacteria as well as certain other antigens may exercise a direct action on the organism, while in the case of other bacteria the pathogenic reaction manifests itself only after a special preparation—an indirect action.

Thus, for example, we know that the toxins of diphtheria and tetanus act quite quickly on normal tissues while tuberculin, malein, and very probably also the secretion of the treponema of syphilis do not act under the same conditions, but only on infected tissues and only in a longer or shorter time after the infection. In the first case the tissue is susceptible without preparation of any sort; in the other it becomes susceptible only after a specific preparation. The action of antigens on tissues may then be direct or indirect and this difference can be determined only by the physicochemical properties of these substances, or by the nature of the compounds which they form with their "normal antibodies," or finally, by the biologic properties of the compounds thus formed which may be neutral or more or less pathogenic to the organism.

In order to fully understand the first stages in the evolution of a disease as well as the mechanism of the defense of the organism, the question of the infecting dose is of capital importance. We may assume that no antigen is exclusively pathogenic as none is exclusively harmless. We can always find for the most active toxin a dose, which will provoke no

appreciable trouble in the organism, and the injection of the apparently most innocuous albumin will disturb the normal equilibrium whenever a certain dose is exceeded.

If then we assume with Ehrlich that a cell can be attacked by an antigen only in case it possesses a substance (normal antibody) which has a special chemical affinity for that antigen, and if we complete this hypothesis by the experimental fact analyzed above under the name of "phenomenon of surcharge" we may easily explain the immunizing and pathogenic action of the antigen. This action will be exclusively immunizing when the quantity of antigen fixed by the cell does not exceed or is less than the capacity of neutralization by the antibody; it will be pathogenic when a quantity of antigen fixed is larger than the neutralization capacity. The normal functions of the cells will then be disturbed and they will suffer more or less. Experience has shown that we obtain an active immunity all the more intense and all the more rapidly, in other words, we obtain a quantity of "antibody in excess" all the greater, when injections are restricted and when they never exceed the well-tolerated dose. We may say, in a word, that immunization will be always inversely proportional to intoxication or that the quantity of "antibody in excess" will be directly proportional to the intensity of the immunizing action of the antigen.

The study of certain infectious diseases will permit us to better define our thought. Finally, we may conclude from what precedes that every pathologic state caused by an antigen is determined by the reactions which this antigen may provoke in the organism and that the nature and the gravity of these reactions must necessarily depend upon:

1. The affinities of the antigen for some other substance intravascular or intracellular in the organism.

2. The nature of the reactions of the antigen with preexisting, that is to say, normal antibodies.

3. The importance of the rôle which the antibodies play in the life of the cells and of the cells in the organism.

4. The nature and properties of the compounds which the antigen may form with "antibodies in excess."

Any of these reactions may present special peculiarities

in each pathologic state. It will be necessary to analyze in detail a certain number of pathologic states caused by different antigens in order to study their differences and their common characteristics. We will begin this study by the analysis of the action on the organism of the arsenobenzenes because we know the chemical composition of these substances. We will continue the studies by a series of monographs having for their subjects the pathogenicity and evolution of the better known infectious diseases: diphtheria, tuberculosis, typhoid fever, with other intestinal infections and septicemias caused by various parasites such as plague, malaria and trypanosomiasis.

CHAPTER II.

PHYSICOCHEMICAL PROPERTIES

Transformations of the Arsenobenzenes "in Vitro" and in the Organism.

THE discovery of the arsenobenzenes and especially of their physicochemical and biological properties has opened new horizons for the study of the transformation of antigens. It has been recognized that certain arsenobenzenes, more particularly arsenophenylglycin and dioxydiaminoarsenobenzene (salvarsan) or its compounds, mono- bi- or trimetallic luargol or cupriluargol are colloids and may cause the formation of specific antibodies under the same conditions as the biologic antigens which we have studied heretofore. These substances possess properties essentially analogous to every other antigen. Let us see how it has been possible to consider them in this way.

The product which has been most particularly studied from this point of view is dioxydiaminobenzene-antimonious-silver-bromide (luargol) because it is a strongly colored red-brown solution which allows us to follow it in its transformations much easier than simple arsenobenzene or arsenophenylglycin, the color of which does not differ essentially from that of serum or other organic fluids. Luargol is a yellow powder more or less dark colored, insoluble in the basic state but soluble when slightly acidified with hydrochloric, phosphoric or citric acid; insoluble as a sulphate, but soluble as a sodium compound when made slightly alkaline.

The most convenient preparations for treatments and experiments are the sodium compounds and monosodium or disodium solutions can be obtained as well as intermediary alkalies between these two limits as well as hyperalkaline solutions.

When intravenous injections of these different alkaline

solutions are given to a series of animals, the apparent toxicity of these products diminishes as their alkalinity increases. Thus the rapid intravenous injection of 5 cg. of monosodium luargol will kill a rabbit in a few minutes while an injection of 40 cg. of the same disodium product or a little hyperalkaline will not kill the rabbit. Moreover, it is not the addition of the soda which has rendered this product less toxic because monosodium compounds are ordinarily less toxic than the disodium, provided the injections are made in minutes rather than in some seconds.

We must conclude, therefore, from this primary series of experiments that the rapid death of an animal by no means indicates the degree of toxicity of a product but this rapid death may be a phenomenon of some other nature.

In order to understand the causes of this rapid death it has been necessary to undertake other experiments and especially to study more closely the physicochemical properties of the arsenobenzenes as well as the transformations which these products undergo "*in vitro*" and "*in vivo.*" When we seal in a series of tubes, various solutions of sodium luargol of different degrees of alkalinity in very pure distilled water we find that these solutions remain for a long time perfectly clear and when we expose them to the air and to the light, they undergo no alteration for several minutes. On the other hand, if instead of dissolving these products in distilled water the solutions are prepared with salt solution (6 to 10 per thousand of sodium chloride) we find that the monosodium compounds precipitate in a few minutes; the disodium in a few hours; the hyperalkaline in a few days. Other salts, especially those of calcium are still more active in this regard.

The rapidity with which a precipitate is formed *in vitro* in salt mixtures coincides perfectly with the apparent toxicity of the solutions and when an autopsy is made on an animal which has succumbed in a few minutes to a large dose of one of these solutions, precipitates are easily found in the heart and in the pulmonary vessels as well as numerous infarcts in all the tissues and organs. (Ch. Fleig, "Toxicité du Salvarsan.")

What makes us hesitate to assume that the precipitant action is the only cause of death, is that we may kill the test animal by relatively small doses of the product and under these conditions, although infarcts are found at autopsy, intravascular precipitates are never found. Furthermore, solutions of luargol in serum or in salt solution added to normal serum retain their clarity longer than in pure distilled water. It seems certain that if the precipitate is not found in serum it is only because of the difficulty of demonstrating it and if serum does not precipitate luargol *in vitro*, it is because it has lost the salts which play the greatest rôle in the formation of the precipitate and which are retained by the coagulum, and because albumins prevent precipitation of colloids.

In fact when instead of treating the solution of luargol with serum it is treated with fresh whole blood recently drawn from the carotid and when after violently shaking and centrifuging the mixture, the parts are analyzed separately, much more luargol is found in the sediment than in the supernant fluid and microscopic examination of the sediment shows finely granular viscous masses.

To sum up, one may assume with certainty that the rapid death of experimental animals caused by the sudden injection of monosodium preparations is caused only by the precipitate which fills the capillaries and thus produces congestion and infarcts in different parts of the organism. The symptoms observed: dyspnea, congestion of the mucous membranes, epileptiform convulsions, gastro-intestinal disturbances, fall of blood-pressure, subnormal temperature are identical to those symptoms which are observed in the phenomenon of "anaphylactic shock." The explanation of the mechanism of the reaction and of the crisis which results from it, is, in these cases, easy and simple. We have seen that the arsenobenzenes, soluble in the state of di- or even monosodium salts, are insoluble as neutral bases. The weakest acids replace the sodium of the sodium compounds. Consequently when injected into the blood the compound loses its sodium by reason of the carbonic and other organic acids of the plasma, and becomes insoluble.

It is then evident that the monosodium compounds will be much more easily and rapidly transformed to bases than the disodium or hyperalkaline compounds.

But as the monosodium compounds cause crises only when injected rapidly and do not produce them when injected slowly, we can draw logically this third conclusion, that, if the formation of the precipitate is the primary cause, the origin and the intensity of the disturbance is determined only by the duration of the reaction. And to this conclusion Doerr, Besredka, Mutermilch, and others, have come in order to explain anaphylactic shock as caused by biologic antigens. Thus we see:

1. That intravenous injections can cause immediate disturbance.

2. That this disturbance arises by the transformation of a soluble sodium compound to an insoluble base, that is to say, to a precipitate.

3. That the degree of the disturbance is caused by the rapidity with which the reaction takes place.

And we may therefore conclude that death or non-fatal crisis which immediately follows injection is determined by a reaction which is exclusively intravascular; that it does not result from any toxic reaction of the product but from its mechanical action on the capillary circulation.

Moreover, this is not the only explanation which can be given to this phenomenon. The reactions of the organism, however localized they may be, are never simple. The arsenobenzenes can be combined with a series of other substances which exist in the blood plasma and especially with the calcium salts and can thus form compounds which are more or less insoluble. By removing these substances from the blood the injection causes a rupture of equilibrium and especially a modification of plasma coagulability which necessarily reacts on the intracellular fluids. The purely mechanical intravascular action of emboli may therefore be complicated by intimate and complex intracellular reactions as in the case of biologic antigens. And in this case also, it is the factor "time," the rapidity of the reaction, which plays the principal rôle in the severity of pathologic manifestations.

The first stage of the transformation which the sodium compounds of the arsenobenzenes undergo in the organism consists then in making them change from the soluble state to the insoluble state. They form precipitates or coagula in the interior of vessels and these then provoke disturbances which are more or less severe according to the injected dose, the degree of alkalinity of the product, or what amounts ultimately to the same thing, to the quantity variable from one individual to another, of precipitating substances which preëxist in the blood: Other conditions being the same, the reaction will depend also upon the rapidity with which the injection is made.

There is thus a primary analogy between the action of the arsenobenzenes and of biologic antigens and for greater convenience in the discussion which follows we may call the disturbances which *immediately* follow the injection *primary intravascular* disturbances and we may group the total of substances in the organism which concur in the formation of the precipitate under the name of *preëxisting or normal antibody* (and we know that in this case, these include acids and salts, sodium chloride, calcium phosphate, etc.)

Arsenobenzene which becomes insoluble in the blood plasma does not remain indefinitely in the organism in the precipitated state. We may assume that only one part of the injected product becomes insoluble; another part remains in solution or passes to the precipitated state only after a very short time, a fraction of a second.

In fact when we inject an animal intravenously with a series of small doses of luargol, we obtain after a certain incubation period a serum which precipitates luargol of the same alkalinity *in vitro*. But at the same time we know as a result of seeking to define the conditions of the formation of this precipitate, that the reaction is not simple; whatever may be the proportions of sera and luargol in mixtures, total coagulation of the latter is never obtained. It is found, furthermore, that in certain mixtures the precipitate already formed redissolves in some minutes or some hours afterward.

In order to explain the cause of the particular nature of all these reactions, we must remember these facts: That in

a serum there are both acid functions and alkaline functions in unstable equilibrium which may act more or less rapidly on disodium luargol. That luargol is soluble in the mono- and disodium state and also in the state of a mono- and di-acid compound (hydrochloric, phosphoric or citric); and that in the presence of the salt contained in the blood the "mono" compounds precipitate more easily than the diacid or dialkaline compounds.

The acid function acts first because there is in serum a little free carbonic acid which precipitates one part of the luargol as a base but soon afterward it is the alkaline function which appears to hinder the coagulation of the part which still remains in solution, and even to redissolve a part of the precipitate already formed. In case the serum is hyperacid, the precipitate will not form because certain acid compounds of luargol are soluble.

It is important to note that this state of equilibrium between the acid and alkaline functions may be different in the serum of each normal animal, whether prepared by one or several previous injections. The formation of a heavier precipitate in the sera of prepared animals would indicate a temporary predominance of the acid function or the presence of a larger quantity of substances which form with the arsenobenzenes, compounds less soluble (lime salts, etc.), or, what is more probable, the two factors at once.

Heating to 60° or 65° has the effect of stabilizing or fixing the acid and alkaline functions of serum and rendering it neutral toward luargol. By adding acid to such a serum it is possible to reactivate this precipitate again; by adding sodium one reactivates the solvent action. By treating in this way a serum normally neutral, whether heated or unheated, we find that when heated in order to give us a precipitate more acid is needed and in order to redissolve, more alkali than in unheated serum.

So much of the chemical constitution of serum and antibody remains unknown that it will be hardly possible for us to grasp an exact idea of the chemical mechanism of these reactions. The key to the problem lies in researches of this kind in which the composition of one of the elements of the

reaction is exactly known. For the moment it seems to us important to recall the complete identity of the reactions between serum and arsenobenzene on the one hand and between serums and biologic antigens (albumins, microbes and their secretions) on the other.

In fact it is more than probable that in the two cases the nature and the mechanism of the reactions are the same. It is the reaction of the acid and the alkaline functions of the antibody, favored by the chlorides and phosphates of sodium and calcium as well as certain substances, such as lipoids, lecithin, cholesterin, which cause coagulation or dissolution of the antigen; the action of the acid and alkaline function ought to be fundamental and always the same. Thus should be explained *complement* or *alexine* which is found indifferently in every normal serum, which disappears on heating and which can reactivate the action of a *specific serum antibody* when this is heated. Specific precipitant action should be determined by the salts of calcium and other substances in the plasma which form with arsenobenzenes, more stable, less soluble combinations of which the quantity increases as the result of a series of injections. Thus should be explained the *sensitizing substances* or *amboceptors* which do not disappear on heating, which combine with antigen, but whose action must be assisted first by acids and oxidizing agents, finally by alkalies in order to become appreciable.

Dioxydiaminoarsenobenzene has several affinities. Trivalent arsenic can fix two molecules of metallic salts; amines can be bound by acids or by formic aldehyde and through this latter can fix a series of other substances. The oxyhydrate radicals may exchange their hydrogens for a series of inorganic or organic bases. We know for example that when one binds to the amines of arsenobenzene one or two molecules of formaldehyde sulphonate of sodium, the product becomes soluble in neutral medium and passes from the colloidal state to the state of a salt and that by the substitution for the hydrogen of the oxyhydrate radical one may make these combinations soluble with salts of calcium.

A non-lethal dose of luargol injected into the blood of an animal in the form of a sodium compound ought then to

undergo a series of successive transformations without the whole of the injected product ever being able to take part simultaneously in each of the reactions which follow. We may outline this transformation in a schematic method as follows:

1. One part of the injected product, the more colloidal, combines with the calcium salts, loses its sodium and thus becomes rapidly an insoluble base of which one part continues to circulate in the blood, while the other part is taken up by leukocytes in the liver, the spleen, the lymphatic glands and finally in the local lesions which become the site of an inflammatory process at the point of injection.

2. Another part of the product is not precipitated and continues to circulate in the blood as a sodium compound. This is probably the least colloidal part. It can traverse certain membranes and thus penetrate to the interior of cells where it is fixed as a base; that is to say, as a new insoluble compound.

3. A third part finally becomes rapidly and almost simultaneously a base and a salt and as such may be partially assimilated, that is to say, fixed by certain cells, partially eliminated by the kidneys and intestines. In point of fact, some minutes after the injection, traces of arsenobenzene are found in the urine, to be sure in a soluble state, because when one adds directly to the same urine a little of the same solution of arsenobenzene there immediately forms an abundant precipitate. The product has thus passed into the urine in the form of a compound which is no longer precipitated by salts.

The proportion of the product which is either engulfed by leukocytes as a precipitate, or which continues to circulate in the blood as a precipitate or which passes out and precipitates in the cells of different tissues as a colloidal solution or as a salt and finally the proportion which is immediately eliminated, vary widely according to the injected doses, the degree of alkalinity of the product, and the composition of the blood of the injected animal at the time of the primary injection (or later if injections are made in series). Thus symptoms may vary infinitely.

Experiments with doses of arsenic made by Mlle. Michel (by the method of Bougault) have given the following results.

Experiment 1.—The whole blood of a rabbit bled white is added to 10 cg. of luargol in a solution of 10 c.c. of distilled water, is shaken violently to prevent coagulation and allowed to stand for twenty-four hours. The fluid is centrifuged and 38 c.c. of dark liquid and 30 c.c. of precipitate are obtained in which are found:

	Arsenic, mg.
In the fluid	4.62
In the precipitate	15.37

in all the same 20 mg. of arsenic contained in the 10 cg. of luargol of which about one-quarter remains in solution in the serum and the other three-quarters have been partly fixed by the formed elements of the blood and partly precipitated as finely granular viscous masses. Only a very small quantity of coagulated fibrin is formed.

Experiment 2.—A rabbit is injected intravenously with 10 cg. of luargol dissolved in 10 c.c. of distilled water and is bled twenty-four hours afterward. At the same time the urine for the twenty-four hours is collected and is added to the feces as well as to the intestinal contents after the bleeding. The blood is centrifuged and we find:

In 55 c.c. of coagulum about	1.0	mg.	of arsenic	3.6 mg.
In 37 c.c. of serum	2.5	"	"	
In 275 c.c. of urine	2.3	"	"	5.5 mg.
In 90 gr. of fecal matter	3.2	"	"	

which means that a little more than a quarter of the injected luargol has been eliminated in twenty-four hours by the kidneys and intestines; about one-eighth remains in the serum as untransformed luargol and one-sixteenth has been absorbed and fixed in the elements of the circulating blood at the moment of bleeding. In estimating at 10 per cent. the quantity of blood remaining in the vessels, we may assume that after twenty-four hours approximately one-half of the luargol originally injected has remained fixed in the organs or tissues.

By comparing the doses of this second experiment with those of the first, that is to say, by recognizing the large proportion (three-quarters) of luargol fixed by the cells of the blood in a mixture *in vitro* and the very small proportion (one-sixteenth) found in the coagulum in the injected rabbit twenty-four hours after the injection, we may assume that the largest part of the luargol remaining in the organism has been fixed by other elements, probably by leukocytes and transported to the liver, spleen, and to the hemopoietic organs.

By estimating the arsenic eliminated day by day following a single injection, Mlle. Michel found in certain cases traces of arsenic in the urine twenty-four days after the injection of a dose of 10 cg. in a rabbit weighing 2500 gm. In these cases the elimination is not regular but takes place by successive discharges (Emery and Jeanselme) at intervals of three, four or even eight days. The largest quantity is eliminated in the first sixty hours. By estimating the total quantity of eliminated arsenic, we find that up to some tenths of a milligram, the organism retains none of an arsenic compound injected as luargol.

In man therapeutic doses of luargol exactly disodic (5 to 30 cg.) never provoke primary reactions but very small doses of 5 to 10 cg. may produce a slight reaction of another nature, rarely in two to three hours, generally in twelve to twenty-four hours after the injection. These reactions are manifested generally only after the first injection and consist of a mild and transient fever (38° to 38.5° C.) for one to two hours accompanied sometimes by chills and mild headache, very rarely by nausea and diarrhea, corresponding to the fixation of the product by the cells. The nature of the symptoms leads us to suppose principally a reaction of the cells of the central nervous system.

There is not generally a reaction to the second injection nor to following injections even if the doses are progressively increased because as we have seen above the elimination of the product is very slow so that each of the successive doses may be considered as a preparation or vaccination for the following injection. There is even a sort of tolerance or a

cellular immunity identical to that which is observed to toxins and other biologic antigens. Cells multiply their antibodies and may transform larger and larger quantities of antigen (up to a certain limit) without being disturbed in their normal functions.

Thus as far as it is possible to judge by repeated daily analyses of urine and intestinal contents, of blood, organs and tissues in a series of animals from the time of injection to the total elimination of the injected product, we may assume that arsenobenzene injected into the blood as a soluble colloid passes partially as a precipitate into the organs (liver, spleen, etc.) and partially as a solution into the cells of different tissues where it becomes insoluble. That part fixed by organs and tissues is transformed either into soluble crystalloids which again pass into the blood and are eliminated by the kidneys and intestines, because they have no longer any affinity for the contents of the cells, or into soluble semi-colloidal products which also pass into the circulation but may again be fixed by the cells to be finally transformed into neutral salts and eliminated as such. Some of the injected arsenobenzene is transformed directly in the blood to a neutral salt which is rapidly eliminated without passing through the tissues. It is this last portion which forms the primary discharges of the product eliminated in the first twenty-four hours and which marks the first summit of the elimination curve. The second summit which is generally ended on the third or fourth day after the injection indicates the second discharge of the product which has been fixed and dissolved in the organs and tissues. Little summits which are noted up to the tenth and thirteenth day correspond to little successive discharges of the product which have once or twice been refixed and redissolved in the tissues.

SUMMARY.—Arsenobenzene is an arseniated or arseno-antimonious or multimetallic amine which in the form of a sodium compound does not exist as a free molecule but whose component molecules in greater or less number, form colloidal granules. When injected into the blood, the colloidal granule passes through a series of transformations which lead to its disintegration and to the liberation of its molecules.

From the physical point of view the transformation consists of a series of successive passages from the state of colloidal solution to the state of coagulum and from this latter to the state of crystalloid solution.

From the chemical point of view, judging by experiments *in vitro* the disintegration of colloids and the liberation of molecules takes place by a binding of amines and the fixation of bases by oxyhydrate radicals.

From the physiological point of view, the formation of coagula may cause intravascular and intracellular disturbances because in the blood, the reactions are rapid and sudden. In the interior of cells reactions may be also violent but take place only after a longer or shorter incubation period.

When at the end of these transformations, the molecule of arsenobenzene has fixed to itself substances for which it has an affinity, it becomes neutral for the organism and is eliminated.

In a word, the processes are of exactly the same sequence and of the same nature as those which an albumin undergoes when submitted to digestion.

Digestion has no other effect than to liberate molecules of amino acids. By certain substitutions of unsatisfied bonds, these molecules are rebound by certain lateral chains to form colloidal aggregates. It is very probable that these chains which vary infinitely, constitute the specificity of albumins and of antigens in general and that antibodies are thus nothing else than the substances of the organism which replace the chains and bind the affinities of the amino groups.

CHAPTER III.

EVOLUTION OF THE INFECTIOUS DISEASES.

DIPHTHERIA.

When one injects a non-fatal, but at the same time, a highly pathogenic dose of diphtheria toxin under the skin of a guinea-pig one sees a large edema develop at the site of injection four to six hours afterward. From this edema and at this time, almost all the injected toxin, can be extracted. The edematous fluid injected into a second guinea-pig will produce the same effect as the toxin injected into the first. After a maximum development which is reached at the third day, the edema is resorbed little by little and finally disappears at the end of fifteen to twenty days. The quantity of toxin which may be extracted diminishes at the same time.

When this edema is allowed to develop normally we will find from the center to the periphery every degree of reaction which toxin can produce on the cellular tissues of the guinea-pig. At the center the most concentrated solution will destroy the cells; there will be necrosis of the epidermis and even of the dermis and the area will be marked by an eschar; at the periphery where the limit is marked by pallor, the tissue will appear normal. When we try to produce the Schick reaction at the site occupied by the edema after the complete subsidence of the latter, we find that the zone limited by the pallor neutralizes more of the toxin than the central part formerly occupied by the eschar and more than every other part of the animal's skin. The center of the area previously occupied by edema will give a positive reaction to a dose which gives a negative reaction on the periphery. That is to say, there is a local immunity at the site of the injection of the toxin and this immunity is most marked at the site which has suffered least by the injection.

This fact agrees with the observation of L. Martin[1] that in mild cases of disease immunity is established more rapidly than in severe cases.

We may thus consider as proved:

1. That a certain pathogenic dose of diphtheria toxin is fixed by the cellular tissues of the guinea-pig and that it is retained in place eight or ten days without being either neutralized or transformed.

2. That immunization or, in other words, the excess production of the "normal antibody" is inversely proportional to the intensity of the reaction and to the gravity of the lesion.

These facts which do not accord with the theory of Ehrlich are very easily explained in the light of experiments concerning the nature and properties of mixtures of toxins and antitoxins. We have seen in fact[2] that diphtheria and tetanus antitoxins as well as antiricin can fix their toxins *en surcharge;* that is to say, in a quantity greater than they can neutralize.

The passage into the wash water of tetanus toxin fixed *en surcharge* by the nervous tissue *in vitro*[3] as well as the toxicity of the edematous fluid in the experiment above are explained very simply in the following manner:

Normal antibody contained in the nervous cells or in the cellular tissue (diphtheria in a guinea-pig, horse or man) can neutralize a definite quantity of toxin. The product of this combination is neutral for the cell and if the quantity does not exceed its digestive capacity, the cell digests it, eliminates it and reproduces the substance neutralized in a little larger quantity than it normally contained. The cell will then be capable of neutralizing and digesting without difficulty a larger quantity of toxin. In this way it will establish a certain local immunity and the tissue so immunized will give a Schick reaction negative for a dose of toxin which otherwise would give a positive reaction. But we have seen that the *normal antibody* can fix more toxin than it can neutralize

[1] Bull. méd., 1917, 10 fevrier.

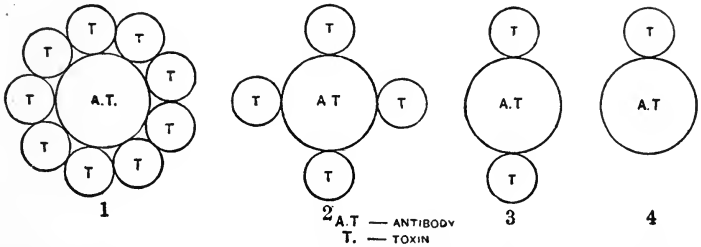
[2] Danysz, J.: Les propriétés et la nature des mélanges de toxines avec leurs antitoxines, Ann. de l'Inst. Pasteur, mai, 1902.

[3] Danysz, J.: L'étude de l'action de la toxine tétanique sur la substance nerveuse, Ann. d. l'Inst. Pasteur, 1899, p. 156.

and the more it fixes, the more difficult it is for the cell to transform and eliminate the compounds thus formed. The cell may then succumb to the task, that is to say, to a veritable indigestion and may even become incapable of reproducing *antibodies in excess.*

It is useless to complicate the problem by assuming with Ehrlich the existence in every toxin of a *haptaphore* group which is exclusively immunizing and of a *toxophore* group which is exclusively pathogenic, but we may certainly conclude from what precedes that the same substance will cause one or the other of these reactions following doses measured according to the degree of sensitiveness of the animal, that, in a word, the immunizing or pathogenic reaction is a function of *quantity and not of quality.*

We may represent the process which can go on in the edematous tissues of the above experiment according to the following scheme:



T, toxin; *AT*, antitoxin. 1, pathogenic compound; the antibody is surcharged with toxin; 2, 3, intermediate compounds; 4, non-pathogenic compound; the antibody has fixed the quantity of toxin necessary only to produce an immunizing reaction.

Between the two extremes, all intermediary steps are possible but the quantity of toxin which an antibody can fix *en surcharge* is not boundless and certain facts lead us to suppose that this faculty of a tissue to fix larger or smaller quantities of antigen depends not only on the local condition of this tissue but rather on the general state of the organism. Thus a dose of toxin fatal for a guinea-pig in three or four days will produce on the second day an edema less volu-

minous than a non-fatal dose. A dose fatal in thirty-six to forty-eight hours will not produce edema at all. We must assume first that the cellular tissue can retain only a maximum of toxin beyond which the excess will be fixed by other tissues more vital to the life of the animal and second, that this general reaction of nervous origin influences the local reaction by diminishing the fixation capacity of the cutaneous cellular tissue.

There is no doubt but that all these reactions depend upon physicochemical affinities and if we do not know the exact mechanism we can at least say for the present that toxins as well as antitoxins are colloidal substances, are aggregates of molecules of varying size, and as seen in the ultramicroscope are spherical in form. We know that when causing toxins and antitoxins to dialyze across collodion or gelatin membranes of greater or less density, toxins pass easier than antitoxins, from which we can conclude that toxins form aggregates less voluminous than antitoxins. The recognition of these facts is sufficient for the moment to explain the curious properties of mixtures of toxins with their antitoxins which we have noted above.

In a rabbit treated by diphtheria toxin, the phenomena observed are quite different from those in the guinea-pig. Hypodermic injections provoke only a little redness at the point of inoculation and if the dose is not speedily fatal the rabbit succumbs almost always some weeks afterward to a cachexia accompanied by nervous disturbances. In this animal, the toxin is not retained in the cellular tissue, but passes to the nervous tissue and produces disturbances which are relatively much more severe. The same result may be obtained in the guinea-pig by injecting a mixture of toxin and antitoxin containing a slight excess of toxin or of toxin fixed *en surcharge*. In this case the toxin fixed by antitoxin (*in vitro*) is retained to a less extent by cellular tissue; it diffuses into other regions of the organism and may produce in the guinea-pig the same cachectic state and the same nervous disturbances as toxin of itself produces in the rabbit.

The susceptibility of man seems to be intermediary between that of the guinea-pig and that of the rabbit. In man toxin

is fixed by the cellular tissue but may also be fixed by nervous tissue. The preventive vaccination of children by mixtures of toxin and antitoxin may have, as noted by L. Martin[1] consequences which are disagreeable if not serious. The susceptibility of the horse is intermediary between that of man and of the guinea-pig. In a horse treated by diphtheria toxin nervous symptoms are less common than in man. Edema of the subcutaneous cellular tissue develops in almost the same way as in the guinea-pig.

We may thus explain why an exactly neutral mixture, that is, one which contains no excess of antitoxin but may contain an excess of toxin which is not pathogenic for the guinea-pig will be also neutral for the horse, slightly pathogenic for man, more so for the rabbit, and frankly toxic for birds which are the most sensitive animals. For the same reasons, fixation of diphtheria toxin by cellular tissue should be considered a reaction of preservation against reactions more pathogenic for nervous tissue. The larger and stronger the barrier which holds toxins in place in cellular tissue, the less will be the chance for these toxins to approach nervous tissue.

The total of these facts permits us to represent the pathogenicity and evolution of diphtheria in the following manner. Toxins secreted by bacteria are developed in the mucous membranes of the throat, penetrate to the subjacent cellular tissue and combine with the normal antibody of this tissue. The two extreme things which may then happen are:

1. The quantity or the virulence of the toxin secreted may correspond exactly to the quantity of normal antibody which can neutralize and digest it without difficulty and there will thus be *local immunity;* and if the process lasts long enough for the antibody to be able to reproduce itself in excess and to pass into the blood as antitoxin there will also be *general immunity.*

2. The quantity or the virulence of the secreted toxin or rather the rapidity of the secretion may be too great for the cellular tissue to be able to fix and retain it, so that a part of this toxin will then pass into the organism and will produce

[1] Loc. cit.

severe disturbances which, if there is no timely intervention, may result fatally. Between these two extremes we may imagine an infinite variety of pathologic manifestations and local or general immunizations. As we have indicated above, acquired immunity will always be inversely proportional to the severity of the attack.

But in this short discussion which has at the moment no other object than to present in a certain order and to correlate a total of experimental and clinical facts most of which result from the memorable researches of Roux and Yersin, Behring and Kitasato, Vaillard, Ehrlich, L. Martin, Grancher, Marfan and others: and to bring out the difference in the evolution of diphtheria and most of the other infectious diseases, we must dwell upon the exact significance of the "*incubation period*" in pathologic states caused by antigens.

We are accustomed to designate the time which intervenes between contagion and the appearance of the first symptoms or, in other words the onset of disease, as the "period of incubation." The studies of Ch. Richet, Hamburger and Moro, Krauss, Besredka and Mlle. Harde, Vaughan, Jobling and others have shown that in the great majority of infectious diseases as well as in pathologic states caused by previous injections of heterologous albumins, of antigens, the "period of disease" coincides almost exactly with the appearance of *specific antibodies in excess* in the blood and we have been able to establish that the symptomatology of all these pathologic states is determined by the nature and the site of the reaction between antibodies and antigens.

We may thus characterize the "period of incubation" by reactions of antigens with normal antibodies; and the "period of disease" by the reaction of antigens with antibodies in excess.

But if we admit these distinctions and this seems necessary, we assume that in diphtheria and in the diseases analogous by the nature and action of their antigens (tetanus and botulism), the pathological manifestations appear *during* the "period of incubation" while the "period of disease" is concerned with recovery; all of which is contrary to what happens in the great majority of infectious diseases and in

every case of *anaphylaxis*. This fact is explained quite naturally when we assume that toxins form with their antitoxins compounds which are absolutely neutral for the organism and that antitoxins in excess can neutralize not only the excess of toxins which has passed into the circulation but also by virtue of its mass action the toxins fixed "en surcharge" by the cells.

To summarize. By taking as a basis, the nature of the infection, the nature and physicochemical as well as biological properties of the secretions of the diphtheria bacillus, in other words, of its antigen as well as the nature and the physicochemical properties of the compounds which this antigen can form with its normal antibody and with the antibody in excess (antitoxin), we may characterize diphtheria in the following way:

Diphtheria—local, infectious disease.

Antigen colloidal, soluble, directly toxic. Without incubation. Affinity especially for the cells of tissues of ectodermic origin.

Normal antibody—intracellular. Can fix the antigen "en surcharge." Compounds of the antigen with antibodies are soluble.

Intracellular Reactions:

1. *Immunizing* for the cells and for the organism, if the quantities of antigen and antibody are equivalent or if there is an excess of antibody.

2. More or less *pathogenic* if there is an excess of antigen and fixation of this latter by the cellular antibody "en surcharge."

Intravascular Reactions.—Neutral compounds soluble and directly assimilable or eliminable provided the quantities of antigen and antibody (antitoxin) are equivalent or if the latter are in excess. Can never provoke anaphylactic hypersensitiveness.

TUBERCULOSIS.

A type of evolution quite different is represented by tuberculosis.

Contrary to what we have seen for diphtheria toxin, the

tuberculous antigen, tuberculin, exerts apparently no direct pathogenic action on organs or normal tissues. But we know that a dose of tuberculin known to be harmless for the normal organism, or even a much smaller dose, will provoke in a tuberculous patient a general reaction more or less severe when injected under the skin or into the blood and a local reaction when a drop of it is placed on a break in the skin (cutireaction) or on the cornea (oculoreaction). We also know by the reaction of complement fixation that this general and local hypersensitiveness coincides with the existence of a specific antibody in the blood.

But this antibody does not neutralize tuberculin *in vitro*. A mixture of it with tuberculin will cause a general and local reaction identical to those provoked by tuberculin alone. We have a total of facts which seem contradictory. The problem of the evolution of tuberculosis is much more complicated than that of diphtheria. To solve it, it is necessary to analyze carefully each of the elements which compose it. Before beginning this study it is necessary to explain the exact meaning of the terms which will be employed in what follows.

We will define:

1. *Artificial tuberculin* as the total of the secretions of the tubercle bacillus obtained *in vitro*, whatever may be the culture medium and the method employed in its preparation.
2. *Natural tuberculin*, as the total of the products secreted by the bacilli *in vivo* during infection.
3. *Normal antibody*, as the intracellular substance which possesses a specific affinity for tuberculin and which combines with it in the interior of cells; and
4. *Antibody in excess*, or antituberculin as the same substance as the normal antibody but multiplied and existing in excess in the tissues and in the blood of the diseased.

After reviewing the total of experimental work and clinical observations published on tuberculosis and tuberculin since Koch's discovery of the germ and the facts well established and verified by numerous experiments; we know that *artificial tuberculin* does not act on normal tissues and that repeated injections of this product do not provoke the formation of an

antibody in excess comparable, for example, to diphtheria antitoxin in the organism. But that *natural tuberculin* becomes pathogenic for these tissues after a longer or shorter incubation and that this natural tuberculin provokes in the affected organism the formation of specific *antibodies in excess* which can be found in the blood (reaction of fixation) and in the tissues (cutireaction).

From the fact that a true antigen can act only on a susceptible organism, one ought to assume that artificial and natural tuberculin are two different substances since the normal organism seems insensible to the action of the first and on the contrary, acquires a specific sensitiveness to the action of the second.

This suggests that there is in the cells a *normal antibody* for *natural tuberculin* but no *normal antibody* for *artificial tuberculin* and from the point of view of specificity of antigens this would be a very important point of difference. Moreover we know with some certainty that artificial tuberculin produces on the tissues of an organism infected by tuberculosis, reactions which are identical to those which natural tuberculin produces in tuberculous foci. There is then a contradiction, but a close analysis of the known facts will easily demonstrate that this contradiction is only apparent.

By studying the development of a tuberculous lesion, we find, according to the researches of Besredka and others, that lesions around tuberculous foci become manifest only some time after the appearance in the blood of patients of the antibody in excess and a positive cutireaction shows at the same time that the tissues of a tuberculous individual are impregnated with this antibody in excess at a time when not a single clinical symptom reveals the presence of a tuberculous focus. *The presence of antibody in excess in the blood is thus an indispensable condition to pathogenic reaction* and if this is so, we may represent the evolution of the tuberculous lesion in the following manner:

The bacteria of a tuberculous focus secrete natural tuberculin of which a part is fixed by the cells of the surrounding tissue while another part, "the excess," diffuses into the general economy. We will see later what happens to this excess.

For the moment we can say with certainty that this natural tuberculin is no more pathogenic for healthy tissues than artificial tuberculin. The one and the other become pathogenic only when in combination with tuberculous antibody in the interior of cells. If natural tuberculin provokes the formation of antibodies in excess, and if it has not been possible up to the present time to obtain an analogous hypersensitization by repeated injections of artificial tuberculin, it is very probably because the injections, even if often repeated, do not act in the same way as the slow but steady diffusion of the bacterial secretion from a tuberculous focus. We can also say with certainty that it is in consequence of the action of these bacterial secretions, harmless for normal tissues, that antibody in excess is formed and we must necessarily conclude that normal intracellular antibody can fix tuberculin in *quantity strictly immunizing or, in other words, easily digestible and hence not pathogenic for the cell.* There is here no fixation by the normal antituberculin of tuberculin "en surcharge," which might be directly toxic as in the case of diphtheria antitoxin and toxin. This immunizing action has the effect of multiplying the normal antibody of which a certain quantity remains in the sensitive cells and of which the surplus passes into the circulation. Experience has shown that tuberculin secreted by a tuberculous focus penetrates throughout the organism and that it provokes immunizing reactions in every tissue, especially in those of ectodermal origin.

At a given moment after an incubation period, longer or shorter according to the virulence of the bacteria and the number of foci, all the sensitive cells of the organism especially those near the infectious foci are surcharged with antituberculin. That phase of the evolution of the disease which corresponds in diphtheria to immunization and recovery (because the combination of toxin with an excess of antitoxin is completely neutral for the organism) determines in tuberculosis the beginning of the pathologic state because the compound of tuberculin and antituberculin fixed in the cells is pathogenic for the cells.

Thus for diphtheria *it is the surcharge of toxin;* for tuber-

culosis *it is the surcharge of antibody* in the interior of the cells which determines the pathologic moment and the lesion.

It seems that this intracellular surcharge of antituberculin is not indifferent for the organism even without the intervention of tuberculin. In fact although an animal strongly immunized and surcharged with diphtheria or tetanus antitoxin does not seem to suffer at all, a man or an animal surcharged with tuberculous antibody becomes rapidly hypersensitive to all sorts of external agents such as changes in temperature, fatigue and especially a series of non-specific products such as the antigens of pneumococci, pyocyaneous, Metchnikoff's vibrio, divers sera, creosote, etc. This non-specific hypersensitiveness may be explained by the hypothesis that the substance which constitutes the tuberculous antibody in the cell is called upon to play a more important rôle in the life of this cell than, for example, diphtheria antibody, and that the cell cannot easily rid itself of the excess of antibody which it has produced. In a word there results a sort of hypertrophy of an intracellular organ and of a function which thus becomes abnormal and harmful for the cell and for the organism.

An interpretation according to these theories of some of the facts determined experimentally by A. K. Krause[1] may serve to clarify the discussion:

This investigator found that a subcutaneous injection of living tubercle bacilli into a normal guinea-pig will cause in this animal a local lesion (reaction) which will appear only after a relatively long incubation period.

However, a guinea-pig treated in this way, will, after the healing of this local lesion or tubercle, always react to a new dose of tubercle bacilli (or tuberculin) in a very different way from the first reaction.

The second dose, if given subcutaneously, will produce a second tubercle but in a very short time and the lesion will be by comparison, large and severe. However, instead of slowly progressing in size perhaps until the death of the animal, the initial severity will soon subside and the "tubercle" will heal.

[1] Krause, A. K.: Jour. Med. Research, 1916.

Another point: Artificial tuberculin applied to the skin or the eye of the first guinea-pig will not evoke a reaction until after the tubercle has been established and has begun to heal—and this test can thereafter be elicited throughout the life of this guinea-pig unless at some time the animal is overwhelmed by a "miliary tuberculosis."

In a normal pig, a "tubercle" does not appear until the production of antituberculin in excess. This antituberculin in excess remains in all the cells of the guinea-pig "en surcharge" and can fix to these cells in equal quantity its own "anti"—that is to say, tuberculin whether artificial or natural whenever injected. And in this way is explained the local and general reactions of the second injections. That this second dose produces only a temporary reaction and that the animal ultimately recovers (showing immunity) is explained by the persistence of antituberculin.

However, when the available antituberculin is less than the new dose of tuberculin, the organism will be overwhelmed, local skin and eye reactions can be no longer produced and the animal will die.

Let us now return to the tuberculous focus. The bacteria of this focus secrete tuberculin which spreads to the surrounding tissues and causes in the cells a multiplication of antibodies. These cells then become capable of fixing larger and larger quantities of tuberculin *without pathologic manifestation* up to a certain limit (greater and greater immunity to tuberculin). When this limit is passed the quantity of antituberculin *en surcharge* forms with tuberculin pathogenic compounds and it is only then that the lesion appears.

The first phase of the infection, therefore, corresponds to the incubation period, the second phase to the period of disease. It is thus evident that from the beginning of the infection, the evolution of a tuberculous focus will be determined by the three following factors:

1. The quantity of tuberculin secreted by the bacteria.
2. The multiplication of the antibodies in the cells which surround the focus.
3. The quantity of tuberculin which is fixed by the cells and which will diffuse into the general economy.

Experience shows clearly that the production of antibody far exceeds the production of tuberculin. Besredka determined that in the blood of guinea-pigs, antituberculin in excess appeared four days after the infecting injection and before any pathologic manifestation, either local or general. In consequence there is in the evolution of a tuberculous focus a period during which *all the tuberculin* secreted by the bacteria will be fixed in the focus or the surrounding tissue. During this period the excess production of antituberculin will be forcibly stopped, the quantity of it which circulates in the blood will progressively diminish and at the same time, thanks to the intervention of leukocytes, the tuberculous focus can be isolated from the remainder of the organism without forming a sequestrum. The lesion may definitely heal by a mechanism which we will examine later leaving a scar, or a focus can remain in a latent condition for a longer or shorter time and can be revivified by the onset of another disease or sometimes even by a simple traumatism. The excess production of antibody in the cells thus becomes the cause of the lesion and of a possible cure.

SUMMARY.—There results from the total of studies on the properties of tuberculin and antituberculin as well as on the reciprocal reactions of these substances on the organism:

First.—That all tuberculins, regardless of their method of preparation and origin (in artificial broth cultures or infectious foci), act by the same principle of pathogenicity, and that the observed difference of action results only from their concentration and from the medium in which they are placed. The biologic differences which are observed may be of the same sort as those, for example, which are found in wines of different ages in which the alcohol, always the same, but in greater or less quantity may be associated with all sorts of substances which modify its action in a very definite way. We may assume with the certainty that the virulence of all germs depends only on the quantity of the pathogenic substance secreted which passes to the free state in the external medium.

Second.—That antituberculin which multiplies in the cells by the action of tuberculin remains attached in the cells probably

by bonds which have vitally important functions to fulfill; the cells may thus be surcharged with antituberculin.

Third.— That the cells surcharged with antituberculin fix corresponding quantities of tuberculin and that it is on account of this abnormal quantity that the compound of tuberculin and antituberculin becomes pathogenic for the cells.

Fourth.— That the excess of antituberculin confers on the cells and on the organism a non-specific hypersensitiveness to every sort of foreign agent as well as a specific hypersensitiveness to tuberculin.

Fifth.— That granting this is true, the impossibility of an antituberculin immunity such as one finds in d phtheria is easily explained.

Moreover the studies of Koch, Neufeld, Klimmer, Behring, F. Arloing, Chauveau, Calmette and Guérin, Vallée, and others, on vaccination of calves have shown that it is possible to increase the resistance of these animals to experimental tuberculous infection or to natural contagions and although it is impossible to obtain this relative immunity by bacterial secretions, it ought to be obtained by the intervention of bacterial bodies, in other words, by the reactions of the organism against the germ.

What are these reactions? The study of this question is less advanced than that of the reactions between tuberculin and antituberculin although it has been established with certainty.

First, that the "preparatory" injections of tuberculous cultures, dead or alive, but not virulent, provoke in the organism the formation of an antibody which agglutinates and precipitates the germs *in vitro*.

Second, that the bacteria, dead or alive and avirulent, are more or less rapidly absorbed; that is to say, digested by the organism.

Third, that if this absorption is complete, acquired immunity is of short duration, less than one year.

Fourth, that if, on the other hand, digestion of living germs injected as a vaccine is not complete there are formed small latent infectious foci. Immunity against one injection or one virulent contagion lasts a long time as the bacteria in these foci live.

Fifth, and finally, an attack of tuberculosis spontaneously cured does not confer a longer immunity than a healed vaccination (Calmette, Vallée). Tuberculosis thus resembles syphilis in which the possibility of a spontaneous reinfection is considered as a proof of previous cure.

In considering the total of reactions provoked in the organism by the secretion of living tubercle bacilli and by the digestion of these bacilli which goes on under conditions which are as yet impossible for us to define in a wholly satisfactory way, we can represent the evolution of spontaneous tuberculous infection in the following manner:

The bacteria which penetrate into the organism by the digestive or respiratory tracts are taken into the circulation and may remain there for a longer or shorter time before being fixed in the different tissues, glands and organs. A certain proportion of these fixed bacteria, all the greater when the bacteria are less virulent (when they secrete less pure tuberculin), and *vice versa* are certainly digested and produce a precipitating antibody which we may call *antibacillin*. This function belongs properly to the bacteria fixed in the organs. Those which are fixed in the tissues secrete tuberculin and become the origin of infectious foci and of lesions, whose evolution has been analyzed above. The successive phases of the disease are thus determined first by the digestion of bacteria and the production of antibacillin, and second by the secretion of tuberculin and the production of antituberculin.

If the bacteria are less virulent the proportion of those which are digested and which produce antibacillin is greater than the proportion of those which are fixed in the tissues and which produce the formation of antituberculin in excess. On the contrary, when the bacteria are virulent it is the antituberculin reaction which predominates; infectious foci become more numerous and lesions more severe.

The experiments of Besredka, and of Manoukhine show with sufficient precision the evolution of the antituberculin reactions in the successive phases of tuberculosis in the guinea-pig. In these very sensitive animals antituberculin appears in the blood four days after the injection of the virus;

its quantity increases up to the fiftieth or eightieth day, falls and increases again at about the ninetieth day and disappears completely some few days before death. Thus the disease develops parallel to the production of antituberculin. The temporary disappearances of antituberculin from the blood are the consequence of the limitation of the bacterial secretions to the tissues which surround the infectious foci because of antituberculin in excess and as soon as this excess disappears from the circulation the same process begins again if not finally stopped by the death of the animal. The extreme susceptibility of the guinea-pig for tuberculosis probably arises from the almost absolute incapacity of this animal to digest Koch's bacillus and to produce antituberculin.

Such are the general principles which determine the evolution of pathogenicity of tuberculosis in so far as experiments and clinical observations permit us to formulate them. They may be summarized in a few lines:

1. Infection is followed by an incubation period during which the digestive attack of the bacterial secretions and of the bacteria themselves results in the production of antituberculin and antibacillin.

2. The period of disease begins at the moment when intracellular antituberculin in excess has fixed a sufficient quantity of tuberculin so that the compound of tuberculin with antituberculin which is fixed in the cell can become pathogenic (undigestible) for the cells themselves.

3. Antibacillin aids in the destruction of the bacteria which are multiplied in the organism.

4. The different phases of the evolution of the disease are determined on the one hand by the number and the stage of development of the tuberculous foci (that is to say by reactions successively immunizing and pathogenic between tuberculin and antituberculin): on the other hand by the reactions of the antituberculin with the bacteria. During this disease period pathologic impulses which follow one another at longer or shorter intervals and characterized by fever, lassitude, sweats, etc., are provoked by the local or general rupture of the antituberculin blockade. In case

of local rupture the tuberculin thus liberated provokes a congestive reaction in all the other foci; quite as an artificial injection of tuberculin.

5. Each of these impulses may be followed by a definite recovery, thanks to the intervention of antibacillin or by an aggravation of the disease caused by the bacteria thus liberated and not destroyed, which become centers for new foci and new lesions.

6. Immunity acquired by the healing of a spontaneous or artificial infection is of short duration, most probably because the production of antibacillin is rapidly stopped after the disappearance of bacteria.

7. We may consider it as proved that the presence of living avirulent bacteria in the organism confers on cattle a complete immunity against virulent reinfections.

TUBERCULOSIS MAY BE CHARACTERIZED in the following manner:

Disease of local infectious foci which may give rise to septicemic metastases.

Antigen soluble (tuberculin), non-pathogenic for normal tissues as it cannot be fixed by antibodies *en surcharge.*

Normal antibody intracellular can multiply in the cells in excess and remain fixed in the interior of cells "*en surcharge.*"

Intracellular antibody "en surcharge" (antituberculin) is pathogenic for the cells—hypersensitiveness non-specific.

Intracellular compound of normal antibody and antigen is non-pathogenic (digestible) and causes the multiplication of antibodies.

Intracellular compound of antibody en surcharge and of antigen is pathogenic (non-digestible) for the cells and causes the destruction of the cells.

Bacterial antigen (bacterial bodies cause the formation of a specific agglutinating antibody (*antibacillin*).

Antibacillary immunity not antitoxic immunity.

Intracellular anaphylaxis and not intravascular anaphylaxis.

From the total of the theories which we have just reviewed we are forced to conclude that in tuberculosis it may not only

be a question of an immunity from antituberculin but since it is shown that tuberculosis can heal spontaneously and that a certain relative immunity may be obtained by bacterial vaccination we should necessarily assume that a bacterial therapy and a specific chemotherapy should very appreciably aid the destruction of the bacteria. Serum therapy would be applicable only in the stages of the disease during which one could establish the absence in the organism of antibody in excess.

TYPHOID FEVER.

We know that completely digested albumins, that is to say, those which are transformed to their amino-acids are not antigens, while albumins themselves as well as all incompletely digested compound are antigens. We must suppose that in infections of intestinal origin bacteria as well as the products of bacteria can resist digestion and can penetrate into the cells and capillaries of the intestinal mucosa and that only the individual and the species unable to digest the bacteria and reduce them to amino-acids can be infected in this way. It is at present not possible to follow all the phases of the pathogenicity of typhoid fever in man, but it can be done in paratyphoid fever of young rodents and the pathogenicity can be represented as follows:

Bacteria enter by the mouth, are in large part destroyed in the stomach but the products of this destruction are not completely digested and pass with the surviving bacteria into the intestines where these latter can multiply until the bacterial products which resist intestinal digestion are in part absorbed by the cells of the mucosa.

This primary absorption determines the formation of more or less severe areas of congestion analogous to those which are observed when a small quantity of dead bacteria are introduced under the skin. This congestion favors in its turn the penetration into the mucosa and into the capillaries of fresh quantities of bacterial products and even of living bacteria. The result is that the severity of the congestion is increased.

The first bacteria which penetrate into the blood are engulfed by leukocytes and taken to the hemopoetic organs where they are more or less completely destroyed and where those which remain viable produce little foci of infection and lesions. During all this period typhoid antigens, bacterial secretions as well as products of bacteriolysis are found in excess of the *normal antibodies* which preëxist in the cells of every organism susceptible to the action of antigens. The areas of congestion are caused by the fixation "en surcharge" of antigens by normal antibodies. Thus, for example, when an injection of antigen is made into or under the skin, a mild local congestion is produced; but when it is given into a vein, there will be no appreciable reaction because here the antigen will be distributed to a much larger number of cells and will therefore never be in excess.

Under the continued action of new quantities of antigen which increase steadily until the spontaneous death or destruction of the bacteria, there are formed in the organism larger and larger quantities of antibodies. The excess of these is at first stored "en surcharge" in the cells in which it is formed; but after a certain maximum is reached, this excess is finally thrown off into the blood by a series of sudden discharges.

At a certain given moment the antibody thus appears in excess in the blood in spite of the continued multiplication of bacteria and we must necessarily conclude that the production of antibody is more rapid than that of antigen. The moment at which we begin to find antibody in excess in the blood coincides generally with the appearance of the first severe symptoms which characterize the disease. This is the end of the period of incubation and the beginning of the period of disease.

If then one could describe the condition in which the infected organism is found from the point of view of immunity and anaphylaxis or if we could stop the evolution of the infection at the end of the incubation period or at the moment of the appearance of antibodies in excess we would find that the organism had developed a greater resistance to a new infection, in other words, that it had acquired a certain degree of active anti-infectious immunity, and also that it had become susceptible to active anaphylaxis.

The theories of this condition cannot be demonstrated by experiment but the result would be the same if in place of an infection by living bacteria the organism had received an injection or a series of injections of dead bacteria. At the moment of the appearance of antibodies in excess it would be immunized against the dose of living bacteria pathogenic for controls and would be hypersusceptible (anaphylactic) to a non-pathogenic dose of dead bacteria and finally hypersusceptible to a dose of living bacteria greater than its degree of anti-infectious immunity.

Whether the bacteria be living or dead at the end of the incubation period, the organism will be exactly in the same condition from the point of view of immunity and anaphylaxis. If the results are different it is because living bacteria continue to multiply, but if the injections of dead bacteria in considerable doses were continued after the time when the organism became surcharged by an excess of antibodies the picture of spontaneous infectious disease would be very probably and almost certainly duplicated. In fact practical antityphoid vaccination has shown that the subjects more or less immunized by a previous healed typhoid infection are infinitely more sensitive to the vaccine than normal subjects and in the cases of alimentary poisoning caused by paratyphoid swallowed in modified doses the crises are all the more severe if the subjects are already strongly immunized.[1]

But then one may ask why does a spontaneous infection not stop at the end of the incubation period since the patient is at this moment more immunized than at the start of the infection? This very thing happens much more often than has been supposed at the present time not only in typhoid but in every other infectious disease. In certain cases the few mild symptoms permit the recognition of a disease which aborts, but the great majority of these cases escape observation and acquired immunity can be revealed only by a study of the serum, by vaccine reaction or by the opsonic index.

[1] A dozen persons, at least one of whom was immunized normally against paratyphoid, swallowed by accident a heavy dose of paratyphoid bacilli in milk. All of them were more or less indisposed, but only the immunized individual was severely ill.

The explanation of these facts appears very simple. The continued development of the disease after the end of the incubation period or the abortment necessarily depends upon the degree of acquired immunity or on the quantity of formed antibody and on the quantity of bacteria which exist at this moment in the organism because immunity is only relative and the protection is only against a certain minimum dose of bacteria. Thus the relation between these two quantities which tip the balance to one side or the other, individual differences between the degrees of natural or acquired immunity at the moment of infection and finally differences of quantity or virulence of the infecting bacteria may be very variable.

In the explanation of the results of these reactions it is necessary to note: on the one hand, the fact, proved by experiment, that the quantity of antibody formed at a given moment as well as the rapidity with which it is formed is, within certain limits, inversely proportional to the quantity or the virulence of the injecting antigen; and, on the other hand that the final result of all these reactions may depend not only upon the direct action of the antigen upon the antibody or the cell which contains it but on the disturbance which the lesion or the "complication" once produced will cause in the function of the organism. If this is true, how can we represent the causes and the origin of each pathologic manifestation which characterizes the septicemic infectious diseases, typhoid fever in particular?

We know that, for the diseases caused by toxins (diphtheria), cure begins with the appearance of antibodies in excess while in the case of typhoid it is the disease which begins precisely at this moment. We then affirm that the incubation period of typhoid coincides with the disease period of diphtheria or, to be more exact, that in diphtheria there is simultaneously incubation, from the point of view of production of antibodies, and disease with its pathologic manifestations. And if this is true, we may assume by correlating what precedes that in diphtheria pathologic manifestations result from the direct action of the antigen-toxin on the normal intracellular antibody and that the compounds of

this antigen with antibody in excess do not produce an active anaphylactic state. In typhoid, however, we may suppose that the bacterial antigen secretion is not pathogenic for normal tissue or else that this secretion is not the whole antigen and that the pathologic symptoms which are manifested at the moment of appearance of antibodies in excess can be only the result of the combination of these antibodies with *antigens* produced by bacteriolysis. Thus the syndrome of the period of disease in typhoid in exclusively anaphylactic. From the point of view of pathogenicity we may thus review the two cases by the following formulæ:

Diphtheria: Toxin + Normal antibody = Disease.
Toxin + Antibody in excess = Immunity and cure
Typhoid: Toxin(?) + Normal antibody = O ?
Products of bacteriolysis + Normal antibody = Incubation.
Products of bacteriolysis + Antibody in excess = Immunity and anaphylaxis.

Thus we have seen that in typhoid there is no toxin-secretion nor bacterial-antigen analogous to that of diphtheria or if there is one, it is neutralized at the end of the incubation period by the appearance of antibody in excess (as in diphtheria) and can no longer produce any apparent disturbance. If at this moment it becomes pathogenic it will produce only anaphylactic disturbances. But in typhoid there is certainly penetration and multiplication of bacteria, or at least of products of bacteriolysis in the form of albumin and it is absolutely certain that there are albumins which cause disturbances characteristic of the period of disease as in the case of every other heterologous albumin when combined with its antibodies in excess.

Thus we may conclude with certainty that in typhoid the disease consists of an anaphylactic crisis which is chronic or, in other words, of a succession of anaphylactic crises which are determined at each moment by the three following factors:

1. The appearance of the albumin antigen as a result of the multiplication of bacteria.
2. The quantity of antibodies in excess formed by the organism.

3. The influence of the lesions in the different tissues and organs on the general state of the organism.

Most if not all septicemic infectious diseases belong necessarily in the same class. A septicemic bacteria can be pathogenic only in case its albumin is antigenic for the organism; in which case there will always be anaphylaxis.

It is possible that in certain cases the action of albumins may be completed by that of toxic secretions but the study of these secretions in the pure state, that is to say, completely separated from the products of bacteriolysis is still too incomplete to enable us to know whether or not they may be toxic and may produce antibodies. At all events, and we cannot repeat it too often, this question can have only a secondary importance in the pathogenicity of disturbances observed during the disease period because as these appear simultaneously with the appearance of antibodies in excess, they must be of an anaphylactic nature. And it is of little importance whether these products originate exclusively from albumins or from exotoxins.

Spontaneous Cure.—Immunity and anaphylaxis are phenomena of a general nature which may be applied to all living beings, vegetable or animal, uni- or pluricellular; to bacteria as well as to man. A bacterium which has penetrated into the interior of a higher organism must adapt itself to this interior. The organism will produce an intracellular antibody and will be surcharged with it and this surcharge will increase the degree of its immunity but at the same time it will also increase the degree of its anaphylaxis. The antibody of the infected organism will become antigenic for the bacteria in exactly the same way and will produce on the bacteria the same effects as the bacterial antibody produces on the organism.

It is this balance between the degrees of immunity and anaphylaxis of the infecting bacteria on the one hand and the infected organism on the other, that determines the issue in the struggle between the two opponents. A bacterium surcharged with its antibody, will fix a quantity of antibody of the organism (which is antigenic for itself) all the greater if its degree of immunity-anaphylaxis is higher. It will be

"sensitized" and when this surcharge exceeds certain limits it will burst by autolysis or will become the easy prey of leukocytes according to the phenomenon of positive chemotaxis (Ch. Bordet and Massart). In this way, the source of the infecting antigen will be exhausted. How can we intervene successfully in order to throw the balance toward the recovery of the organism?

Therapy.—To judge by the results of experiments and clinical observations we are obliged to assume that the presence of a great excess of antibodies on the exterior of a cell hinders hydrolysis of the antigen fixed to the interior of this cell; in other words, if an infecting bacteria has produced an excess of its intracellular antibody (which is antigenic for the organism) and if it has fixed to this antibody a corresponding quantity of antigen (which is the antibody produced by the organism) it will not suffer until there is antigen in excess on its exterior (antibody of the organism in the plasma). Bactericidal anaphylactic shock is produced only when there is an excess of antibody in the exterior.

Numerous studies have shown that when one injects a typhoid patient with a certain quantity of dead bacteria the content of antigen is increased and, by the same amount, the quantity of antibody contained in the blood is diminished. At the same time a diminution or even a complete disappearance of bacteria and a rapid amelioration of all pathologic manifestations is found. This result is obtained very often, but there are also failures, relapses and sometimes complications and this is not surprising because to obtain a result which is constant and proved beforehand it would be necessary to know the exact quantity of antigen to inject in each special case in order to produce an anaphylactic crisis fatal to the bacteria. Thus the antibody of the organism may act on the bacteria as an anaphylactic or anaphylatoxic antigen and in order to provoke an anaphylactic crisis fatal for the bacteria, certain optima proportions between the quantity of antibody and fixed antigen held by the bacteria and the excess of this antigen in the plasma, its external medium, are necessary. But these optima proportions may vary widely in different cases and as there is no theory to explain

the therapeutic action of antigens, we can establish only an empirical means which may not always be the best.

In laboratories it would not be difficult to estimate the excess of antibody in the blood of the organism, as well as the degree of immunity anaphylaxis of the bacteria and by always using the same antigen in exact titer one would obtain essentially comparable results. In the practical medical clinic all complications would very probably be avoided by injecting the antigen in progressively increasing doses at intervals of some minutes. The injections of dead bacteria ought to be given intravenously and if the total dose was, for example, 500 millions, one might begin by injecting 1, or 2, then in ten minutes 10 and finally 40 and 450 millions at intervals of five minutes. Two successive injections, 1 of 5, the other of 500 millions at ten-minute intervals might be perhaps sufficient. If the principle of skepto- or tachyphylaxis is good, the technic would be easy to work out.

Preventive Vaccination.—The effects of preventive vaccination on the morbidity of typhoid are today indisputable; what is not indisputable is the method of preparation of vaccine and the technic of vaccination. The heated bacterial bodies of Chantemesse and Widal; the more or less autolized bacteria of Vincent; the lipovaccines of LeMoignic and Pinoy may confer the same degree of immunity on the organism but never lasting very long.

It would be perhaps more interesting to try to make the human organism refractory to typhoid fever as all other mammals are refractory to typhoid and for that it would suffice to teach it to completely digest typhoid and paratyphoid bacteria as it, for example, digests plague bacilli. Bacteriotherapy by mouth practiced successfully by Dr. L. Fournier at the Cochin Hospital for more than three years, proves indisputably that the products of bacteriolysis of Eberth's bacillus are absorbed by the intestinal mucosa as antigens and it is very possible to assume that one would be able to stimulate complete gastro-intestinal digestion of bacteria by a suitable means by causing children to ingest more or less autolyzed bacterial bodies in progressively increasing doses. By proceeding in this way, one would

perhaps anticipate a two-fold result, a certain degree of immunity for an infection by inoculation and a refractory state for an infection by ingestion.

PARATYPHOID FEVERS.

The evolution of these diseases is as a rule very analogous to that of typhoid fever. So that it is sufficient to repeat in a few words the differences sometimes observed in those diseases caused by paratyphoid which are commonly called "ptomaine poisoning." In these cases the ingestion of infected food is followed very rapidly in a few hours by a violent crisis which simulates an acute attack of cholera. When all the elements are analyzed it is found that the evolution of these crises is only a repetition of the typical evolution of a normal typhoid infection. There is no incubation period; the disease begins full blown. The differences in the progress of the evolution of infection will be determined in the two cases:

1. By the difference of the ingested infecting dose.
2. By the degree of the permeability of the intestinal mucosa at the moment of infection, and
3. Especially by the preëxistence of a certain quantity of antibodies in the blood.

Bacteria ingested in massive doses are in part destroyed and in part digested. The colloidal products of this digestion pass rapidly into the intestinal mucosa and into the blood causing congestion and facilitating the passage of living bacteria. Bacteria in the blood are rapidly "sensitized" by antibodies in excess and autolized and the crisis may be terminated by death or recovery in a few hours or few days at most. Repeated intravenous injection of specific antigens or heterologous antigens should be the most appropriate treatment in these cases.

CHOLERA.

The same point of view of the pathogenicity of the evolution of intestinal infectious infections which we have just

discussed in typhoid is equally applicable to cholera. The cholera vibrio is very proteolytic. It will destroy itself in its own culture. It is unable to penetrate alive into the blood and the products of its bacteriolysis find in the blood precipitating antibodies already preformed in combination with which they produce all the known disturbances. They act like the arsenobenzenes which have been insufficiently alkalinized. In the case of fulminating cholera, the crisis is caused by the rapid passage into the blood of a great quantity of products of bacteriolysis and in fact here we find none or very few living bacteria in the intestines (at autopsy).

It is impossible to know today whether the subjects overwhelmed in this way have been more or less immunized by spontaneous immunizing infections but it is very probable that if they had been immunized, we should find that the reaction would be here exclusively intravascular.

When the crisis lasts for several hours it begins with intravascular reactions which cause disturbances of the circulation: embolism, dilatation of capillaries, congestion of mucous membranes and, in consequence, gastro-intestinal disturbances and fall in temperature: sometimes dyspnea, convulsions, and syncope which may result fatally. When the crisis is prolonged, there are very probably intracellular reactions which are expressed by fever and may in turn lead to death. But in the latter case, the pathologic state may result, not from the direct action of the cholera antigen but from lesions more or less severe and numerous or from complications produced by the reactions.

To sum up: the total of our knowledge concerning the pathogenicity and evolution of gastro-intestinal infections produced by the bacteria of the typhoid-colon and cholera group permits us to conclude:

1. Only the animal species or individuals which are incapable of completely digesting, that is to say, of transforming into non-specific amino-acids the albumins of certain bacteria can be spontaneously infected by those bacteria.

2. The severity of the disease is determined on the one hand by the dose of bacteria injected as well as by the intensity and rapidity of bacteriolysis; on the other hand, by the

quantity of normal antibodies or those which preëxist in excess; in other words, by the degree of immunity, natural or acquired.

3. By taking into consideration:

(*a*) The frequency of these different bacteria in nature and consequently the frequency of infections and of possible spontaneous vaccinations:

(*b*) The gastro-intestinal digestibility of bacterial bodies and of the products of their cleavage.

(*c*) The permeability of the intestinal mucosa for these products.

(*d*) Finally the digestibility of these products which have passed as antigens into the interior of the organism; we may classify these organisms in the following way:

1. *The bacilli of Eberth* are the least frequent, giving the poorest growths in all the known culture media. The products of their proteolysis are most difficult to digest in the digestive apparatus of man. The products of bacteriolysis always begin by penetrating in small quantity (immunizing quantity) into the blood where they stay during a relatively long incubation period. The compounds of the antigen which have penetrated into the blood with their antibodies are digestible with difficulty in the interior of the organism; on account of which lesions are severe and the period of disease is relatively long.

2. *Paratyphoid bacilli* are more frequent, giving more rapidly most potent cultures, are perhaps more proteolytic and more difficult of digestion for certain animals (hog cholera, typhoid of mice, psittacosis) and spontaneous vaccination is more frequent. The products of bacteriolysis may penetrate from the intestines into the blood in massive doses and cause rapid crises of considerable violence but of short duration, since the subject contains a larger quantity of antibody in his blood and in his tissues, or, in other words, is more strongly immunized. The compounds of antigen with antibody are more easily digested and in consequence less pathogenic than those of typhoid.

3. *Colon bacilli* are the most widely distributed of this group of organisms and the easiest to cultivate. The prod-

ucts of their bacteriolysis are very probably completely digested in the digestive apparatus and do not penetrate into the blood as antigens and are only very exceptionally pathogenic when taken by mouth.

4. *Cholera vibrio* are very widespread in nature, and very often provoke apparently spontaneous vaccinations, they are very proteolytic and the products of bacteriolysis are not completely digested in the human gastro-intestinal tract. These products penetrate into the blood as antigens and provoke (as in the alimentary intoxications caused by paratyphoid) various circulatory disturbances more or less severe according to the quantity of antigen absorbed and the quantity of preëxisting antibody. The living germ does not penetrate into the blood.

We may conclude that for every disease of intestinal source, the most convenient and efficacious *method of vaccination* would be the prolonged ingestion of dead bacteria, while the most efficacious *method of treatment* would be specific bacterial therapy by fractionated intravenous injections.

CHAPTER IV.

MECHANISM OF INFECTION.

Infection or Contagion—Virulence—Immunity—Refractory State.

We may deduce from what has preceded that, if vaccinations, either spontaneous or artificial, can increase the resistance of the organism against spontaneous infection by increasing within certain limits the parenteral digestive power and probably also the digestive power of the intestines: for the cells of the mucosa and of the intestinal glands may quite as well as those of other tissues and organs participate in the production of antibodies and distribute them partly into the circulation and partly into the intestinal contents; they (vaccinations) may at the same time increase the susceptiblity of the organism to the reaction of albumins and thus put the organism into a state which we may rightly call "anaphylactic."

If then, as seems probable, bacteria of the colon-typhoid group as well as cholera vibrios do not secrete a toxin-antigen of a crystalloid poison, diseases caused by these bacteria are nothing else than anaphylactic crises, whose violence and duration is determined by the total of conditions which we have analyzed above.

In typhoid fever these crises may last for several weeks and there is not one single crisis but a series of successive crises. Paratyphoid may develop in the same way as typhoid or much more quickly (in one or a few days) according to the state of sensitiveness of the subject and the dose of bacteria injected and the differences of development depend principally upon differences in the rapidity with which bacteria multiply. Cholera develops always very rapidly, because the bacteria rapidly yield very abundant cultures and also because bacteriolysis takes place rapidly. Colon

bacilli only rarely become pathogenic, because the digestion of the bacterial body and the products of bacteriolysis ought to be complete in the intestine.

A true and lasting immunity would consist in rendering the organism refractory to anaphylactic hypersusceptibility; that is to say, to render the organism capable of completely digesting bacteria or products of bacteriolysis in the stomach and intestines so as to hinder these products from penetrating in the form of specific colloids into the blood as well as into the cells of the mucosa and of the intestinal glands.

Some experiments on mouse typhoid permit the hope that this will be not impossible of accomplishment. One may demonstrate that if some or rather some dozens of bacteria are necessary to infect an animal by subcutaneous injection, several thousand times as many are necessary to infect an animal by the ingestion of a pure culture and several millions if this pure culture is mixed with another substance of whatever nature.

If then, after having determined the minimum lethal dose by ingestion of a pure culture, the animal is treated during and after by hypodermic injections of sodium cacodylate or calcium glycerophosphate in convenient doses, it is found that the animal thus treated resists doses which are very fatal for controls. It is also found that animals treated in this way are not vaccinated and have no specific antibodies in their blood which proves that the bacteria or their antigens have not been able to penetrate into the interior and that they have been very probably digested in the stomach and intestines, or perhaps evacuated without having been attacked by digestion.

From another aspect it is possible to determine by a series of tests that the same paratyphoid pathogenic for mice and completely harmless in the beginning for *Mus Decumanus* and *Mus Rattus* can little by little become more and more pathogenic for these species by ingestion as a result of a series of alternate passages: (1) *In vitro* in a broth culture prepared with the flesh of the animals of this species; and (2) in collodion sacs inclosed for twenty-four hours in the peritoneal cavity of these animals. Cul-

tures are finally obtained, of which a small dose will kill by ingestion field and white mice in four to six days and rats in six to twelve days.

These cultures have been preserved in sealed ampoules for one to ten years and tested as to their virulence once to twice a year. They have always preserved their virulence and have even become a little more pathogenic for mice, but at the same time they lose their virulence for rats, so that after ten years they have become completely avirulent for these animals. By passing a culture, virulent for the two species, through ordinary broth, the virulence for the rats remains constant for one or two years, but finally diminishes and almost disappears at the end of a longer or shorter time. Thus we conclude:

1. That the bacterial substance virulent for mice is different from that which is virulent for rats.

2. That the bacteria can produce, augment and lose this specific pathogenicity substance.

3. That this property is progressively acquired by being nourished with the "substance rat" and that it is lost when not nourished in this way.

By analyzing these facts we are obliged to assume that in order to nourish itself with the "substance rat," the bacteria has been obliged to learn to fix this substance by a special chemical affinity, and the fact that the bacteria can multiply this fixation substance, even when transplanted into a non-specific nutritive medium, obliges us to assume that the fixation is intracellular.

Thus, in the last analysis, the substance of the bacteria acquires a specific affinity for the "substance rat" and it is, thanks to this acquired affinity, that the bacteria, or more exactly, its own specific substance, can fix and digest the "substance rat" and render it assimilable.

But it is evident that affinities ought to be always reciprocal and that in consequence the fixing substance of the bacteria, freed by bacteriolysis, can fix itself by the same affinity and produce reactions of the same nature in an extra- or intracellular substance of the rat when it finds itself in the organism of this animal.

The "substance rat" may thus be considered like an antigen for paratyphoid and this antigen provokes the formation of an antibody exactly in the same way, and by the same mechanism, as the fixing substance of the bacteria becomes antigenic for the rat and produces in the organism of the rat the formation of a specific antibody.

We may assume that bacteria become pathogenic for an animal species exactly in the same way as the organism of these species becomes in its turn pathogenic for the bacteria. The procedure which we have employed for rendering paratyphoid, which is primarily pathogenic only for field mice, virulent for rats does not apply only to this particular case.

Dujardin and Beaumetz have rendered virulent, for sheep and goats, a culture of pleuropneumonia which had been considered as pathogenic exclusively for cattle, by cultivating the bacteria of this disease in incompletely digested mutton broth, and we know from Pasteur that anthrax may become avirulent and may re-acquire its lost virulence by passages through more sensitive animals. We know that the bacillus of tuberculosis may lose its virulence after a long series of passages in exclusively crystalloid media, and that the tubercle germ of cold-blooded animals is entirely harmless for the guinea-pig, but may become pathogenic for this animal by appropriate cultures and passages.

The processes may vary for each particular case in their details, but the principle ought to be a general one and should apply to all living beings. The indispensable condition under which bacteria can become pathogenic and under which an organism can produce a specific antibody consists in penetration into the interior of the bacteria or into the interior of the organism of a substance in colloidal state, that is to say, incompletely digested, whose digestion can be completed by the cell. Thus, bacteria which are completely transformed into amino-acids by gastro-intestinal digestion cannot become pathogenic, nor can bacteria nourished exclusively by the amino-acids split off from animal albumins become pathogenic for this animal.

The study of bacteriolysis in anthrax as well as the study

of the evolution of anthrax in the white rat has given us the most interesting side lights on the nature of the reciprocal relations between bacteria and organism. We know by the studies of Savtchenko that anthrax bacilli are very rapidly destroyed in rat sera. However, by starting the first cultures in a mixture of a very small quantity of serum with a large quantity of ordinary bouillon, and by continuing passages through mixtures containing relatively larger and larger quantities of serum, we finally obtain a fairly abundant culture in pure-rat serum; that is, we obtain a race of bacteria which resists the destructive action of this serum. If we again transplant this race into ordinary bouillon and if we make several transplants in it, we find that even in spite of the change in media, that the properties of serum resistance are obtained.

If one of these twenty-four-hour cultures is filtered through a porcelain bougie so as to completely remove the bacteria and if a small amount of the filtrate is added to rat serum, and this mixture is added to broth which is then inoculated with a non-serum-resistant strain, a growth will be obtained quite as abundant as in ordinary broth. Anthrax bacilli can thus acquire the ability little by little to fix and digest rat serum by increasing the quantity of a "fixing substance." The ability to produce this substance is retained even when there is no longer any rat serum to stimulate it. The excess given off to the exterior and when added to rat serum, can neutralize *in vitro* the bactericidal properties of the serum, and again render it all the more assimilable for a non-serum-resistant race. Finally a filtered broth culture originating from a non-serum-resistant culture mixed in equal proportions with rat serum will hinder the bactericidal action of the latter, but in a much less degree.

Anthrax bacilli can produce then a specific antibody under different conditions, but by the same process as paratyphoid as studied above. Moreover, contrary to supposition, a culture of anthrax avirulent for rats does not become virulent when rendered serum-resistant; so that we must conclude that it is not by acquiring an affinity for any animal substance that a bacterium can become pathogenic for the animal, and that it is not by virtue of its

combination with this substance or with all the bactericidal substances in rat serum that bacteria become pathogenic for these animals.

What proves this is that, in spite of the bactericidal property of their serum, rats do not generally resist a virulent inoculation of anthrax. Another peculiarity, all the more important from this point of view is that when a rat has resisted a primary inoculation it becomes more sensitive to a second inoculation of the same virus. It happens sometimes that an animal can resist three or four successive injections and succumbs only to the fifth. There is here a collection of facts which could not be correlated and which puzzled bacteriologists of the period of 1889–1890. It was not known by what mechanism bacteria might become pathogenic for an animal. Today this mechanism can be explained in the following way:

Rats in general, especially white rats, resist virulent inoculations of anthrax better than all the other test animals and they owe this relative resistance to the more or less marked bactericidal properties of their plasma. If the dose is not too large the bacteria are destroyed by bacteriolysis and by phagocytes before being able to develop into a more resistant race and the rat recovers. But although the living bacteria may disappear in this way products of bacteriolysis remain in the organism. The products provoke the formation of specific antibodies which are not bacteriolytic, but which neutralize a certain quantity of the normal bacteriolytic substance of the organism. The same phenomenon is seen *in vitro* when the same tube of serum is mixed several times. The second or third mixing will give a culture.

Something happens here very analogous to what we have seen in the first stage of typhoid infection when bacterial products are incompletely digested in the stomach and intestines, and have penetrated into the blood and into the cells of the intestinal mucosa, and by the formation of an antibody, have rendered the organism more sensitive to bacterial invasion. The bacteria of the second injection will thus resist better and longer the bactericidal properties of the organism; their more rapid multiplication will suc-

cessfully resist destruction and each successive generation will be more resistant to bacteriolysis. At the same time the compounds of the bacterial products with antibodies will cause the formation of more and more severe lesions. Infections, at first local, may become generalized and the animal may die.

The numerous experiments of Loeffler, Behring, Metchnikoff and others on anthrax in rats do not give us a sufficiently accurate explanation of all the conditions of the evolution of this disease in animals, because all their experiments were in reply to other questions which need not occupy us here. But such as they are, they permit us to conclude that hypersensitization of the white rat to anthrax, by one or several inoculations which may be considered as vaccinations, is not in contradiction to the principle of vaccination which makes no exception for anthrax in animals nor for any other known septicemic infection.

Relapses in typhoid, auto-reinfections in tuberculosis and syphilis, reinfections in cyclic diseases (malaria, trypanosomiasis) and all the chronic infections in which attacks alternate with more or less prolonged remissions (gonorrhea, influenza) are all phenomena of the same category. They all presuppose a certain reciprocal adaptation or a symbiosis of the parasites and the organism: The difference in the observed results, that is to say, the increase or diminution of resistance or of sensitization of the parasite or the organism, the final destruction of one or the other are determined only by secondary factors, notably: By the degree of reciprocal adaptation of the parasite and the organism at the moment of infection; by the infecting dose; by the general condition of the organism before the infection and the severity of the lesions which are produced during the period of disease or during the attacks. The mechanism of these reactions will be under all circumstances the same.

Résumé and Conclusions.

1. *A pathologic state* can be caused only by:

(*a*) The penetration into the interior of the organism of bacteria or of bacterial products in a colloidal state.

(*b*) The existence in the organism of chemical affinities for these bacterial products.

2. *Infection or contagion* is brought about by the penetration of bacteria or colloidal bacterial products across the mucous membranes of the digestive or respiratory apparatus or by means of intra- or hypodermic inoculations.

3. *Incubation in infection* is the time necessary for a bacterium with the products of its secretion or bacteriolysis to adapt itself to its medium and to cause in the organism the formation of specific antibodies in excess.

4. *The preëxistence of antibodies* in certain organisms for certain bacteria can be explained:

(*a*) By heredity, and

(*b*) By individual spontaneous vaccinations.

5. *The formation of normal antibodies*, or in other words, specific affinities, when they do not preëxist, can be explained by the infection itself, or, in other words, by the penetration into the interior of the organism of colloidal bacterial products in immunizing doses during the incubation period. In this case the bacterium itself will create the affinity.

6. Every bacterium which can adapt itself to an animal medium, that is to say, which can digest and assimilate certain animal substances in the colloidal state, can become pathogenic for that animal.

7. The state of resistance on ingestion to bacteria when ingested is due to the complete digestibility of all bacteria and all their products by gastro-intestinal digestion.

The state of resistance on inoculation results from the absolute inability of the bacteria to be nourished in the animal medium.

8. Active immunity is a state of resistance of the organism to a certain dose of infecting bacteria which is rapidly and easily digestible. It will be complicated by an anaphylactic hypersensitiveness whenever the compound of antigen with antibody in excess is insoluble, and therefore, more or less difficult to digest. There will be no hypersensitiveness when this compound is soluble and neutral.

CHAPTER V.

IMMUNITY AND ANAPHYLAXIS.

If we analyze the total of studies accumulated to the present time on immunity and anaphylaxis we may isolate a certain number of facts which we will review as briefly as possible with the interpretations which have been given them. But first let us see if it is possible to separate from the total facts a general idea which will explain the nature and the mechanism of the reactions which determine the different phases of evolution of the infectious diseases and of the various pathologic states no matter whether these states are caused by animal or vegetable albumins considered as normally toxic, such as venins, the serum of eels and turtles, ricin, abrin, etc.; by synthetic colloids such as the arsenobenzenes; or, finally, by albumins considered as exclusively nutritious when they penetrate into the internal substance of the organism by the intestines after complete digestion, but which provoke anaphylactic states when made to penetrate into this interior by subcutaneous, intravenous or even intrarectal injections.

We have not failed to notice how difficult it is to define the limits between the different groups of substances just enumerated. Thus, a certain number of toxic albumins or of pathogenic bacteria may be absorbed by mouth without causing symptoms, others remain pathogenic after having undergone gastric and intestinal digestion. All possess a certain number of characteristics in common and the value of these characteristics for any classification whatever will always furnish material for endless discussions. It is necessary to note that the distinctions indicated above and now made again have no absolute value and that they are made only provisionally for the clarity of the discussion which follows.

We have then the following facts:

1. *The toxins of tetanus and diphtheria* may be injected into sensitive animals in non-toxic or toxic doses and then:

(*a*) Each injection of a non-toxic or slightly pathogenic dose protects the injected animal after a certain incubation period against a larger dose: *active immunity.*

(*b*) The serum of the animal thus actively immunized will neutralize the pathogenic action of the toxin *in vitro,* and if injected prophylactically into a new animal will protect this animal against a pathogenic dose: *passive immunity.*

(*c*) The injection of toxic mixtures of toxins with their antitoxins as well as the preventive injections of "anti" sera from animals of the same species never causes anaphylactic disturbances.

Thus for tetanus and diphtheria toxins there is active and passive immunity; but there is never anaphylaxis, either active or passive.

2. *Living pathogenic bacteria* may be easily injected in non-pathogenic doses, but in the technic of vaccinations it is convenient to employ either living cultures with attenuated virulence, or bacterial bodies killed by heat or other procedures or filtered broth cultures without bacteria. The injection of all these products in non-pathogenic doses provokes in part reactions of the same nature as in the preceding section, that is to say:

(*a*) An active anti-infectious immunity in the treated animal.

(*b*) The serum of the treated animal can confer a *passive* immunity on a normal animal but at the same time this same treatment has caused

(*c*) A state of *active anaphylaxis* in the treated animal and the serum of this animal has become able to transfer passively anaphylaxis to a new animal.

Thus, for all living or dead pathogenic bacteria as well as for their filtered broth cultures there is at one and the same time active and passive anti-infectious immunity and active and passive anaphylaxis.

3. *Pathogenic albumins* behave, from the point of view of their immunizing or anaphylactic reactions, exactly the

same way as pathogenic bacteria and it is natural that it should be so, because bacteria can act only through their soluble products of secretion or through bacteriolysis. There is at once antitoxic immunity and anaphylactic sensitization, active and passive.

4. For *exclusively nutritive* albumins there can be no active and passive immunity, but there is active and passive anaphylaxis.

All these substances have a common property. Injections of them into a normal animal in non- or slightly pathogenic doses always causes a reaction of the same nature: the formation of an antibody which is specific without being always exclusively specific. They are all grouped under the name of *antigens*. The substances which are formed in the organism by these antigens and which possess a special, if not always exclusive, affinity for the corresponding antigens are called *antibodies*.

In attempting to define the physicochemical properties of antigens, it is recognized that they are always albumins or colloids; as to antibodies it is not possible to isolate them from the albumins of the serum in which they are found. They should be considered as colloids or at least having an action like colloidal action.

All albumins are not "antigens." This property belongs only to albumins called heterologous while homologous albumins—that is, belonging to the individual of the same species—do not produce the formation of antibodies, and therefore do not produce anaphylaxis. The reaction which causes the formation of antibodies and which confers immunity alone, or both immunity and anaphylaxis, or finally anaphylaxis alone, is not determined solely by the physicochemical nature of antigens since homologous albumins are, from this point of view, identical with heterologous albumins. This reaction depends upon the state of the treated organism with reference to the injected antigen.

For example, an organism strongly (actively) immunized against tetanus or diphtheria toxin will react in the same way to a second dose of one of these toxins as a normal organism would react to a homologous albumin. In other

words, the transformation by which toxins and albumins after injection become either assimilated or eliminated is accomplished by a reaction of the same nature.

It is hardly probable that an albumin, even homologous, when injected into the blood or under the skin can be assimilated without undergoing some sort of transformation and the mild anaphylactic disturbances which are seen after the transfusion of 100 c.c. or 200 c.c. of whole blood: chills, excitement, dyspnea, peripheral pallor seem to show that in this case there is no assimilation without previous transformation. In every normal organism there is an antibody in excess for homologous albumins and this antibody reacts with these albumins in a way quite analogous to the reaction of toxin with antitoxin.

We will return later to this question which we can only indicate here. For the moment it is important to recall from what has preceded, that if the *nature* of the reactions caused by antigens seems to be determined by the physicochemical properties of the colloidal state of these substances, the *effects* of these reactions on the organism will depend principally, if not exclusively, on the nature, the biologic properties and the quantity of antibodies, normal or in excess.

From the *biologic* point of view, we may divide the reactions between antigen and antibodies into two great groups:

1. Those which produce immunity alone—diphtheria, tetanus toxins, perhaps botulism and homologous albumins.

2. Those which produce immunity and anaphylaxis or only anaphylaxis—all the other antigens, bacteria and heterologous albumins.

From the *physicochemical* point of view it may be said that:

1. Antigens which are exclusively immunizing form with their antibodies *soluble* compounds.

2. Those which are immunizing and anaphylactic or exclusively anaphylactic form with their antibodies *insoluble* compounds.

In the first instance the antibodies in excess dissolve the colloidal antigens; in the second, they precipitate and this difference in the nature of the resulting compounds is of the

greatest importance from the biologic point of view as well as from the point of view of evolution of pathologic states.

When antibodies form with their antigens *soluble* compounds, the appearance of antibodies in excess coincides with the cure. But in all the other cases when insoluble compounds are formed, the appearance of antibodies in excess always coincides with the beginning of the disease period or, in other words, with the first appreciable pathologic symptoms.

Up to the present we have had no idea of considering these reactions together and in detail. There is, to be sure, a theory (Ehrlich) to explain the origin of the pathologic state or the recovery in diseases caused by the true toxins (diphtheria and tetanus). It was assumed generally that in the other infectious diseases the different aspects of the pathologic state were caused by the combination of different bacteria and by exo- and endotoxins produced in the organism by these bacteria without attempting to explain the mechanism of the reactions. After Ch. Richet, several theories were formulated to explain the nature and the mechanism of anaphylactic reactions but without attempting to explain the exact nature of the origin of these reactions.

And although clinicians have, at one time or another, called attention to "anaphylactic syndromes" in some infectious diseases (Ivanoff in malaria) or to "anaphylactic crises," following the injection of certain drugs (iodine, antipyrin, arsenobenzene), the true students of anaphylaxis could see only superficial or accidental analogies because these anaphylactic crises were not produced under the same conditions as in their experiments.

But we have seen that immunizing or anaphylactic reactions with production of antibodies can be provoked only by colloids and that crystalloids never cause analogous reactions, because an antigenic albumin loses its antigenic properties at the time when it ceases to be a colloid, that is to say, when it is transformed into free amino-acids. The nature of all these reactions ought thus to be sought in the colloidal state of antigens and it is only by attempting to analyze the physicochemical properties of colloids as

well as the transformations which these substances undergo in the interior of the organism that it will be possible to discover why the organism is obliged to produce antibodies in excess, what the rôle of these antibodies is and what the nature of the reaction between antibodies and antigens.

These reactions can be reduced to three different types which we have treated in detail in the preceding chapter: The evolution of diphtheria, of tuberculosis and of typhoid fever. These types differ among themselves according to the primary and secondary action of the antigen on the organism and to the action of the antibody in excess on the antigen.

These differences can be reviewed in a few words: In diphtheria the antigen acts directly on the tissues and the antibody in excess neutralizes the antigen without precipitating it. The appearance of the antigen in excess coincides with recovery. There is no anaphylaxis.

In tuberculosis and in typhoid the antigen is not directly toxic. In these cases the antigen is not an exotoxin as in diphtheria, but is the albumin of the bacterial body whose pathogenic action on the organism is manifested only by the appearance of antibody in excess. The antigen (bacillin) forms with antibody in excess insoluble compounds. All the symptoms of the disease are anaphylactic in nature.

ANAPHYLAXIS.

The study of the pathogenicity of infectious diseases has led us irresistably through a series of logical deductions drawn from exact experiments to the conception that the pathologic manifestations in disease are exclusively anaphylactic in nature.

To explain the nature, the mechanism and the basis of anaphylaxis demands a knowledge of the nature of all the septicemic diseases, and a general idea of all the researches concerning these diseases. Let us see what this knowledge includes:

To Charles Richet, to whom belongs the credit for the discovery of the biologic importance of the subject and of

the word, "anaphylaxis" was a state of hypersensitiveness in which an organism found itself as a result of a series of preparatory injections of an antigen. The same antigen, non- or very slightly toxic in the first injection was very toxic in the second or "shock" injection and, according to Richet, this toxicity resulted from the formation of a particular poison "apotoxin" which was formed by the combination of the antigen with a hypothetical "toxogenine."

According to Besredka there is no poison in anaphylactic hypersensitiveness. He said, some years ago (1907), "In a general way, the majority of the reported facts seem to indicate that the formation of anaphylaxis and of anti-anaphylaxis may be reduced to the actions of precipitation and absorption which resist the reactions of colloids between themselves." He had, as he said in a quite recent work,[1] "A single purpose; to contrast the idea of a physical process with that of a poison determined chemically."

Finally, after having analyzed with clarity and customary ability the numerous studies of Friedberger, Neufeld and Dold, Doerr and Russ, Levaditi and Mutermilch, Bordet, Kraus, Nicolle, Vaughan and Wheeler and others and selected the theories of these authors, whether chemical or physical, Besredka completed his first conception by saying, "What dominates anaphylaxis and anti-anaphylaxis is neither poison nor antipoison but it is on the one hand the rapidity with which the union of 'sensibiligen' and 'sensibilisin' takes place and, on the other hand, the site of this union which is probably the nervous system."

The causes of the crises of anaphylactic shock are then, according to Besredka, partly physical; at all events we read a few lines further in the same work (page 142): "What happens after the test injection? The new antigen meets the sensibilisin already transformed. Their *affinity* results in an intense reaction. Whether this reaction ruptures the equilibrium of certain nervous cells in which the *combination* takes place or whether it is accompanied by a loss or by an absorption of caloric or other energy, there

[1] Anaphylaxis et Anti-anaphylaxie, Masson et cie. ed. Paris, 1917.

takes place a series of phenomena always the same, which constitutes anaphylactic shock."

Besredka does not explain either by physical or by chemical means or by both together the affinities and combinations which he considers take part in the reaction, but the apparent contradiction expressed in the two phrases which precede may be explained with a little latitude. The affinities are very probably chemical in nature and the combinations as well; but in Besredka's conception the product formed by the combination does not act by its chemical properties (poison), but only by its physical properties (precipitate). It is not the product already formed which causes the pathologic manifestations of the anaphylactic state, but only the rapidity with which products are formed; in his opinion, precipitates are not necessary.

Thus, in the last analysis whether a precipitate is formed or not, the experiments of Besredka and the intrepretations which he himself puts on them indicate that it is the factor *time* which is at least one of the conditions of the reaction, and may be the single cause of anaphylactic shock. (This one factor ought, we think, to be chemical or rather physico-chemical since the reaction concerns colloids.)

F. G. Novy and P. H. de Kruif[1] return again in an extensive work which has just appeared, to the idea of a soluble anaphylatoxin or "taraxin" formed in the organism by a substance "taraxigen." Anaphylactic shock would be the result of a sort of tautometric intramolecular rearrangement of certain very labile substances contained in the blood.

Fundamentally it is evident that all these different ideas are only plays on words. There has been, and is, much discussion in current chemical literature on the subject of the different phenomena and processes surrounding immunity and anaphylaxis just as our fathers and grandfathers discussed symptoms, pathogenicity and evolution of infectious diseases before the discovery of bacteria, and in order to explain these things there has been created a complicated and barbarous terminology which has incidentally the great

[1] Anaphylatoxin and Anaphylaxis, Jour. Am. Med. Assn., May 26, 1917.

inconvenience of giving grand illusions with a precision which does not exist.

Confusion and misunderstandings result in the vast majority of cases from the forced use of inaccurate terms which are necessary in order to visualize reactions between substances of which only a few biological properties are known.

And the differences which we have desired to establish in the nature of the reactions of anaphylactic shock and of chronic anaphylaxis (Arthus phenomenon) between the guinea-pig, rabbit, goat, horse or rat, and even between French and American guinea-pigs could arise only from the fact that up to the present we have had only a general idea of the interpretation of various observed phenomena, clinical or experimental.

But although the words, "anaphylaxis," "taraxis," "apo- or anaphylatoxins" or "taraxins" are not important, the distinctive characters of shock as well as of crises of longer duration and other delayed reactions of a different nature are defined as much by the pathogenicity as by the symptoms.

To define a phenomenon, it is not sufficient to indicate the process by which it is produced: We ought to know of what it consists; in other words, its symptoms, the methods by which these symptoms are produced and particularly the properties of the elements which combine to produce them.

But if we do not know all the properties of all the antigens and of all the antibodies as of all their compounds, we can know with certainty that the anaphylactic state can be produced only by antigens which form with their antibodies insoluble compounds. We have seen that there is no anaphylaxis for toxins which form with their antitoxins soluble compounds, and that there is always anaphylaxis for albumins, bacteria and their broth cultures which provoke the formation of precipitates.

The most convenient theory which could best explain the total of actually known facts would show that the anaphylactic crisis is a brisk reaction of coagulation caused by the union in the organism of a certain dose of antigen with a

certain dose of antibody, no matter whether the antibody preëxisted normally in the organism or whether it was formed as a result of special treatment. In the case of true antigens these latter are coagulated or precipitated by the antibodies of the organism. In the case of non-antigenic substances such as iodoform, antipyrin, peptones, etc., it is the injected substance which causes the coagulation of some substance of the organism; in either case the nature of the reaction will be always the same, and although the last case does not come within the limits of this study, it is not without interest to note it in order to avoid confusions and possible misunderstandings.

The effects of these coagulating reactions will be different according as the precipitate is formed exclusively in the blood or both in the blood and in a certain number of cells or even exclusively in the cells. If formed in the cells, the effects will depend upon the importance of the intracellular antibody in the life of the cell as well as the importance of the rôle of the cell in the life of the organism.

It would be superfluous to dwell here upon the symptomatology of anaphylaxis in its different degrees or its different localizations as this is found today in all the text-books of pathology; but it is important to note that the total of symptoms which characterizes anaphylactic shock includes:

1. The action of the recently formed poison—a word in incorrect but current use (Richet, Vaughan, Wheeler, Friedberger and others).
2. A chemical reaction (combination of antigen with antibody).
3. A physical or absorption reaction (Mutermilch).
4. A mechanical action of the precipitate: embolism, infarcts.
5. The function of time or the duration of reaction (Besredka).
6. The intervention of leukocytes in the transformation and transportation of precipitates to the hemopoietic organs.
7. Finally dominating the mechanism as well as the effects of all these reactions the influence of the central nervous system.

According to the point of view of the experimenter it is now one, now another of these agents which predominates in his mind and determines his preferences for this or that interpretation of the effect. Each of these theories contains a part of the truth but not the whole truth, and it is therefore necessary that the apparent effects of the reaction should be considered separately without attempting to understand their basis and their intricate mechanism.

But we have seen that only antigens can give rise to the anaphylactic state in the organism. We have seen that all antigens are colloids; that only colloids are antigens, that in consequence, the nature of the formation of antibody should be sought in the colloidal state of antigens, or in other words, by seeking to understand the physicochemical and the biologic properties of colloids and by studying the transformation which heterologous and homologous colloids undergo in the interior of the organism, that we will learn to know:

1. Why colloids cause the formation of antibodies.
2. Why and under what conditions colloids form with antibodies soluble or insoluble compounds.
3. Why the compounds of antigens with their antibodies are harmless when they are soluble and pathogenic when they are insoluble and why this should necessarily be so.

COLLOIDS.

We know that colloids are substances which do not crystallize and which therefore cannot be isolated from their medium in pure state and we know that in attempting to purify a colloid we generally cause it to cease to be a colloid. According to the happy simile of E. Duclaux, "When we try to analyze an albumin by chemical methods, we act as if we were analyzing a watch enclosed in a case. We would find iron, copper, silver, gold and the elements which compose glass but we would never conclude from this analysis that these elements arranged in a certain way and put in motion in a certain state of equilibrium would constitute a total which would enable us to measure time. One would admit that after analyzing a watch in this way, by grind-

ing it in a mortar to facilitate the action of strong acids or by melting it at a temperature of about 1000°, one would destroy not only the instrument which tells time but also those landmarks which might permit us to identify the individual rôle of each of them in the function of the whole; that is, in the movement of the hands."

But since then we have learned to do better. By submitting an albumin to an action less brutal than that, for example, of gastro-intestinal digestion, we may break it down little by little without destroying the entire complexes —"the wheels"—which compose it, and by continuing in this way through a series of successive disintegrations, we would find that every albumin which is a colloid is at last split to amino-acids which are crystalloids. We know that the molecules of a salt in solution coalesce one with another to form crystals when there is not enough solvent to keep them a certain distance apart, but we do not know how and why amines, which can exist as free molecules, and which then obey the laws of salt solutions may congregate into such complex elements as colloids.

It would be especially interesting to know by what physical or chemical agent (electricity, magnetism, affinity) these molecules of amino-acids are bound and held together. We will know this certainly some time. At the moment we must confine our study to the biologic and physicochemical properties of the albumin as we find it in its complex medium and to the substances which result from its successive disintegrations. Although incomplete, this study already gives us a series of interesting reflections which are sufficiently exact for our purpose; to learn how and why an organism can become diseased, and perhaps also how it can recover under the best conditions.

We have then determined that of all the products of the disintegration of an albumin, those only are antigens which are still in the colloidal state.

Free amino-acids are no longer antigens. There is here a confirmation of the fact which we have noted above, that only colloids can be antigens and it is possible to conclude from this that foreign albumins taken as a food which gastro-

intestinal digestion is incapable of splitting, that is to say, of transforming into amino-acids and which may pass into the interior of the organism as colloids will provoke the formation of antibodies and in consequence the anaphylactic state. These are the causes of the habitual or accidental anaphylactic intolerance for certain foods, as well as for infections by mouth, individual or specific, in typhoid, cholera, tuberculosis, etc.

The organism can nourish itself on foreign albumins only in cases it can assimilate them, that is to say, can transform them into albumins of its own species; and we know that to do this it can absorb them only in the completely disintegrated state of the amino-acid. This disintegration is the rôle of gastro-intestinal digestion. What then becomes of the incompletely digested albumins which have penetrated into the interior of the organism in the colloidal state? They can neither be assimilated nor eliminated in the colloidal state.

Two hypotheses are possible: Either they would accumulate in some part to which would be brought every other unassimilable foreign body where they would be surrounded by leukocytes; or else the interior of the organism would finish the incomplete gastro-intestinal digestion and would render them assimilable or eliminable as amino-acids. It is this last hypothesis which happens in all the known cases. It is true that up to the present we have never been able to prove this parenteral digestion, but if we have no direct experimental proof of it, we know with certainty by numerous experiments (Hamburger and Moro and others) that when we inject a rabbit with horse serum, we can recover this serum in the rabbit's blood some time after the injection but that finally this serum will disappear at a given moment and that this disappearance, often quite sudden, will always coincide with the appearance in the rabbit's blood of specific antibodies. From the point of view of the reaction which follows, it is of little importance by what route (intestinal, subcutaneous, intravenous) the colloidal antigen penetrates into the organism.

The transformation in the organism of a colloid into a

salt can be followed at the present time with some precision only for a colloid obtained by synthesis which quite recent researches permit us to consider as an antigen. This synthetic colloid is disodo-dioxy-diamino-arsenobenzene-antimonious-silver-bromide (or product 102).

Judging by the experiments and analyses of Mlle. Mitchel this product injected into the blood of rabbits as a colloid is entirely eliminated by the kidneys and the intestines as a salt. We, therefore, say that the colloid has undergone in the organism a transformation commonly called digestion and since this colloid possesses all the biologic and physico-chemical properties common to an antigen, since it gives in the organism the same series of reactions under the same conditions, we may assume by comparison, that all other antigens undergo in the organism transformations of the same nature; that introduced as colloids they will be digested, and transformed into salts and as such either assimilated or eliminated.

In consequence by taking a purely biologic point of view, and by using all the experimental material known, we must admit that the injection into the interior of the organism of a colloid antigen which is digestible will always produce a reaction of digestion on the part of the organism quite as the introduction of an albumin into the digestive apparatus. And we may add with some certainty that the formation of antibody in excess which appears in the blood at the end of the incubation period can be only the result of the normal reaction common to every living cell which will always try as long as it lives to reproduce and multiply a substance of which it has need or which it loses by a neutralizing combination with a foreign substance.

We may thus represent the steps of this process in the following simple way:

Every organism possesses for every normally digestible albumin a certain normal affinity (and this is not surprising since every albumin is constructed on the same plan and belongs to the same chemical family) or, in other words, a certain *dose* of normal affinity for a certain dose of foreign albumin.

If the dose of albumin injected is strictly equivalent or less than the dose of normal affinity every antigen injected will be fixed by normal antibody, digested, assimilated or eliminated and the organism will reproduce and multiply this normal affinity-antibody which then will become the antibody in excess. If the injected dose of albumin is greater than the dose of normal affinity the antigen will fix itself to the normal antibody *en surcharge* and the organism will suffer or rather the antigen in excess will circulate in the blood up to the time when the organism can produce a quantity of antibody sufficient to fix and digest this excess of antigen. It is only after a total disappearance of antigen that the antibody in excess will appear.

In this way is explained quite easily a fact which until now has seemed inexplicable. We know that if a small injection of antigen causes an excess of antibody and the anaphylactic state to appear in ten to fifteen days, the injection of a large quantity of the same antigen into an animal of the same species will produce the same effect only after an incubation period of some weeks or even months simply because the existence of an excess of antigen in the circulation excludes the possibility of the simultaneous existence of an excess of antibody in the organism.

More recently, however, Longcope and Rackemann[1] have been able to demonstrate that in the serum disease, which as originally shown by Von Pirquet and Schick[2] often follows the injection of antitoxic or antibacterial serum in man, there may be a coexistence of antigen and antibody in the circulation.

Working with cases of pneumonia, which had been treated with antipneumococcus serum obtained from horses, they found that the horse serum persisted unchanged in the blood for several days, and that in a few cases circulating antibody could be demonstrated in the same specimen of patient's blood serum in which horse serum could also be demon-

[1] The Relation of Circulating Antibodies to Serum Disease, Jour. Exp. Med., 1918, xxvii, 341.

[2] Die Serumkrankheit, Leipsic and Vienna, 1915.

strated. They found that "the rapid diminution of antigen follows the rapid rise of precipitin and is coincident with recovery from serum disease"; so that although the two reagents can coexist, they cannot both be "in excess."

Under what conditions then is an organism sensitive to anaphylaxis? There will be a surcharge of antibodies. That is, all the cells which possess a special affinity for the injected antigen will have multiplied a substance which fixes the antigen, holding a certain quantity *en surcharge* and allowing the remainder to pass into the blood. There will thus be an excess of antibody in the cells and in the blood. If at this time we inject a sufficient quantity of the same antigen there will be produced a reaction of the same nature as the first time but the effects of this reaction on the organism will be different, because the quantities and the proportions of the two products will be no longer the same and because the reaction will take place not only in the cells but also in the blood.

We have seen above that the compounds of the antigen with their antibodies may be soluble and under these conditions they are neutral for the organism (diphtheria, tetanus) or else they form coagula or precipitates, and are pathogenic. Whenever there are antibodies in excess both in the blood and in the cells, there will be pathogenic reactions intravascular and intracellular.

The reactions will be pathogenic not because there is formed on the second injection a toxic body different from that which is formed at the first injection, but only because this new body will form much more rapidly and in much larger quantities than the first time. Precipitates formed in the blood will result in emboli, infarcts, etc., from which apoplectic attacks, syncope, abdominal congestion, pulmonary and cutaneous edema accompanied by fall of temperature and intracellular lesions will be expressed by a variety of symptoms, all the more severe as the cells in question play a more important rôle in the general economy. These last reactions, especially when they concern the nervous cells to a greater or less degree, are accompanied by fever. Let us note in passing that intravascular reactions when they

are not rapidly fatal will always be less dangerous than intracellular reactions.

We may thus affirm that the basis for the production of antibody in excess is the obligation to digest colloids under which the organism finds itself in order to assimilate or eliminate these colloids. We know that this digestion will produce pathologic manifestations when the compound of antigen with antibody causes a precipitate: but on the contrary when this compound is soluble, this digestion is completely harmless.

This difference in the intimate mechanism of the reactions which together result, on the one hand, in the formation of a coagulum or of a precipitate and, on the other hand, of a product which is soluble remains to be explained.

For this explanation only a very limited amount of experimental material is at hand. The basis of the reply is the physicochemical constitution of colloids which is still little understood. Let us also see what we know and what conclusion we can draw from the point of view which is presented to us.

From the physical point of view a colloid can be represented as formed by granules or "micelles"[1] composed of a variable number of molecules of a single or of several different substances. The structure of these "micelles" is unknown, but we may assume that when they are in suspension in a liquid, they have, because of surface tension, a spherical or ovoid form. The volume of the granules of the simplest and most homogeneous and antigenic colloid which we know, arsenobenzene, is variable not only because the "micelles" may contain a larger or smaller number of molecules but because several "micelles" may be combined into a single granule. Experiments show, moreover, that in every liquid containing a colloid in suspension there is also a certain number of free molecules. Thus, when we allow a solution of luargol (1 to 400) in 0.5 to 0.7 per cent. salt solution, to

[1] The word "micelle" is used to define the units of albuminoid matter of every colloid in the same sense that the word "molecule" expresses the unit of chemical compounds. The word "particle" is used by many American authors in the same sense.

stand, we find at the end of twenty-four hours that there is formed in the liquid which was first uniformly colored and uniformly fluid, four layers distinctly superimposed one above the other. At the top is a layer of clear, highly colored fluid; below this, two layers darker and more turbid and at the bottom a translucent flocculent precipitate. At the end of two or three days there will be in the tube only a sediment and a perfectly transparent slightly colored liquid. This liquid will, even when saturated with salt, be no longer turbid and will traverse dialyzing membranes. There is thus no more colloid and the manner in which the precipitate is formed and digested in the remainder of the original fluid shows that there were in this fluid granules of different sizes.

In a solution exactly disodic there will be at the end of twenty-four hours about 50 per cent. of the product in the precipitate and respectively 25, 20 and 5 per cent. in the layers above it.

The proportions of amino-acids as free molecules or grouped into more or less voluminous granules may be different for different colloids and for the same colloids according to the conditions of the medium in which they occur. But if we judge by the total of reactions between colloids and cells and by the results obtained in submitting colloids to dialysis, we can see that in serum as in egg-white or in a bacterial albumin, or in a toxin, that these fluids contain granules of very different volumes as well as amino-acid existing as free molecules, quite as has been established for the arsenobenzenes.

Thus in recognizing that there are very distinct differences between the formation of a crystal in which the molecules of salt are mechanically deposited one on the other and a colloidal granule in which the molecules are very probably bound together by a single affinity we must note that there are no clear-cut distinctions between the two sorts of substances when considered from the point of view of their physical property of crossing dialyzing membranes.

There is no membrane which cannot be traversed by the smallest granules of every colloid and it is very important

to appreciate this because it is the smallest granules of antigens, which, by traversing the membranes of cells, provoke the condition of congestion and dilatation of the cellular membrane which then becomes permeable for more voluminous granules.

From the chemical point of view, we know that each molecule of the chlorhydrate of dioxydiamino-arsenobenzene may theoretically combine with two molecules of silver chloride but when a dilute solution of silver chloride in potassium cyanide is added drop by drop to a dilute solution (1 to 500) of arsenobenzene, we find that each drop of silver chloride is precipitated *en masse* without forming a globule and is then redissolved. If the liquid is carefully shaken, the dissolution of each drop which follows becomes more difficult. When we reach the proportion of almost one molecule of silver chloride to one molecule of arsenobenzene, dissolution no longer takes place.

An insoluble precipitate is also obtained by adding quickly one molecule of a concentrated solution of silver cyanide to twenty molecules of arsenobenzene, although there is still in the liquid enough of the latter to fix and hold in solution nineteen other molecules of silver cyanide. The difference in these two cases may be explained by assuming that in the first case by adding slowly into dilute media and by shaking the mixture the silver chloride is more or less uniformly distributed among all the molecules of arsenobenzene while in the latter case each molecule of arsenobenzene which comes into contact with silver chloride fixes two molecules of it and there is thus formed an insoluble compound.

The granule of arsenobenzene may thus fix a salt for which it has a certain affinity in quantity equal to the sums of the affinities of the molecules which compose it, but it is evident that it can also fix less of them and it is thus that we can explain the "phenomenon of surcharge" and the "phenomenon of least saturation" already described, in studying the properties of mixtures with their antibodies *in vitro* and *in vivo*.

For the arsenobenzenes we know exactly the chemical equivalents; for biologic antigens we do not know them but

the similarity, and even the identity of all the reactions of arsenobenzenes with those of all the other antigens, allows us to assume that the physicochemical constitutions are also identical. This phenomenon of least saturation will explain the formation of toxons, toxoids, epitoxons, epitoxoids in mixtures of toxins and antitoxins (Ehrlich).

For phenomena of absorption and hydrolysis, the precipitant action of neutral salts and the dissolving action of acid or alkaline media which characterize every colloid permit us to consider each colloidal granule as a sort of cell which can be hydrated and inflated, dehydrated and retracted, which can absorb, retain and secrete all sorts of salts by the purely physical phenomenon of osmosis without regard to chemical combinations which can affect its amino groups and other molecules by their special affinities.

The nature of the reactions between colloids or between colloids and salts as well as the quantity of the substances which can be combined or absorbed are determined especially by the physical characteristics of the colloid. These include the form and volume of the granules which compose the colloid as well as the proportion of the different sized granules. So long as "the choice" of substances with which a colloid may combine and the nature of the compounds thus formed, depends eventually on chemical affinities of the molecules which enter into the composition of the granules, it is very possible to imagine, that in a granule composed, for example of one hundred molecules, ten or twenty or sixty of these molecules will form new combinations while the others will remain intact. According to the proportion of different granules the physicochemical properties as well as biologic effects of the colloid will be different.

Arsenobenzene is the simplest colloid-antigen which we know; its granules are of different and variable size but all are composed of molecules of the same amine. Biologic antigens in general have a much more complex composition; casein, for example, is composed of a dozen different amino-acids (alanin, leucin, serin, glutamic acid, aspartic acid, arginin, lysin, hystidin, cystin, tyrosin, phenylalanin, tryptophan) and it is certain that between casein and

arsenobenzene we can find all intermediary substances. It would thus be very interesting to know whether all the different amino-acids which are found in casein, in serum, or in bacterial antigens are united in different proportions in each granule or whether each of them forms different granules. Biologic chemistry will probably undertake some day to solve these problems which we cannot take up now. What appears certain is that all the colloids of egg-white or of serum or of bacterial bodies when introduced into the interior of the organism do not become antigenic, nor do all the colloidal granules of heterologous origin take part in the same degree in the formation of specific antibodies. Levaditi and Mutermilch[1] have shown by their studies on the production of anti-nagana antibodies in the guinea-pig, rabbit and rat on the one hand and in the hen on the other hand, that antibodies produced by the same antigens in animals of different species are not identical.

Different antibodies can be produced only by different antigens, which means that in the particular case brought forward by Levaditi and Mutermilch, products of bacteriolysis of the trypanosome do not form a uniform antigen but these products contain a mixture of colloidal granules whose composition and affinities are different. In consequence the colloidal granules which are antigenic for the organism of the rabbit, guinea-pig and rat on the one hand and of the hen on the other hand are not compounds of the same amino-acids or at least are not grouped in the same way. We have also seen that in the case of *Bacillus typhi murium* the substance virulent for mice is not the same which gives this bacteria its virulence for rats. These two examples allow us to conclude that in complex colloids formed of every sort of amino-acid these latter are not uniformly distributed among all the granules but constitute groups of granules of different chemical compositions.

And if this is so, we should necessarily conclude that every colloidal granule of an albumin or of a complex colloid which is not antigenic ought to be immediately digested and trans-

[1] Antibody and Animal Species, Ann. de l'Inst. Pasteur, 1913, xxvii, 924.

formed to crystalloids in a way different from antigenic colloids. This allows us to approach the question of the digestion of homologous albumin, which with the exception or crystallin (the substance of the lens) can be assimilated without producing the formation of an antibody and without ever giving rise to a state of anaphylactic intolerance.

But how can we represent this assimilation of homologous albumin? It is impossible to imagine an unbroken albumin penetrating into a cell. Consequently a homologous albumin must be transformed into free amino-acids just like a heterologous albumin; only this transformation must operate in another way.

By studying this, after what we know, it seems as if a homologous albumin was directly transformed into free amino-acids in the blood and fluids in the organism without passing through the stage of coagulation or, in other words, as if there were in each organism a substance capable of destroying or of binding the ties by which amino-acids are united in granules and of thus freeing them and making them assimilable. The example of the transformation of a colloidal arsenobenzene into "novo-arsenobenzene" which is a salt by the fixation of formaldehyde sulphoxalate of sodium to the amino group of dioxydiamino-arsenobenzene permits us to assume that this is the case.

It is thus very probable that the colloids of foreign albumins which are not antigens are transformed to crystalloids in the same way as homologous albumins. This is not surprising when we think, as already indicated, of the original unity of every animal species and of the similarity of the elementary composition of all albumins, which differ among themselves much more by the proportions than by the qualities of the chemical parts which compose them. What should differ especially are the ties by which the molecules are bound together into colloidal granules. Whatever are the differences of detail between different albumins and the colloids which compose them, the total of our knowledge of the digestion of non-antigenic and antigenic colloids in the interior of the organism permits us to visualize the mechanism of these two sorts of processes in the following

way: Every organism possesses in its fluids certain substances (normal antibodies) in a sufficient quantity to rapidly transform by a single operation any quantity of non-antigenic colloids into crystalloid solutions which can be assimilated or eliminated and by the same procedure which permits it to digest these in its own tissues.

Every organism can produce, as a result of a suitable preparation, a specific antibody by which every antigenic colloid can be transformed into a crystalloid but here the process of this transformation may take place in one of two different ways, either as a single reaction in the case of non-antigenic colloids (toxins, antitoxins) or by two successive reactions, of which the first consists of the formation of a coagulum and the second of the dissolution of this coagulum (all the other albumins and colloidal foreign antigens).

From what we know of the transformation of the arsenobenzenes, we may assume that in the case of non-antigenic colloids as in the case of toxins, the antibody, whether normal or in excess, acts especially upon the ties which bind the amines into colloidal granules to neutralize these ties. In the case of antigenic colloids the antibody in excess forms first new combinations with the molecules of these antigens by rearranging the granules among themselves and thus causing the formation of precipitates or coagula which render the subsequent liberation of molecules slower and more difficult.

ANTIBODY.

It remains for us to investigate the physicochemical nature of antibodies and we must recognize that this is the least known element of the problem. We know that the production of antibody in excess is the result of a *vital reaction* of the cell because even if a dead cell or a dead tissue could fix a certain quantity of antigen in the same way and by the same affinity as living tissue it would be impossible for it to reproduce and multiply this fixation substance which in the living organism becomes the antibody in excess. This explains why the production of antibody is necessarily

always inversely proportional to the pathogenic action of antigens.

We know that the substance to which the rôle of normal antibody belongs can fulfil different functions which are more or less important in the normal life of the cell. This "substance" may be in an organ of sense or a function of nutrition or of reproduction or finally a substance of reserve and in each the immunizing excitation or the lesion will be manifested by its different effects on the function of the particular tissue and on the general economy. We know, further, that it is not always the same cells of an organism which are sensitive to the action of an antigen. Where, for example, it is the cells of the central nervous system which are exclusively or more particularly sensitive to the action of an antigen, the production of antibody is very precarious if not absent, probably because the nerve cells do not recuperate and because the excitation even of this tissue, however slight, always results in profound disturbances of the general economy. We may conclude that the less important the rôle of the particular tissue, the easier and less harmful will be the process of immunization. This is almost all that we can say as to the biologic origin of antibodies.

As to their physicochemical nature, we know that antibodies are one of those components of "antiserum" which it has been quite impossible to isolate by dialysis. We assume, at least tentatively, that they are colloids, but we cannot prove it directly. The example of the transformation of coagulated arsenobenzene when one adds to the molecules an acid or base which holds the colloidal granules in suspension in water; the redissolution of the coagulum as well as the dislocation of the colloidal granules by a sort of sulphonation will serve to prove that antibodies may be something much more simple than a colloid, but if this is possible for arsenobenzene it seems today too simple for antibodies and all the other antigens. Let us be content for the moment to remember the essential simplicity of the reactions which determine the transformations of arsenobenzenes and to hope that later researches will help us to recognize the nature and the mechanism of biologic antigens.

SUMMARY.—1. Salts introduced into the interior of an organism may be assimilated or eliminated without undergoing any transformation because they can cross dialyzing membranes.

2. Colloids cannot be assimilated or eliminated under the same conditions because they cannot cross dialyzing membranes.

3. Gastro-intestinal digestion results in the transformation of specific-colloid-albumins into salts (amino-acids) which are no longer specific and with which the organism reconstructs the albumins of its species.

4. When, as a result of incomplete intestinal digestion an albumin penetrates into the interior of the organism it is this interior which must achieve digestion and this doctrine applies to all albumins or colloids introduced into the interior either subcutaneously, intravascularly or through the intestines.

5. Cells, tissues and organs of the interior of the organism are adapted only in a certain measure to this function of digestion and in a given time can transform only a certain quantity of albumin or of foreign colloids. Each time that a cell fixes a quantity of a substance to be digested in excess of what it can easily digest (phenomenon of surcharge), there will be intracellular indigestion which disturbs the vital functions and the physiologic state of the cell for the reason that there is no method for the evacuation of the undigested surplus. This is the case for toxins, ricin, abrin, venins and certain sera which are directly toxic for some tissues.

6. Intracellular digestion can be explained only by an attraction and fixation of the substance to be digested by a substance of a cell; or by a chemical affinity between these two substances, which results in the formation of a new compound. When this operation is not pathogenic for the cell the cell reproduces and multiples what it has lost in the combination; in this way we may represent the formation of antibody in excess.

7. The presence in the organism of antibody in excess in the cells and in the blood, which can of itself produce certain

functional disturbances (tuberculosis), increases the digestive capacity of the organism for the corresponding antigen, but at the time renders the digestion more rapid and more tumultuous and one of two different processes may then take place:

In the first, digestion takes place at one time and the antigen, transformed to an assimilable or eliminable product, becomes completely neutral to the organism. The antibody-antigen compound produces no disturbances at all: diphtheria, tetanus, non-antigenic colloids.

In the second, digestion takes place in two successive phases: first, coagulation and second, dissolution of the coagulum. Here the sudden formation of the coagulum will produce immediate or delayed pathologic manifestations whenever the quantity of antigen is greater than the capacity for the rapid dissolution of the coagulum: septicemia and heterologous albumins.

8. All the pathologic symptoms caused by an antigen which are manifested in the organism at the time when it contains corresponding antibody in excess are anaphylactic in nature. A crisis of anaphylaxis is nothing but a crisis of indigestion. The disturbances are produced by a sudden rupture of the normal equilibrium between the state of *gel* and the state of *sol* of those colloids which enter into the composition of cells and blood.

The severity of the disturbance produced by these reactions is determined by:

(*a*) The quantities and relative proportions of the reacting substances.

(*b*) The concentration of these substances and in consequence the duration of the reaction.

(*c*) The intracellular and intravascular localization of lesions.

(*d*) The secondary and often delayed effect of these lesions on the general economy.

In the spontaneous infectious diseases, intravascular reactions are always less dangerous than intracellular reactions because these latter often result in the destruction of cells and consequently in lesions of the tissues which are severe and

persistent. In contrast with intracellular reactions, intravascular reactions may be considered as therapeutic.

9. The necessity or the production of antibody in excess results from the obligation under which the organism finds itself to transform antigenic colloids, which have penetrated by any way whatever into its blood and tissues, into salts.

10. The mechanism of this digestion is still unknown but we may suppose following the example of the transformations of arsenobenzenes, that in certain cases (toxins) the antibody is a substance which binds the ties which unite the amines in colloidal granules and thus transforms the colloid into a salt neutral for the organism; and that in every case there is first fixation by the molecules of a colloidal granule of a substance which unites the granules to each other to form a coagulum or a precipitate and finally there is another substance which dissolves the precipitate and destroys the ties of the molecules.

We may note in passing that the same substance may coagulate or dissolve according to the proportions of the reacting substances. Thus in two words:

The pathologic state in infectious diseases is due to anaphylaxis.

Anaphylaxis is an indigestion which may be intracellular or intravascular or both.

This indigestion consists in the inability of the organ to rapidly transform colloidal antigens into salts.

When it is intravascular, the disturbance will be rapid and immediate: anaphylactic shock; when it is intracellular the disturbance and the lesions which result may be more or less delayed and will last for hours, days or dozens of years (tuberculosis, leprosy, syphilis): chronic anaphylaxis.

From the point of view of the evolution of infectious diseases, anaphylaxis ought to be considered as a pathologic reaction of the process of immunity.

CHAPTER VI.

THE INFLUENCE OF THE CENTRAL NERVOUS SYSTEM ON IMMUNIZING REACTIONS AND ON ANAPHYLAXIS.

The influence of the central nervous system on the processes of immunity and anaphylaxis is not at the present time understood, at least from the biochemical point of view. It is indisputable that the cells of an organism, even the leukocytes, have no individual independent life, concur in all their functions to make a perfectly coördinated whole. In other words, that the specific functions of each tissue, organ, gland and cell are strictly dependent, not only on the physicochemical affinities of the substances which compose them, but also and especially on the action and condition of the central and sympathetic nervous system, and on its conscious and subconscious reactions.

Syncopies, respiratory and gastro-intestinal disturbances produced by emotions, whether spiritual or psychic, real or suggested, which simulate so accurately the syndrome of anaphylactic shock in total or in part, the chronic disturbances of general nutrition produced by grief; the activation of salivary or gastric secretion by the sight of certain foods—all prove that the nervous system can produce in the cells all manner of reactions without the direct intervention of any foreign product whatever.

Moreover in a diarrhea caused by a violent emotion or in an urticaria of hysterical origin it is certainly not the direct action of the peripheral nerves which can in a few moments liquefy the intestinal contents or produce edemas in different areas of the skin. These reactions in the last analysis can be the result only of physicochemical modifications which are produced in the interior of particular

cells. We know, moreover, nothing of the exact mechanism of these reactions nor of the substances which enter into them but we may assume that there is a disturbance of that metabolism which regulates intracellular nutrition and causes the capillary dilatation.

What is certain, and what is important to remember, is that excitations of a purely psychic order which involve those highest nerve cells which determine conscious states may result in functional disturbances of certain tissues or organs, that is to say, in purely physicochemical reactions.

We do not know with any certainty whether the inverse is often true, whether, for example, it is possible to ward off a contagion or its effects by a particular state of mind but we do know that it is possible to mitigate anaphylactic shock by certain narcotics as shown by the experiments of Besredka inspired by E. Roux. Besredka noticed that the surest method of producing anaphylactic shock in the guinea-pig is to inject the antigen into the brain. At that time E. Roux suggested to him the idea of anesthetizing the animal before the second injection. The result was as hoped for; animals narcotized by alcohol, ether, ethyl chloride, urethane or chloroform, especially by the first two, were rendered insusceptible to anaphylactic shock while controls succumbed almost always in a few seconds or in a few minutes. The first was found vaccinated against a later injection (anti-anaphylaxis). This experiment leads us to a combination of very complex phenomena which it is almost impossible to interpret.

The effect produced by an antigen on a hypersensitive organism depends to a certain degree, as we have seen above, quite as much on the dose of the antigen injected as on the rapidity with which the reactions take place. For each condition of hypersensitiveness a dose of antigen can be determined which will produce no apparent trouble, a dose which will vaccinate and a dose which will kill. However, no dose is always constant in its effect. A dose which will produce violent death in an animal when quickly injected within a few seconds, will become protective if the injection is allowed to last a few minutes. The effect

thus depends upon the time during which the intracellular reactions are allowed to take place and anesthesia has no other rôle than to prolong the duration of the reactions. By anesthetizing the nerve cells the transmission of the excitation to the nerve centers and to the particular tissues is impeded.

The combination between antigen and antibody in excess takes place in spite of narcosis, because the animal is vaccinated by the dose, but the pathologic effect of the reaction between the two substances is lessened either because the duration of the reaction is longer, or better, because the hypersensitiveness of important nerve cells has prevented organs of tissues from reacting pathologically. We can explain this better by a somewhat exaggerated comparison:

When a stone engages in a gall-duct or in the urethra the walls of the canal contract as if they were trying to hinder the passage of the foreign body. Local or general anesthesia will prevent the contraction (and the pain at the same time) so that if the dimensions of the stone do not exceed the capacity for expansion of the canal, the stone will continue on its way without pathologic manifestations.

Experiences have shown that certain nervous excitations may produce pathologic manifestations, analogous to those which characterize anaphylactic shock, and that anesthesia of the nerve centers may hinder these manifestations by moderating the resulting reactions and especially by hindering the secondary reaction of the organism.

We know only two sorts of nervous influences but it is very probable that there are many others and that their effects may be different, either good or bad for the organism. We suspect, for example, that when in an infectious disease (typhoid fever, pneumonia, tuberculosis, etc.) nervous symptoms are predominant, the process of immunization does not take place or takes place incompletely and the prognosis is, therefore, always grave. We also know that in antitoxic immunization, the production of antibodies is all the more rapid and abundant when the nervous sensibility of the treated animal is better protected against intoxication.

Thus, the guinea-pig is much more easily immunized against

diphtheria toxin than the rabbit because in the guinea-pig the non-fatal dose of this toxin is completely fixed and retained by the cellular tissue and never produces nervous crises; in the rabbit the same toxin is not retained by cellular tissue and always paralyzes. But in attempting to immunize these two animals against tetanus toxin the reactions and results are exactly reversed. It is thus very probable that in these two cases the production of antibodies is, in a certain measure, modified by the influence of the central nervous system.

We may quote here the experiences of Kendall[1] on the action *in vitro* of suprarenal cortex on ammonium carbonate. This action is very different according to whether the operation for the removal of the cortex is done in an animal normally sluggish without having undergone any nervous excitement or whether in an animal recently and violently frightened. In the first case the ammonium carbonate undergoes no modification; in the second, it is transformed into a poorly defined substance which Kendall has called pre-urea because when excreted in urine it is transformed into urea.

The researches of Cannon[2] demonstrate beautifully the actual physiological changes brought about by the central nervous system. Cannon showed that after any violent emotion, such as fear or rage, there is a marked liberation of "epinephrin" from the suprarenal cortex and a liberation of glycogen from the liver. This sudden liberation of epinephrin, which takes place in a matter of seconds, causes in turn the production of many and varied disturbances in the organism such as stimulation of the sympathetic nerves, increase in the blood coagulability and in the relative proportion of red blood cells.

Psychic excitations can thus produce a proved modification in metabolism and resulting from this a change not only in the substances contained in the suprarenal cortex but in the quantities of substances secreted.

[1] Experimental Hyperthyroidism, Jour. Am. Med. Assn., 1917, lxix, 610.
[2] Am. Jour. Physiol., 1915–16, vols. xl–xlii.

SUMMARY.—If the facts actually known hardly permit us to understand the nature and the mechanism of the influences which different varieties of excitations of nerve centers exert on the reactions between antigens and antibodies we may assume that these reactions are probably never purely local, that they are always influenced by nervous states, conscious or subconscious, direct or reflex. The suggestion which we may draw from this is to investigate the action of different anesthetics, hypnotics and narcotics or infections, especially in the severe cases with nervous disturbances.

CHAPTER VII.

THERAPEUTIC MEASURES.

In the evolution of pathologic states caused by actually known antigens it is necessary to distinguish between a latent state of anaphylaxis and an actual state of anaphylaxis.

By latent anaphylaxis we mean that the organism is surcharged with antibodies in excess as a result of the previous injections or ingestion of the antigen or as a result of the periods of remission of those diseases with relapses and with long and slow evolution such as tuberculosis, syphilis, trypanosomiasis and malaria. Each time that a sufficient quantity of antigen in fresh doses is joined with these antibodies in excess more or less violent crises will occur.

By actual anaphylaxis, we mean that the organism shows symptoms of disease in which a state of anaphylactic crisis is maintained on the one hand by the presence of new quantities of antigens due to the multiplication of bacteria and on the other hand by the continued formation of antibodies on the part of the organism so that antibodies will always be in excess. The formation of momentarily insoluble compounds of antigens and antibody constitutes the pathologic state of chronic anaphylactic crises.

We know that we can abort a crisis or an anaphylactic shock by anti-anaphylactic vaccination. According to Besredka and Steinhardt and according to Al. Wright, cases of definite anaphylaxis can often be treated successfully by an identical method—bacteriotherapy, that is to say, by injections of small doses of antigen—the cause of the disease.

From the work of Besredka we know that preventive vaccination is rigorously specific and for bacteriotherapy we seek likewise to obtain curative preparations made with a culture of the bacterial species which is the cause of the infection or with the actual germs in the infection, "auto" vaccines.

In both instances, the preventive and curative action can be explained by a progressive neutralization of the antibody in excess which results in making the organism return to the normal state following a new injection of the same antigen and in the two cases "prophylaxis" or therapy confers very rapidly on the organism a temporary anti-anaphylactic immunity, but a new dose of the antibody will establish the preceding anaphylactic condition even more acutely.

The anti-anaphylactic vaccination of Besredka as well as the bacteriotherapy of Wright are discoveries due to one of those happy chances in the course of experiments which have revealed to the experimenters facts which they did not seek but which, from the practical point of view, have shown themselves to be more important than those which they did seek.

And it is interesting to realize that this principle of anti-anaphylactic vaccination should arise from the false idea that antitoxic vaccination should lead to an anti-anaphylactic analogous to antitoxin (Roseneau, Anderson, Otto) quite in the same way as bacteriotherapy (or vaccine therapy) arose in the mind of Wright from anti-infectious vaccination (anti-anthrax vaccination, and the treatment of rabies: Pasteur, Roux, Chamberland). Nobody has sought to establish any relation whatever between those two phenomena.

Besredka was far from doubting when an anaphylactic shock was aborted by his successive injections, that he obtained the same results by reactions identical to those of Wright with his vaccine therapy, but if Besredka reached little by little an exact conception or at least the only probable conception of the mechanism of anti-anaphylactic vaccination, the explanation of the facts of bacteriotherapy is still and will always be an "article of faith," or a "religion" for all those who pretend to see in the pathologic manifestations of an infectious disease the effects of a poison and nothing else and in the recovery an "antitoxic virtue" of a drug or serum.

Moreover close inspection will reveal that the mechanism of vaccination and of the treatment of anaphylaxis is simple and easy of explanation only when previous vaccinating or

curative antigens are specific or homologous (autogenous vaccines). The mechanism is singularly complicated when it is attempted to associate the identical results obtained by non-specific antigens especially by the skeptophylaxis of Ancel and Bouin or by the tachyphylaxis of Gley and Champy, with lymphotherapy from the preventive point of view or with chemotherapy from the curative point of view. In skepto- or tachyphylaxis, whose discovery in 1880[1] may be considered chronologically, as the origin of all the researches on anaphylaxis and bacteriotherapy, the crises of anaphylaxis can be aborted by a vaccination injection of any antigen whatever (Roger and Josué Lambert, Ancel and Bouin).

In proteosotherapy, Rumpf used injections of sterilized cultures of pyocyaneus with success in typhoid fever (1893); Hallopeau and Roger cultures of streptococci and of prodigiosus in tuberculous lupus (1896) and quite recently Ch. Nicolle, James W. Jobling and his numerous collaborators, Bull, Dunklin, Eggstein, Manier, Peterson, and others, have obtained undoubted results in treating acute and chronic rheumatoid arthritis of unknown origin by different proteoses, peptones or bacterial bodies.

In lymphoserotherapy (Baillon, Artaud, de Vevey, etc.) as well as in chemotherapy, it is quite impossible to imagine the direct action of the particular antigen on the antibody in excess as in proteosotherapy.

From this is the conclusion that either the mechanism of anti-anaphylactic vaccination and that of specific bacteriotherapy are different from those of tachyphylaxis, of proteosoand of chemotherapy; or else the explanation which we have just given is inexact or more or less incomplete.

The experimental material at our actual disposal does not permit us to answer this question in a sufficiently exact way. What we can say with certainty is that if the effects obtained

[1] A. Schmidt Mulheim has shown that a non-pathogenic dose of peptone rendered an animal insusceptible to a pathogenic dose injected shortly after the first (Beiträge zur Kentniss des Peptons, etc., Arch. f. Physiol., 1880).

About the same time, Woolbridge established the same result by parenteral injections of organ extracts and Martin (Australia) by parenteral injections of certain venins.

by vaccination as, for example, in treatment by homologous and by heterologous antigens are in certain cases undoubted, we cannot place these two methods in the same category. Statistics and clinical observations as an index of successful treatment must be relied on with caution since the degrees of disease vary so widely. We know that an elevation of temperature of 3 or 4° can help the organism to rid itself of certain bacteria (gonococci) by aiding the dissolution of certain precipitates and we know that the introduction of any antigen whatever, in immunizing doses, produces certain abnormal reactions or stimulates those which are already begun. (Action of pilocarpine in the production of antitoxins (Madsen and Salomonsen).)

It is always the specific agents which exercise the most obvious action and if the neutralization of antibody in excess plays an important rôle in the cure of anaphylactic crises, this rôle is only concomitant with other reactions of a nature and mechanism little understood. We do not know whether in skepto- or tachyphylaxis and in proteosotherapy all the antigens are distinctly interchangeable or whether in anti-anaphylactic vaccination, the vaccinating antigens are or should always be as rigorously and exclusively specific as in experiments with egg-white.

Friedberger and others have said that after a pathogenic injection of anaphylatoxin the serum of the treated animal contains less "complement" than it contained before the injection and that at the same time the blood becomes incoagulable as in tachyphylaxis. It is then very probable that in certain cases, if not in all, that the neutralization of the excess of complement may be equivalent to the neutralization of the excess of antibody rendered inactive.

A vast field is here open for experiments which will not fail to influence the therapy of the future. By these researches medicine and its methods will be sooner rendered more exact and comprehensive. The problems to be solved will always be infinitely simplified if it is borne in mind that all the phenomena described under the names of skepto- or tachyphylaxis, anaphylaxis, anaphylactic crisis, anti-anaphylaxis, bacterio-, proteoso-, lympho-, and chemo-

therapy and even under serum therapy whose discovery has arisen in different ways and in which researches have developed parallel to the others, but without touching, are all provoked by reactions of the same nature.

In fact, the products which provoke skepto- or tachyphylaxis are no other than the anaphylatoxins so that skeptophylaxis is synonymous with anti-anaphylatoxic vaccination. An anaphylactic crisis is produced by reactions identical to those produced by anaphylatoxin and in these two phenomena there is this single difference that in the first, the organism furnishes the reactive substance (antibody in excess) while in the second, the antigen furnishes it. A series of injections of a disodic arsenobenzene will render the organism anaphylactic to a later or second injection of the same product. The serum of the treated organism will become more precipitating than normal serum: Monosodium arsenbenzene is an anaphylatoxin because this product on injection is more easily precipitable than the disodic compound.

Finally latent anaphylactic crisis is made to abort exactly by the same method as an outspoken anaphylactic crisis is cured. The confusion of facts is caused only by a lack of understanding of the background on which each develops and to coördinate these it is only necessary to find in the experimental material at hand suggestions useful for therapeutics.

CHEMOTHERAPY.

Chemotherapy may well profit by all the experiments discussed above. We know (Dalimier) that the injection of a small dose of a disodic arsenobenzene can protect the organism from the pathologic effects of a larger dose and that the pathologic state already existing and caused by a large dose may lead to recovery or rapid improvement by a mechanism identical to that of bacteriotherapy. It would be interesting to see whether it were possible to cure and especially to prevent anaphylactic or anaphylatoxic accidents caused by arsenobenzenes by using other antigens—for example, peptone, sera, or bacterial bodies. If this were possible, it would

be easy to increase the actual dose of arsenobenzene. On account of individual intolerance which is always possible and difficult to foretell, it is not safe to inject at once a strong dose of arsenobenzene, but by proceeding with a series of small injections the risk of habituating a parasite as well as the organism to the drug would be diminished. There is therefore every inducement to attempt to find whether by the injection of vaccinating doses of other antigens, the tolerance of the organism for arsenobenzene can be increased so that a more surely curative dose of this drug can be injected safely. As to the curative or parasiticidal action of chemical compounds, we can say with certainty that since they kill infecting bacteria directly, all these products prevent the anaphylactic state caused by bacteria much more than they themselves cause them.

The disappearance from the lesions and from the blood of treponema, spirilla or trypanosomes following an injection of arsenobenzene by no means proves that the product has directly poisoned them. Quite frequently the same result is obtained by bacteriotherapy. Cases of typhoid fever have been cured by bacteriotherapy in twenty-four hours (Widal) or forty-eight hours (Fournier) and here it is impossible to conceive of a direct destruction of living bacteria by the injection of dead bacteria.

But at the same time we know:

1. That to cure a case of recurrent fever or to make treponema disappear from chancres in twenty-four hours requires the following drug doses:

Novoarsenobenzene	0.45 gm.
Arsenobenzene	0.25–0.30 "
Luargol	0.10–0.15 "
"Product No. 219"	0.03–0.05 "

(This last is a product of luargol in which the silver bromide is partially replaced by copper bromide).

Intramine (of MacDonagh)	1.00 gm.

2. That in the different experimental trypanosomiases luargol and "product No. 219" are much more active than

606 and galyl for Trypanosoma gambiense, Rhodesiense and Surra but they are less active for nagana. The product No. 219 is the only one with which up to the present time it is possible to destroy the trypanosome dimorphon in the blood of mice. The principle is probably similar to that of an antitrypanosome serum which causes agglutination of the parasites.

3. In infectious lymphangitis, galyl (of Mouneyrat) is much more active than 606 or luargol.

4. In bacterial septicemias (acute and chronic) all these products are of equally little efficacy. The injection of 606 may prevent the development of anthrax when injected at the same time or very shortly after the virus, but luargol in which the bromide is replaced by the iodide of silver is much more active than 606, probably on account of the specific action of the iodine. A prolonged treatment with the product 219 has brought about the fairly rapid recovery (two to three months) of several severe cases of generalized glandular tuberculosis.

The conclusions which these facts suggest are:

1. Although the action of every arsenobenzene is equally anti-anaphylactic, that is to say, causes in the organism reactions of the same sort, the substances of the organism and the substance of the infecting parasites which react with the drug are not the same for each drug. By multiplying the different affinities of the product the fixation and neutralization of a much larger number of different substances of the parasite is brought about and thus the field of action of the product is extended to a greater number of parasites.

For example, if 606 acts only by the free affinities of its arsenic, 219 may act by its own affinities of arsenic and in addition by those of antimony, bromine, silver and copper.

2. It is probably not necessary to complicate the composition of therapeutic products by elements with great antitoxic or antiseptic power as these might in the long run become themselves dangerous for the tissues.

It is true that certain organic compounds (toxins, venins, sera) are more pathogenic than the most toxic metallic salts but since it is a question of obtaining anaphylactic effects

and since it is possible to attain these effects without using in the composition of drugs any toxic metals, the idea of MacDonagh of replacing the arsenic of arsenobenzene by a sulphate or iron salt deserves to be given serious consideration.

BACTERIOTHERAPY AND SERUM THERAPY.

As long as it is possible to produce antigens and antibodies by synthesis, bacterio- and serum therapy will be the methods of choice in the treatment of infectious diseases. In bacteriotherapy the uncertainty in the dose is most often the cause of partial failure or of severe accidents which have made clinicians hesitate to adopt this method and to apply it to all cases where practically possible.

But experiments in anti-anaphylaxis and in skepto- and tachyphylaxis permit us at the present to make this method more sure and efficacious. We may assume that, other things being equal, specific or autogenous bacteriotherapy will always give us the best and most constant results; but it is necessary to find the best curative preparation; the best method of its administration (whether by mouth, by rectum, subcutaneously or intravenously) and finally the best dosage.

Curative preparations may be either:

1. A culture on a gelatin emulsion in saline or distilled water killed by heat (58° to 100° C.) and as fresh as possible.
2. The same cultures prepared in the same way but more or less autolized.
3. The same culture killed by antiseptics.
4. A living culture of attenuated virulence.
5. A living culture of attenuated virulence and then sensitized.

The best method of administering curative preparations is always by intravenous injection. It will always give the quickest results and will not aggravate the condition of the patient. When the quantity of antigen is predetermined (by determining the quantity of antibody in excess), vaccines can be injected without danger.

The least dangerous method is to give the vaccine by mouth but it is evident that this method can be applied with

success only in case gastro-intestinal digestion is incapable of transforming the bacterial albumins into their amino-acids (typhoid, cholera, furunculosis).

The dose should be regulated according to the quantity of antibody in excess contained in the blood of the patient. Too large a dose may produce a rapidly fatal anaphylactic crisis: too small a dose will give a slight or inappreciate result. As it is often difficult to rapidly determine the exact quantity of antibody in the blood of the patient one may replace a single injection by a series of injections made under the following conditions:

Supposing, for example, that the total quantity of bacteria to be injected is five hundred million, there would be given by vein:

First, a primary injection of 500,000 bacteria; a second injection, ten minutes later 5,000,000 bacteria; a third injection, five minutes later 50,000,000 bacteria; a fourth injection, three to five minutes later 450,000,000 bacteria; by exhausting little by little the antibodies in excess, one could more easily reach the dose of antigen necessary to neutralize all the antibody without provoking a pathologic reaction.

SERUM THERAPY.

It is evident that an injection of antibacterial serum, that is to say, of an antibody, into an organism containing already an excess of this antibody can have no curative effect where the disease is due to a chronic anaphylactic state. In fact we know that the injection of such a serum always causes a passive anaphylactic state and we know that in a certain number of diseases, tuberculosis, plague, typhoid, streptococcus, antisera have given up to the present time no appreciable result. There are, moreover, septicemic diseases such as erysipelas, anthrax, pneumonia, cerebrospinal meningitis, in which the action of specific sera is indisputable. Either the bacteria of these infections secrete in the organism toxins analogous to those of diphtheria and tetanus and the serum acts in this case by its antitoxic properties; or else the action of the serum is analogous to that of a proteose or of a non-

specific protein. The two actions may furthermore take place simultaneously.

Diphtheria and erysipelas are very instructive in this way. Most, if not all, horses yield in the normal state antidiphtheritic and antistreptococcus serum of very appreciable potency (up to 50 antitoxic units per c.c. for diphtheria) and although it is unlikely that horses which are naturally refractory for these two diseases could acquire this spontaneous immunity, it is possible that the serum of normal horses acts like a non-specific antigen and this is not surprising since we know that carmin will neutralize tetanus toxin. In other words, a biologically neutral and non-specific substance can produce a reaction of the same nature as a specific antitoxin. The differences are only in proportions and degrees.

It would not be difficult to elaborate a program of studies which would enable us to exactly differentiate the cases of intoxication, due to the direct action of toxins, from cases of anaphylaxis caused by bacterial albumins, or in other words, the cases amenable to treatment by antisera from those in which such a serum could do only harm.

CHAPTER VIII.

PRINCIPLES OF THE CLASSIFICATION OF INFECTIOUS DISEASES.

In every infectious disease, the pathologic manifestations are produced by the action of antigens on tissues and organs and the differences in the evolution of symptoms of these different diseases are determined by:

1. The physicochemical composition and the physiological properties of antigens and antibodies.
2. The nature of the compounds formed by antigens with their normal antibodies, whether soluble or insoluble, neutral or active.
3. The elective affinities of antigens for certain tissues.
4. The physiological rôle of the antibodies in the life of those cells which fix the antigen.
5. The rôle of the fixing cells in the life of the organism.
6. The adaptation of the infecting bacteria to life in the infected organism.
7. The nature of the complications which may result from the lesions produced.

The similarities and the differences in the physicochemical properties of antigen, in the biologic action of the reacting substances, in the nature and effects of the reactions; all serve as a basis for a natural classification of infectious diseases; but it is evident that such a classification will only be of purely theoretical interest.

Every therapeutic intervention ought to be based on the knowledge of the facts which we have just reviewed, because they are facts which determine successive stages in the evolution of each disease caused by an antigen. A classification permits us at the same time to group in a rational manner therapeutic methods and to foretell the results

which a certain preventive or curative method should be capable of yielding in each particular case. By proceeding in this way, we ought little by little to make therapeutics an exact science.

Thus, for example, the fact that in diphtheria the antigen in excess forms with the normal antibody a pathogenic compound while the antigen with antibody in excess forms a compound which is neutral for the organism, permits us to conclude that preventive or curative treatment by antitoxic serum is the most efficacious method. And we should conclude that in all other cases when reactions between antibodies and antigens are of the same nature the same treatment will yield analogous results. On the other hand where the antibody in excess forms with the antigen an insoluble compound and where it is precisely this excess of antibody which is the cause of the pathologic manifestations (anaphylactic state) (as in typhoid fever) the disease cannot be treated by injections of antibody, which already exist in excess but, on the contrary, must be treated by anti-anaphylactic methods—that is, by injections of antigen which will neutralize this excess of antibody.

There are diseases in which the antibody in excess neutralizes the antigen without producing appreciable disturbances and there are others in which the antibody in excess, while neutralizing the antigen, produces by its combination with the latter a pathologic reaction. This difference between the properties of the compounds of antigens with their antibodies in excess allows us to divide the known diseases into two great groups. Our knowledge of the properties of antibodies and of antigens as well as of the compounds formed by these two substances is altogether too incomplete in most cases for us to assign at the present their exact place in each disease. Judging from what we actually know, we can group together on the one hand, diphtheria, tetanus, certain pneumonias, perhaps anthrax fever, erysipelas, and certain cerebrospinal meningitides in which the antigen acts directly and rapidly on tissues and is neutralized by the antibody in excess without anaphylaxis and, on the other hand, all the other septicemias in which the incubation period is more

or less long and in which the pathologic manifestations are anaphylactic in nature.

The characters of the subgroups and species will be determined by the affinities of antigens for different tissues as well as by the nature and properties of antibodies and the rôle of these latter in the life of the sensitive cells. Thus, for example, tuberculosis, glanders and leprosy on the one hand; syphilis, trypanosomiasis, relapsing fever and malaria on the other hand form two closely allied groups of diseases. As common characteristics they have the physicochemical properties of their antigens and the nature of their antibodies. In both groups immunity and anaphylaxis persist only as long as the infection itself. The quantity of antibody produced in excess is relatively very small and the sensitive cells cease to produce it immediately after the disappearanec of the infecting bacteria. On the other hand the bacteria seem to adapt themselves very easily to the medium of the infecting organism and may live in it for years or even dozens of years. This facility of adaptation on the one hand, determines the more or less regular cyclic evolution of these diseases whose mechanism has been the object of the very interesting study of nagana in the guinea-pig by Levaditi and Mutermilch.

Typhoid and paratyphoid fever, plague, eruptive fevers, yellow fevers, the hemorrhagic septicemia in animals, bovine plague, the horse sickness of South Africa form another group of diseases which are related to the preceding group by the physicochemical properties of their antigens as well as by the pathogenic properties of the compounds of these antigens with antibodies in excess. This second group differs from the first by the nature and origin of the antibodies which sensitive cells produce in relatively large quantities and reproduce for a long time after recovery from the disease. In these cases acquired immunity-anaphylaxis may persist for several years.

Gonorrhea, influenza, aphthous fever form still another group which is related to the type of tuberculosis by the intracellular origin of the antibodies which determines the short duration of immunity-anaphylaxis but differs from it by

the nature and the localization of the sensitive cells and in consequence by the lesions produced especially by the rapidity of the evolution because the bacteria of these diseases are less easily adapted to the infected medium than those of tuberculosis or of syphilis.

SUMMARY.—From the point of view of their evolution, all infectious diseases have as a common characteristic the formation of antibodies in excess under the action of antigens.

The common distinguishing characteristic between the different diseases lies in the physicochemical nature and the biologic properties of the compounds formed by the action of the antibodies in excess with their antigens. These compounds may be either soluble and neutral and here the immunizing action of the antigens will confer on the organism immunity without anaphylaxis (diphtheria); or compounds may be insoluble and pathogenic and here the immunizing action of the antigen confers on the organism immunity and also anaphylaxis (almost all septicemias).

The two great families of infectious diseases can be subdivided according to the affinities of antigens, the relative quantity of antibodies produced, and the duration after recovery of the production of antibodies. This latter probably depends upon the nature and upon the rôle which the mother substance of the antibody fulfills in the life of the cell.

In the second great group three types can be distinguished:

1. Tuberculosis.
2. Typhoid fever.
3. Gonorrhea, aphthous fever, and a subtype; syphilis and malaria.

The species in these groups may be differentiated and characterized by the affinities of antigens for different tissues, by the nature of lesions produced and by the adaptation of bacteria to their host.

CHAPTER IX.

GENERAL CONCLUSIONS.

The collection of studies on the evolution and nature of pathologic states which we have just analyzed, especially the phenomena of surcharge or of least saturation which are found in mixtures of antibodies and antigens; the recent researches of physiology, more particularly those of Willcock and Hopkins,[1] and of Osborn and Mendel[2] on the importance of certain amino-acids (tryptophane and lysin) in the nutrition, growth and reproduction of higher animals as well as the quite recent work of Van Slyke.[3] The present significance of the amino-acids in physiology and pathology shows that the amino-acids pass from the intestines into the blood without undergoing any transformation and at least in part are absorbed directly by the tissues.

These researches lead us to consider the organism from the point of view of its physicochemical composition as a total composed of colloidal "micelles," formed by the union of a larger or smaller number of homo- or heterogeneous amino-acids held together by certain chemical affinities. By reason of surface tension, the molecules are more dense at the periphery than at the center so that the peripheral layer acts like a dialyzing membrane.

A "micelle" thus constituted can fix salts by chemical affinities of its molecules and can absorb them by osmosis and can exchange salts as well as water with the exterior. It can also by the same affinities fix itself to other units and form much larger voluminous granules. It is thus not the molecule but the colloidal "micelle" which is the chemically

[1] The importance of Individual Amino-acids in Metabolism, Jour. of Physiol., December, 1896, p. 8.

[2] The Rôle of Different Proteins in Nutrition and Growth.

[3] Arch. Int. Med., 1917, xix, 56.

indivisable unit of living matter. The "micelle" is the organ of intracellular nutrition which by the stability of its chemical composition and the resulting physical constitution maintains the specificity of different tissues and of each species and determines the cycle of evolution of each cell. Separated into the salts, lipoids, and amino-acids which compose it, the "micelle" no longer possesses any specificity nor any of those properties which characterize living matter.

What is the mechanism of the autoreconstruction of the living "micelle?" The most recent researches mentioned above oblige us to assume that animal "micelles" can assimilate untransformed amino-acids and they cease to live if they have not certain preformed amino-acids (tryptophane) at their disposal; which suggests that they are incapable of constructing these substances from the simplest chemical units. Van Slyke has shown that tissues absorb amino-acids: the presence of amino-acids in the blood has been proved by Delaunay and the works of Fischer, Kossel, and others on the polypeptids permit us to conceive of the construction of a biologic particle of a still more complex composition and constitution.

Is there a ferment analogous to that which hydrolyzes albumins, which causes the synthesis of albumins? That is hardly probable. If we imagine that a "micelle" of a certain composition can attract and assimilate by a total of its physicochemical properties, the amino-acids of which it is composed, as a crystal attracts and fixes by analogous properties molecules identical to those of which it is formed, we can readily understand the autoreconstruction of particles of the plasma with the materials which are found in abundance in the medium in which they are constantly bathed: and we do not need to consider a "ferment" whose existence has at the present time never been proved.

When the "micelles" are free in a state of fluid, the colloid is in the state of *sol;* when they are in unity in granules the colloid is in the state of *gel* and in a living organism these two states are always in unstable equilibrium; each "micelle" is constantly in a state of change between *gel* and *sol.* Every sudden stop, every rupture of equilibrium in this continuity

of exchange and in the passage between *sol* and *gel,* every stabilization of one or the other of these states results in more or less severe disturbances of stabilization which in turn, depend upon the dose and preparation of the stabilizing agent.

The biochemical experience of Loewe, of which the true significance has been brought to light by the studies of Amé Pictet on the life and death of plasma, definitely confirm these ideas and allow us to understand the probable chemical mechanism. Loewe found that those substances which are poisonous for living plasma and exercise no appreciable action on dead albumin, act chemically by transforming unstable linear compounds into relatively stable, cylic compounds and Pictet drew from this work the conclusion confirmed by new and very ingenious experiments that it was this chemical stabilization added to the durable stabilization of a certain state of biologic equilibrium which might be the cause of a pathologic state of the plasma of the cell and of its death.

It may be that as, for example, in the case of mercury salts and certain venins by acting not on the molecule but on the "micelle," the same product produces the stabilization of the colloid in various forms: gel, sol, etc., according to the quantity or the proportion of the product which is fixed: and that the rupture of equilibrium in certain "micelles" will in a sense, necessarily result in a contrary reaction in other "micelles."

All substances, salts as well as colloids, may disturb vital functions, that is to say, the functions of nutrition of colloids, and hence of the cells by virtue of their being in solution in the interior of the organism and of possessing affinities for the substances which compose the cells.

From the chemical point of view these substances can be divided into two great groups—those which are nutritive and those which are not. In the first category will belong all the substances which normally enter into the composition of the organism; in the second those of which analysis shows no trace. The alimentary composition of all organisms is very uniform but the relative proportions in which the different elements are found differ infinitely.

Specific differences are very probably determined by the arrangement and by the proportions of different amino-acids, the quantities of mineral substances, iron, arsenic, potassium, sodium, magnesium, calcium, etc., which vary widely from one species to another and by the ties which bind amino-acids into "micelles."

Nutritive salts are fixed in definite proportions: the excess being rapidly eliminated. Non-nutritive salts may be neutral and then are rapidly eliminated but they are pathogenic whenever their quantity disturbs the sol-gel equilibrium of the colloids. Nutritive salts, like pathogenic salts, will not produce the formation of specific antibodies because the reactions between salts are innocuous and, furthermore, because a salt produced in excess is rapidly eliminated.

Colloids may also be nutritive, neutral or pathogenic but only after having undergone a complete digestion, that is to say, a disintegration into free molecules. They will always be pathogenic, when in the colloidal state they have penetrated by any way whatever into the interior of the organism which must then digest them, without being specifically adapted for this function. Certain colloids (toxins) composed of very small "micelles" may be directly pathogenic, when they are fixed "en surcharge" to certain cells. On the other hand, other colloids with more voluminous, less penetrating "micelles" do not become pathogenic until after a longer or shorter incubation period, when having entered the cell and distended its membrane by the multiplication of normal antibodies, they become able to penetrate to the interior of the cells. In one case as in the other the cells not fatally attacked will transform the colloid antigen into nutritious or eliminable crystalloids and will multiply the transforming substance which will then become antibody in excess.

This antibody in excess will be specific because the colloid antigens are specific individually and the antibody will accumulate in the cells and in the organism because as much as we know of it, it is a colloid. The production of antibody in excess is a vital reaction of the cells. Whenever the antibody in excess forms with its antigen an insoluble compound, there results an increase in the degree of immunity and at

the same time of the natural sensitiveness or anaphylaxis. In every case, for salts as well as colloids, the differences and the same contrasts in the reactions (nutritive, immunizing or pathogenic) will be determined by the proportion of the reacting substances.

A pathogenic bacterium will naturally obey the same general biochemical law as any other cell in order to nourish itself in the interior of the organism to which it has penetrated. If by its albumins or by its secretions, it is antigenic for the cells of the organism the albumins or secretions of these latter are antigenic for it and like the organism the bacterium will produce antibodies intra- and extracellular against these antigens. At the same time it will become more immune and more sensitive and whenever the organism produces its antibodies more rapidly than the infecting bacterium, the bacterium will succumb to anaphylaxis. It will be autolized or surcharged with antibody or antigen (sensitized) and will become the easy prey of phagocytes on account of the phenomenon of positive chemotaxis of Charles Bordet and Massart. In this way the conditions of normal or pathologic nutrition of a "micelle" and in consequence of the cell may be understood.

In an organism composed of a combination of different tissues, and of organs and glands with special functions, reactions will obviously be much more complex. In these cases a disturbance will never be strictly limited; it will have always multiple effects. The intervention of the liver, spleen, suprarenal capsule, thyroid and parathyroid glands, hypophysis and especially the central nervous system may greatly modify the rate of each reaction, and may infinitely complicate the study of its mechanism. But whatever these complications may be, whether the objective symptoms are caused by a purely local reaction or whether caused by a reflex action, it is impossible to imagine that any modification whatever in the normal state of the organism could be produced by anything other than a disturbance of the nutrition of the "micelle"; in other words, by a modification of the physicochemical equilibrium of the "micelles."

SUMMARY.—All the studies on physical chemistry and normal and pathologic biology tend to prove that the elementary chemical composition of albumins and of living beings is very uniform and that the specific differences are caused only by differences in the proportions in which these elements are united into "micelles." All albumins are constructed on the same plan. Their reactions are therefore all of the same nature but the chemical, osmotic and physiological equilibria determined by the different proportions of the elements which constitute the "micelles," vary infinitely, so that they can react differently to the same reacting substance.

The chemical and physiological unit of the plasma is the "micelle" which possesses for each animal or vegetable species a particular and constant chemical and osmotic equilibrium.

A "micelle" can be nourished only by the crystalloids of which it is composed, and can assimilate them without trouble only in the proportions in which it normally contains them. It may absorb them and fix them in different proportions but then its equilibrium is changed and it is easy to imagine that by absorbing a foreign substance (salt or crystalloid) in progressively increasing quantity and over a sufficiently long time in order that the new state of equilibrium may become hereditary, a "micelle," a plasma, or a cell may acquire new properties which will constitute a new race or even a new species.

A cell may absorb specifically different "micelles" but it cannot incorporate them as such into its own plasma because they possess a different nutritive equilibrium. It cannot directly be nourished by them without first demolishing them because the "micelles" cannot absorb other "micelles" but only non-specific crystalloid compounds which come to them.

Heterogeneous particles are thus necessarily dissociated when they come into a medium foreign to themselves and this process of intracellular dissociation is the origin of simple immunity on the one hand or of immunity-anaphylaxis on the other according to the rate of the reactions produced and according as the formation of antibody in excess neutral-

izes antigens outside of the cells, and prevents the direct and too rapid transformation of one foreign species to another.

Thus in the last analysis, an organism can be nourished only by simple chemical compounds and can assimilate them only in proportions identical to those in which they are composed in its colloidal complexes. The absorption by the interior of the organism of a complex of different composition and constitution will always result in the creation of a new and abnormal state of equilibrium.

This is a general biologic law applicable to all the manifestations of living matter without excepting the evolution of conscience and the formation of states of mind. In fact in analyzing the evolution of thought we find that a mind can directly absorb only simple ideas and can assimilate them without trouble only in proportions identical to those in which its own complex of ideas is formed. Complexes of ideas foreign to its understanding and which one may compare to specifically different "micelles" can be assimilated only on condition that they can be digested, that is to say, can be analyzed or dissociated. If this is so, a state of simple immunity or immunity-anaphylaxis, a new state of psychic equilibrium will result by a process analogous to that which induces modifications in the states of chemical and physiological equilibrium of "micelles" and cells. A new theory, a new religion, a new political or social system introduced too suddenly or in too large a dose into subjects insufficiently or badly prepared will always upset the normal equilibrium. This is a pathologic state, quite as serious in the soul of individuals and of societies as too large a dose of antigens in the cell and in the organism.

PART II.

CHAPTER X.

EVOLUTION OF THEORIES CONCERNING IMMUNITY, ANAPHYLAXIS AND ANTI-ANAPHYLAXIS.

INTRODUCTION.

Since the origin of infectious diseases has been recognized, we have tried to treat or prevent them by methods based on the reactions produced in the infected organism by pathogenic bacteria or by bacterial products (toxins). In this research, only immediate results were considered: active immunity by preventive vaccination or by bacteriotherapy, or passive immunity by serum therapy. In both cases, the vaccinated or recovered organism was considered normal. In addition to these diseases, correctly designated as infectious, with acute evolution (typhoid fever, cholera, plague, pneumonia, etc.) or chronic (tuberculosis, syphilis, malaria, etc.), there are a great number of chronic morbid states such as gastro-intestinal troubles, asthma, various dermatoses, rheumatisms and arthritides, neurasthenias, etc., of unknown origin.

These diseases are not contagious; we cannot assign a direct bacterial origin to them. Nevertheless they present many analogies in their evolution and symptoms with true infections or with the consequences of such infections (tuberculosis, syphilis, diphtheria, influenza, etc.).

Since the general use of vaccines, such as dead bacteria, curative sera or certain drugs of complex composition, such as the arsenobenzenes, quinine, antipyrin, chaulmoogra oil, peptones; it has been found that reactions which are identical

with those caused by bacteria or bacterial products may be caused by inert substances: identical because they are directly or indirectly *antigenic*. The introduction of these substances into the organism causes in the organism the formation of more or less specific *antibodies*, and it has been found that mixtures prepared *in vitro* of antibodies with their corresponding antigens are either neutral or toxic: neutral when they remain clear (toxins and antitoxins); toxic when they precipitate (bacteria or sera and their antibodies).

Similar results are obtained *in vivo*—when an animal is injected with an antigen which is precipitated by its serum.

The necessary conclusions are that:

1. In those diseases where an antibody is formed which can precipitate its antigen, pathologic manifestations are caused precisely by the very excess of this antibody.

2. The same pathologic manifestations can be caused by inert antigenic substances.

3. In many cases the origin of a chronic disease is not the direct action of a toxic substance itself, but a secondary reaction between the organism and an antigen which may in itself be innocuous—for example, a harmless bacterium, normal serum, or egg-white.

4. Finally, in order to obtain an exact and complete idea of the state of an immunized organism, it is not sufficient to consider the *accrued resistance* to a definite pathogenic agent; but one must also consider the results which this state of immunity, that is to say, the excess of antibody present in the blood and produced by the organs, may have on the nutrition-equilibrium of the immunized organism.

But a mere statement does not suffice. To convince the reader, it is necessary to produce the "proceedings of the court," and to go over again the stages of the road traveled by experimental biology since the time of Pasteur.

RESEARCHES BY PASTEUR, BY ROUX AND YERSIN AND BY BEHRING AND KITASATO.

The researches by Pasteur and by his school have brought out four fundamental biological rules or laws:

1. All contagious diseases are caused by living bacteria, which multiply in the blood or in the tissues of the invaded organism or, in other words: All bacteria able to multiply and to live more or less steadily in the blood or in the tissues of a superior organism, may cause infectious diseases which are directly or indirectly contagious.

2. Bacteria are pathogenic because of the poisons which they secrete or produce.

3. The virulence of pathogenic bacteria may be attenuated or completely suppressed in certain cases by artificial cultures and may be increased by passage through living organisms.

4. The introduction into an animal organism of a pathogenic bacteria attenuated or sterilized, protects this organism against later infection by the same bacteria when virulent. The "vaccinated" animal thus acquires an active immunity, and it is important to note that this immunity appears only after an "incubation period," which varies in time for the different infectious bacteria from eight to fourteen days, and which lasts for several days at least.

Several years later, the researches of Roux and Yersin on the "toxin" of diphtheria, led Behring and Kitasato to the discovery of antitoxin; their researches showed that:

5. By the injection into an animal of a bacterial poison in non-pathogenic or slightly pathogenic quantity, the animal acquires at first a greater resistance to the same poison, and later, when the treatment is continued, there is produced in the blood of the animal a specific antidote, exclusively for this poison. The injection of a toxin causes the production of an antitoxin in the organism. The antitoxin neutralizes *in vitro* and *in vivo* the pathogenic action of the toxin. The product of a mixture of toxin with antitoxin, in suitable proportions, is neutral.

These were the fundamental rules on which was based all ulterior research concerning reactions between the infecting bacteria and the infected organisms. It was then generally thought that, on the basis of these rules, one would succeed rapidly and without too many difficulties in cultivating or at least in demonstrating the bacteria of all infectious diseases, and in preparing preventive vaccines or curative sera for all

these diseases. It was hoped that in the course of this research it would become possible to explain at the same time the mechanism of all these reactions—namely, why a bacterium is pathogenic or may become so, how and why an infected organism may spontaneously recover or succumb to the disease, whether all infectious diseases have the same evolution—and also why the reactions caused by bacteria or by their toxins differed from the reactions caused by most toxic salts, inorganic or organic.

In reality these investigations have met with difficulties as numerous as they were unforeseen. Even today, after half a century of relentless labor, there are very contagious diseases, such as measles, scarlatina, typhus, hydrophobia, of which the germs are unknown; there are others such as leprosy malaria, the trypanosomiases, of which the germs are known but which cannot yet be cultivated on artificial media; there are others for which we have not succeeded in preparing either preventive vaccine or curative serum; lastly, there are others (psoriasis, eczema, cancer, etc.) which are not contagious and of which the germs are unknown, but which have many characteristics in common with diseases of infectious origin.

It was therefore necessary to recognize that all these problems could not be solved by frontal attacks; that if, in certain cases, it was possible to arrive at practical solutions by avoiding obstacles, and that if it was possible to discover preventive vaccines or curative treatments without knowing the causes of the disease—Jenner for small-pox and Pasteur for hydrophobia—in many other cases it was necessary, in order to arrive at the same results, to make a long detour in the attempt to better understand the functions of the organism, and the nature and mechanism of its normal and pathologic reactions.

And thus it is that nearly all the exact and biological sciences, chemistry and physics, general biology together with medicine and bacteriology, have been drawn upon to attack the immunity problem from several angles at the same time. What often happens in the exploration of unknown lands has occurred here: In following different trails, the explorers lose sight of each other at times, their

discoveries lead to results which are apparently irreconcilable, and contrary to the general ideas which inspired their departure; yet in the end all these routes lead to a clearing from which one can survey easily all the roads, and where everything can be explained and mutually understood.

During the study of immunity such phenomena have been discovered that it seemed impossible to find common bonds, or to reconcile them with the laws which logically followed the discoveries of Pasteur; we shall see that it has become possible today to assemble all these phenomena into one harmonious whole which, far from contradicting, confirms Pasteur's ideas and completes them by new laws.

TRANSFUSION OF BLOOD AND INJECTION OF HETEROLOGOUS AND HOMOLOGOUS SERA AND OTHER PROTEINS.

For a long time (since the old Egyptians) it was known that it was possible to "transfuse" blood from one animal to another, and that transfusion between animals of the same kind was less dangerous than transfusion between animals of different kinds; but it was to Landois, and especially to Hayem[1] (1885–1890) that we owe the first precise experimental studies of this question. Among other experiments Hayem injected blood from cattle into the veins of dogs, and determined that while a first injection of about 50 c.c. is endured without noticeable reaction, a second injection, of a dose half as strong, into the same animal twelve days after the first injection, is followed several minutes later by a violent crisis generally ending in death.

"The blood of an animal so treated," writes Hayem, "contains elements more or less changed, and sometimes hyaline concretions which are very refracting and extremely viscous. The blood in a tied vessel, kept from the previous day, remained liquid; there was a formation of clots like a sediment. It is these small masses of albuminoid matter (formation of a precipitate) which are the origin of the emboli.

[1] On Blood and its Anatomical Alterations, Paris, 1889, pp. 240 et seq.

When they are very numerous and able to obstruct the circulation more or less completely, the animal soon succumbs; but it is conceivable that in certain cases, they may determine local lesions of small size and the animals may survive."

Other similar experiments convinced this savant that the injection of blood from cattle into dogs represents only one special case of this kind of "coagulating injection," so that one may generalize this fact and say:

The second injection of blood or of a heterologous albuminoid substance (from an animal of a different kind) into the veins of an animal several days after the first injection, is much more dangerous than the first.

The first injection of a strong dose is usually well endured, the second and lesser dose is usually fatal.

The second dose is pathogenic because it causes the formation of a precipitate which obstructs the capillaries.

Hayem pointed out this phenomenon without endeavoring to explain it, so that his discovery did not awaken at that time the interest which it deserved.

It was only several years later (1894–1900) that all its importance was realized through the works of Pfeiffer, Metchnikoff, J. Bordet, Kraus, Belfanti and Carbone, and others, on the reciprocal reactions between the sera of immunized animals, on the one hand, and bacilli, the broth cultures, sera, blood elements, or other injected cells, on the other. Thus Pfeiffer determined that cholera vibrios injected into the peritoneal cavity of a guinea-pig, previously immunized against these bacilli, were agglutinated and partially destroyed in the peritoneal fluid, without direct intervention of phagocytes.

Soon after, Metchnikoff, followed by J. Bordet, showed that the same phenomena could be reproduced *in vitro* by mixing in a test-tube a culture of cholera vibrios with a small amount of serum from an immunized animal.

Kraus obtained the same result, not only for cholera, typhoid and plague bacteria, but also for the filtrated broth cultures of these microbes. In mixing these broth cultures with a little serum from immunized animals, he saw the formation of a precipitate.

Soon afterward, Belfanti and Carbone (July, 1898) discovered the very important fact that the injection of rabbit serum into a horse made the serum of this horse toxic for all rabbits; and Bordet completed this experiment by showing that the serum of any animal injected with the blood of an animal of different kind, acquires the property of agglutinating and dissolving the red corpuscles and of forming a precipitate with the serum of the animal which furnished the injected blood, on mixing both liquids in a test-tube.

The reactions observed *in vitro* therefore allow us to perceive what goes on in the organism, and to explain the nature if not the fundamental mechanism of a series of pathological reactions that might from this time on have led us to regard immunity and the pathogenicity of certain infectious diseases in a new light.

The results of the experiments of Hayem, Behring and Kitasato, Pfeiffer, Metchnikoff, J. Bordet, Kraus, Belfanti and Carbone, and others, has been to emphasize the following biological rules:

1. The injection of a heterologous albumin (bacterial bodies, blood, serum, casein, etc.) or of a non-albuminoid bacterial product causes, in the injected organism, the formation of a substance in excess which possesses a specific affinity for the injected substance.

The name of "antibody" has been given to all the substances thus formed, and of "antigen" to all those substances causing such a formation.

2. The antibodies neutralize *in vitro* and *in vivo* the specific pathogenic action of the antigen toxin and of the infectious antigen bacilli; but whereas the mixtures of antigen toxins (non-albuminoid) with their antitoxins give a product which is soluble "*in vitro*" and neutral in the organism—the mixtures of the infectious antigen bacilli with their antibodies give a product which forms a precipitate. This precipitate is neutral from an infectious point of view in the case of pathogenic bacilli, and from a toxic point of view for toxalbumins, but in itself it is endowed with a special toxicity.

This special toxicity becomes evident when one eliminates from the mixture the actual "toxin" or "infection" as for

example by mixing with their respective antibodies harmless albumin-antigens (like serum, casein, white of egg, etc.) which are not toxic in themselves. For in such cases, the two substances, each of them inoffensive, form a product—a precipitate—which is toxic.

The pathologic manifestations caused by these toxic mixtures are always the same, regardless of the nature of the antigen-albumin (pathogenic bacillus, toxalbumin or ordinary food albumin).

It follows by deduction that:

The reactions caused by the toxic products of mixtures *in vitro* or *in vivo* of antibodies with their antigens, always affect the same organs and are always of the same nature.

What is the nature of this reaction, and what justifies it?

It may be assumed, with Metchnikoff and his school, that the heterologous albumins like bacteria, undergo intracellular digestion in the blood and in certain organs. Anti-infectious immunity through phagocytosis would be only a particular case of this intracellular digestion, or quoting Bordet, "a fortunate and efficient application, for the defense of the organism, of a primordial function which would exist to the same extent even if there were no pathogenic germs on the surface of the earth." This theory, however, does not explain the pathological manifestations which result from this function. It does not explain and does not try to explain, which substances, innocuous when first injected, become pathogenic at the second injection, whereas true toxins, on the contrary, become innocuous under the same conditions.

These discoveries were registered without connection with any general biological phenomena, and these questions had to remain unanswered for a long time.

ANAPHYLAXIS.

It is evident that for minds that were neither prejudiced nor governed by the theories of the time which inspired all the foregoing experiments, the general rules which we have just formulated, contained already at this time (1897–1898) all the elements which compose the phenomenon of anaphy-

laxis, and that they even gave a sufficiently clear explanation of its mechanism.

In spite of all the foregoing experiments it was as a discovery of a new phenomenon that most biologists regarded anaphylaxis when introduced by Charles Richet and Portier in 1902.

These scientists discovered that an albuminoid substance called actino-congestion, extracted from the tentacles of sea-anemones, when injected into the veins of dogs, was toxic at certain doses, and innocuous at feebler doses. Congestion should therefore have been regarded as a toxin, and behave as such: The injection of a non-lethal dose into an animal should have vaccinated it against a later injection of a dose fatal for the control animals.

To their great surprise, the experimenters had to record a result which was exactly the contrary.

"The characteristic experiment," writes Charles Richet,[1] "the one which showed the phenomenon in all its indisputable clearness, was made on the dog Neptune. This was an animal of exceptional strength and health. He first received 0.1 c.c. glycerinated extract of sea-anemone tentacles without becoming ill. Twenty-two days later, as he was in excellent health, I injected the same dose of 0.1 c.c. A few seconds after the injection, he became very ill; respiration became painful and panting. He could hardly drag himself along, lay down on his side, was seized with diarrhea and bloody vomiting. Sensation disappeared and he died in twenty-five minutes."

Having thus obtained a reaction contrary to vaccination or prophylaxis, Richet called this phenomenon "anaphylaxis."

Neither Richet, nor all those who were interested in these experiments, saw anything in common between anaphylaxis and the phenomena described by Hayem, Krauss, Belfanti, Bordet, and others, because it seemed hardly possible to correlate the action of a poison (actinocongestin) with that of blood or serum from animals of allied species which were obviously considered as essentially alimentary substances.

On the other hand, it was already known that injections

[1] Anaphylaxis, S. F. Alcan, p. 3.

of diphtheria or tetanus toxins could be repeated at will on the same animal without ever causing an anaphylactic crisis, and that, on the contrary, the result of these injections had been the formation in the blood of the injected animal of an antitoxin which neutralized the noxious action of these toxins.

Richet was therefore perfectly justified in considering anaphylaxis as a new and peculiar phenomenon. He specifies the conditions of its evolution by insisting on the necessity of an "incubation period" (as in immunity), during which the organism prepares its anaphylactic state and he explains it by the formation of a "prepoison" (toxogenin), which becomes a poison when in contact with a new quantity of antigen. Interpreted in this way, Richet's discovery contributed a new complication to the explanation of the immunity process.

How and why is *toxogenin* formed, through what mechanism does it become *apotoxin* when it combines with the antigen? These were further questions that had to remain unanswered at the time.

However, in spite of ignorance as to explanation and classification, these phenomena created much interest, exactly because they were in formal contradiction to the fundamental principle on which was founded not only preventive vaccination but also the preparation of antitoxic sera.

These were questions which closely affected the most important, the most stirring problems of general biology. It was impossible to leave them in suspense, or to be contented with provisional, incomplete and often contradictory explanations; and in order to arrive at more satisfactory answers it was necessary to penetrate still further into the mechanism of these reactions. And so research into the properties and the action of heterologous albumins became the order of the day in every laboratory of experimental biology.

Soon after the publication of Richet's work, which concerned itself only with anaphylactic shock, Arthus discovered local and chronic anaphylaxis by showing that successive injections of horse serum into rabbits, no longer into the

blood but under the skin, resulted in the formation of indurated edemas at the point of inoculation. Arthus found at the same time that animals sensitized by a serum also become hypersensitive to peptone or to gelatin, though to a lesser degree; in short that the anaphylactic reaction is not always an exclusively specific one.

Marfan confirmed these experiments by the observation of "Serum Disease" in children repeatedly injected with antidiphtheritic (horse) serum.

In a series of most interesting experiments, Hamburger and Moro showed that a heterologous serum injected into the veins of an animal continues to circulate in this animal's blood up to the appearance of the specific *antibody*. It is at this moment that the incubation period ends, and that the animal becomes hypersensitive to a new injection of the same substance.

Besredka determined that this incubation period was longer as the quantity of heterologous serum injected was greater, and Friedberger's researches completed this series of experiments by showing that, if an animal be injected repeatedly with the same serum in non-pathogenic doses, the incubation period becomes progressively shorter, which means that the formation of the antibody takes place progressively more rapidly.

These researches, therefore, allowed certain elements of the problem to be defined, but at the same time, they brought out others of a complicating nature.

These facts as well as the observations of the unfortunate accidents in the preparation of antibacterial sera already caused the prediction that the phenomenon of anaphylaxis, its causes, nature and mechanism could be regarded, from a different and broader point of view than that which inspired Richet in his experiments and in the interpretation of their results.

ANTI-ANAPHYLAXIS AND THE IMMUNIZATION OF ANIMALS.

The discovery of antidiphtheritic serum naturally suggested the idea of trying in the same way to obtain curative

sera for all the infectious diseases of which the bacteria were known and could be cultivated (cholera, plague, typhoid fever, tuberculosis, anthrax, and others).

Horses and other animals were therefore injected, first with sterilized cultures, then with attenuated and lastly with virulent cultures of these bacilli, repeating these injections for weeks and months and increasing the doses. Rarely was the desired result, that is, a really active serum, obtained. The animals so treated became immune, it is true, never suffered from plague or typhoid fever, but the subcutaneous injections caused the formation of edemas, abscesses and other lesions which complicated the treatment, while animals into whose veins the injections were made often died on the very instant or several minutes after the injection, They fell as if knocked down, and died after a few convulsions. It was, therefore, Arthus's local anaphylaxis or Richet's anaphylactic shock which were in these instances caused by bacterial injections, and which complicated the process of immunization.

In this way it was confirmed that living or dead pathogenic bacteria, and in certain cases, also the filtered broth cultures were able to cause in the organism the same reactions as alimentary or toxic albumins.

Rarely could this be observed in the practice of preventive vaccinations because, in order to protect the organism against spontaneous infection, in which the dose of infecting bacilli is always very small, it was sufficient to inject one or at the most two small vaccinating doses. The serum of an animal so vaccinated had no curative power, and could not cure actual disease; but it was reasonable to suppose that by multiplying injections and by increasing the doses of the vaccine, sera would be obtained similar in curative power to antitoxic sera (diphtheria, tetanus).

It was also thought that the anaphylactic complications were the very obstacles to the formation of large quantities of antibacterial products, and thus endeavors were made to find a new weapon or circuitous road to overcome this obstacle or to avoid it. But this attempt would perhaps not have been undertaken with so much alacrity, had not the accidents

of "serum disease" in children to be fought or avoided. This was a complication which, although rare and often very mild, was nevertheless very troublesome in cases where the illness required prolonged treatment; in relapses, or also when it was necessary to apply serotherapy to the same patient, successively in different diseases.

In this research, as in many other cases where the logical deductions from a general and well established law offers no guide, chance once more proved itself more ingenious than the experimenters. Considering that the serum which causes an anaphylactic crisis must contain a poison, Rosenau and Anderson in America and Otto in Germany, had simultaneously the same idea of endeavoring to immunize guinea-pigs against this poison by intraperitoneal injections of large doses (5.0 c.c.) of horse serum, at regular intervals of from five to six days. In this way they hoped to obtain a specific antidote similar to antitoxin.

It will be conceded that this idea was rather peculiar: they were trying to obtain an anti-anaphylactic product by a process which, as was already well known, should lead straight to anaphylaxis, *which should cause a poison, not a counter-poison to appear;* and they did not obtain what they were seeking.

But a well performed experiment is never completely wasted. Rosenau and Anderson found that when injections were made every twelve days, there were often anaphylactic accidents at the time of the second injection, whereas when the injections were made every five days, no apparent accident occurred at the third injection, that is twelve days after the first one; that, therefore, the intermediary dose protected the animal against the following injection. Soon after this, Besredka and Steinhardt, who at first followed the errors of their predecessors, finally discovered that, in order to avoid an anaphylactic crisis in a duly anaphylactized animal, it was sufficient to inject a very small dose of the product a few minutes before the shocking dose.

The explanation of these phenomena is very simple. It logically follows the results of the series of experiments quoted above, beginning with those of Hayem.

It is not the serum, the blood or other injected heterologous albumin which becomes the "poison" at the time of the second injection since it is always the same substance which is injected, without having undergone any kind of change. If the animal becomes ill after the second injection the necessary conclusion is that he, his blood, his fluid or his tissues were modified by the first injection.

In what does this modification consist?

As already seen in the experiments of Pfeiffer, of Krauss, and of J. Bordet, there is formed in the blood of the injected animal, a substance which precipitates when mixed in certain proportions with the injected albumin. This substance was called by Krauss "precipitin" or "precipitating antibody."

MECHANISM OF ANTI-ANAPHYLAXIS.

We have seen in the experiments of Hamburger and Moro that the antibody appears only after a longer or shorter period of incubation, and that this appearance coincides with the disappearance of the antigen from the organism of the treated animal, and with the moment when the treated animal becomes hypersensitive.

We saw also, in Besredka's experiments, that the "period of incubation" increases in length with the dose of injected antigen, which means, as was seen in the previous experiment, that the length of time taken by the antigen to disappear increases with the quantity of the injection.

Therefore assuming that for a certain quantity of antigen the incubation period is twelve days, if an equal dose of antigen is injected six days after the first injection, the incubation period will be prolonged, and the animal will endure a third injection on the twelfth day without showing any sign of trouble.

Therein lies the explanation of the phenomenon of Rosenau and Anderson and of Otto.

A similar explanat on applies to the anti-anaphylaxis of Besredka. In order to cause an anaphylactic shock, it is necessary to inject into the prepared animal, who already is in a state of anaphylaxis, *a particular dose of antigen.*

With a decreased dose the shock does not take place, which means that the combination of the antigen with the antibody becomes a poison only if the two substances be mixed in certain definite proportions. If the total pathogenic dose is injected in non-pathogenic fractions, the successively formed combinations never become a "poison," and it is found that after one, or after a series of these preventive injections, the blood of the animal so treated no longer contains precipitating antibodies. It is, therefore, to use Besredka's expression, "restored anew," or, to be more exact, it begins a new period of incubation.

The reactions obtained by the "vaccinotherapy" of Al. Wright should be classified in the same category. This method which is based on the principles of Pasteur's preventive vaccination, in reality owes its success to anti-anaphylactic reactions. In acute infectious diseases, the appearance of symptoms coincides with the appearance of antibodies in excess, and the result of an injection of killed or attenuated bacilli is to neutralize this excess antibody. At the same time the symptoms of the disease disappear.

It follows of necessity that the pathological manifestations of disease are anaphylactic in nature, and that the result of the introduction into the organism of a suitable dose of antigen is not only to forestall an anaphylactic crisis, but also to cure the crises as they develop.

Attention must be drawn to the fact, however, that this distinction between the preventive and the curative anaphylactic actions is far more apparent than real. The course of an acute infectious disease (such as typhoid fever), is made up in reality of a series of crises succeeding each other more or less rapidly so that by interfering at a given time, one probably does not affect the current crisis, but prevents the birth of the crisis which would otherwise have followed.

Richet's experiments were thus the origin of a series of researches undertaken, in addition to those previously mentioned, by many scientists of all countries, von Pirquet, Friedberger, Schick, Auer, Ascoli, Nicolle, Doerr, Russ, Bidl, Eisenberg, Vaughan, Jobling, Wheeler, Novy, de Kruif, Levaditi, Mutermilch, and others. . . . It would take much too long to give here even a short analysis.

These researches may be said to have brought out the following general principles:

1. Every organism capable of producing an antibody in excess by the action of a given antigen, normally contains a small quantity of this antibody.

2. For the same quantity of antigen, the amount of precipitate formed in mixtures of antibody with its antigen, *in vitro* and *in vivo*, as well as the speed of this formation, is directly proportional to the quantity of antibody (normal or in excess) which exists in the blood or in the serum.

3. Every anaphylactized animal can be vaccinated in a few minutes against a fatal anaphylactic shock, by the previous injection of a non-pathogenic dose of the same antigen; in other words, a pathogenic anaphylactic reaction may be prevented by a previous non-pathogenic reaction.

TACHYPHYLAXIS OR SKEPTOPHYLAXIS.

Long before the discovery of anti-anaphylaxis, a similar if not identical phenomenon was known, which was discovered and confirmed by a series of researches concerning the direct toxic action of peptones and of certain albuminoid substances such as extracts of organs, eel serum, certain poisons, etc.

It was thus observed that the injection into a vein of 10 to 20 cg. of a peptone solution killed a dog in a few minutes. Beginning with tachycardia, the crisis followed with dyspnea, sometimes diarrhea, and ended with convulsions. The blood of an animal so treated could no longer coagulate. Schmidt-Mulheim was the first to obsèrve that if the animal survived a first peptone injection, its blood also was for a certain time incapable of coagulation, but that this animal would endure a second dose of peptone, even stronger than the first, without any modification in the ability of the blood to coagulate.

This phenomenon, confirmed by Fano (1882), Grosjean (1892), for peptones was restudied more thoroughly by Roger and Josué (1896) for intestinal extract. Delezenne demonstrated this anticoagulating action for the extract from crawfish, eel serum, etc. Delezenne and Bose (1896–1898)

found that peptone protects animals against fatal injections of colon bacilli and streptococci, in short that certain antigens protect the animal against the pathogenic action of other antigens (living bacilli or toxic extracts), and *therefore that these reactions are not exclusively specific.* Gley and Le Bas (1897) showed at the same time that a non-pathogenic dose of peptone, insufficient to prevent the coagulation of the injected animal's blood, protects this animal against an ordinarily fatal dose, and that *this immunity is very rapidly acquired in a few minutes.* Hence the name of *tachyphylaxis* given to this phenomenon.

Schenk (1889) made the same observation for placental extract, and Lambert, Ancel and Bouin later (1910) showed that a first injection of a non-pathogenic dose of a large number of extracts: testicle, thyroid, liver, brain, muscle, kidney, etc., immunized in a few minutes (skeptophylaxis) against the injection of a fatal dose. In this case the immunity was not an exclusively specific one: the first injection of the extract from one organ not only protected against a fatal injection of the same extract, but also against the extract from any other organ.

This category of phenomena should also include *passive anaphylaxis,* first studied by M. Nicolle, Charles Richet (1906–1907), and more recently (1910) by Novy and his collaborators. This research showed that by injecting into a normal animal first a small amount of serum from an anaphylactized animal, and then, shortly afterward, some of the original antigen, there resulted an anaphylactic crisis exactly as with a prepared animal; and that it was possible to prevent this crisis by a small injection of the same antigen.

An anaphylactic crisis is also caused by injecting into a normal animal a mixture made *in vitro* of serum from an anaphylactized animal with the antigen.

In this last case, the mixture therefore of serum with antigen acts in exactly the same way as an organ extract, a peptone, or as other directly toxic albuminoid products, so that all these products can be grouped under the common name of *anaphylatoxins.*

The results of these experiments can be summarized as follows:

1. Certain albuminoid products as such, or partially digested (transformed into albumoses, propeptones, peptones) which when injected in non-pathogenic doses cause the anaphylactic state (active sensitization), are able to cause at first injection a crisis similar in every way to anaphylactic shock, when a strong dose is injected into the veins.

2. The injection of a non-pathogenic dose of these products immunize in a few minutes against a fatal dose, exactly as in the anti-anaphylaxis of Steinhardt and Besredka.

We can conclude therefore that:

The crises which follow the second injection of an antigen, and the first injection of an anaphylatoxin are caused by reactions of the same kind; or, in other words, the normal organism is in the same state of sensitiveness to anaphylatoxins as a prepared organism is to a second dose of the specific antigen.

PHYSIOLOGICAL AND PHYSICOCHEMICAL CAUSES OF THE FORMATION OF ANTIBODIES IN EXCESS BY ANTIGENIC ACTION.

We know now *how* and in what circumstances an animal becomes anaphylactized; there remains to explain *why* anaphylaxis exists, and in particular:

1. Why heterologous albumins and biologic colloids as a class are antigens.

2. Why the process of immunization by albuminoid antigens is complicated by pathologic manifestations.

3. Why diphtheria and tetanus toxins are exceptions to this general rule.

4. Finally, why crystalloids are not antigens.

The result of our summary of the above researches as a whole is that the process of immunization consists in the production by the organism of an antibody which is found in excess in the blood or in the tissues of immunized animals.

This antibody neutralizes in all cases the actual pathogenic principle of the infecting agent: an organism vaccinated

against Eberth's bacillis becomes better able to resist typhoid infection. Where the bacillus acts solely by its albumin (cholera, typhoid fever), or simultaneously by its albumin and its toxin (certain pneumonias, dysenteries, meningitides), the neutralization of the albumin-antigen by the antibody in excess causes a pathological reaction.

In such cases, the pathological manifestations which characterize disease are caused not by the direct action of a bacterial poison, but by a reaction resulting from the combination of antigen with antibody.

It is easy today, by carefully analyzing these experimental facts to understand the causes of the confusions, of the apparent contradictions and of the errors in interpretation of certain experiments: *The process of immunity is never a simple reaction, because biological antigens are never chemically simple substances.* The simplest of all, a diphtheria or tetanus toxin, is a mixture of a large number of complex compounds arising from the culture fluid on the one hand, and from the bacillus on the other. The bacillus body is very probably composed of several kinds of albumins and of substances derived from these albumins, which, when dissociated in the infected organism, may each on its own account be anaphylactic or "antigenic" and may cause different chemical, physiological and pathological, direct or secondary, reactions. Some produce antitoxins, others anaphylactic antibodies, still others produce antibodies which are both antitoxic or anti-infectious and anaphylactic.

With toxins or very virulent bacilli, certain directly pathogenic principles are so predominant that the reactions caused by the other antigens are practically negligible; in many other cases (syphilis, malaria, trypanosomiasis, typhoid fever, etc.), the contrary has been found: In the case of albumins of only a slightly toxic nature the anaphylactic reactions are predominant.

We can consider as the two extremes in this order of ideas: on the one hand the filtered broth cultures of tetanus or diphtheria (toxin) directly and nearly exclusively toxic without anaphylaxis; on the other hand a heterologous serum or white of egg exclusively anaphylactizing; and between these

two extremes we shall find all the intermediaries, that is immunity complicated by more or less anaphylaxis.

We now have sufficient basis to understand the cause of the reactions from antibodies in normal quantity or in excess:

All antigens are heterologous colloids; colloids can neither be assimilated nor eliminated without having first been changed into salts or into crystalloids.[1]

A rabbit can readily absorb horse serum by mouth without ever becoming ill. The reason for this is that the serum thus absorbed penetrates into the blood only after having been digested.

On the other hand we know (Hamburger and Moro) that horse serum injected into the blood of a rabbit always finally disappears and we know that it is not eliminated as serum.

The chemical study of these phenomena is far from complete, but judging by what we do know, we can well assume that serum injected into a vein undergoes the same transformations in the interior of the organism as in the digestive tract, in other words, that it is digested. This digestion occurs in organs which normally are not adapted to this function. They may be induced to so act by repeated injections of serum, and then produce antibodies in excess which *contribute* toward this digestion, as characterized by the precipitation of horse serum *in vitro* and *in vivo*.

The antibodies found in sera of immunized animals do not digest their respective antigens *in vitro*, therefore, they do not contain all the ferments necessary for complete digestion.

Such antibodies as we have so far been able to obtain in sera must be considered as substances which *contribute* to this digestion, which prepare for it by fixing themselves to the antigens, and which give *in vitro* only the first phase of a series of reactions which, effected in the organism, terminate by the total disintegration of the albumins.

[1] Certain crystalloids, such as antipyrin, quinine, some mercury salts, become indirect antigens in the organism, either by forming colloidal compounds with certain substances of the organism, or by transforming certain substances of the organism, which then become antigens (indirect anaphylaxis of Charles Richet).

The causes of the differences in the reactions caused in the organism by the different antigens—immunity without anaphylactic shock, immunity accompanied by anaphylactic shock, or anaphylaxis alone as well as the action of the anaphylatoxins must be looked for, in the different stages of albumin disintegration on the one hand, in the nature and physicochemical or physiological properties of antibodies on the other.

All that we know today is that the antigens which cause the formation of precipitating antibodies and therefore predispose the organism to anaphylactic shock, have a total of properties characteristic of the albumins (animal fluids and formed elements, vegetable albumins, bacterial bodies); whereas antibodies produced by non-albuminous antigens (toxins) do not precipitate antigens and do not predispose to anaphylactic shock.

It has so far been impossible to obtain an antibody in a pure state and to separate from it the albuminoid substances of the serum which are not antibodies (and these always exist, as can easily be recognized by analyzing the liquid which floats above the precipitate formed in a mixture of a serum-antibody with its antigen); nevertheless, since there are albumin-antigens and peptone-antigens or polypeptides, it can be assumed that the differences between antibodies are of the same order as the differences between pepsin and kinase or erepsin.

Pepsin transforms liquid albumin into peptones by first precipitating them; kinase and erepsin transform peptones into amino-acids without precipitation.

We may therefore conclude that:

1. The cause of the production of antibodies in excess, and at the same time, of the state of immunity-anaphylaxis, is the obligation on the part of the organism to digest, by means of its cells, the antigens which have penetrated to its interior.

2. The excess antibody found in the serum and in the fluids is a substance which contributes to this digestion.

3. Salts and crystalloids are not antigens because they are assimilated or eliminated directly without previous digestion or disintegration.

IMMEDIATE AND SECONDARY RESULTS OF THE CONDITION OF IMMUNITY - ANAPHYLAXIS.

An organism which has been immunized or sensitized by an antigen is no longer a normal organism, and it will remain abnormal as long as it will produce antibodies in excess.

The principal object of research concerning active immunity up to the present, was to obtain an immediate result: in immunity an accrued resistance against spontaneous or experimental infection; in anaphylaxis, a more or less severe rapid crisis or vaccination against this crisis.

It was known that although in certain cases (tuberculosis, syphilis) immunity and anaphylaxis ceased to exist during the period of infection in the large majority of cases, immunity and anaphylaxis are more or less lasting chronic states; and we have seen above (Arthus' phenomenon) that experimental intensive immunization of animals ends most often in chronic morbid states.

When horse serum in very small doses (0.01 c.c. to 0.1 c.c.) is injected into the vein of a rabbit, and when this injection is repeated daily, or even two or three times daily for several weeks, no crisis of acute anaphylaxis is ever observed, although the rabbit serum after the first fortnight becomes a strong precipitant of horse serum. The immunity of the rabbit against these injections is explained by the action of the small doses which are vaccinating one for the other.

If, after this series of injections which occasioned no noteworthy incident, the rabbits are kept at rest and under observation, it is found two or three months later that, out of a dozen animals so treated, one or two will show nerve palsies, others dermatoses with alopecia, others rheumatism; and even if no accidental infectious disease interferes with the experiment, at the end of a year only one or two animals will remain alive. All the others will have been affected by more or less well characterized chronic diseases, and will have succumbed to cachexia.

Similar phenomena are observed with all horses that have been intensively immunized for the production of antitoxic or antibacterial sera.

All these animals at first become less active and vigorous and often succumb to internal hemorrhages caused by a rupture of the liver. At autopsy in a certain number of immune horses A. Petit and G. Loiseau[1] found the following lesions: "marked changes in the hemolymphatic organs, which are the seat of definite hyperplasia (spleen and bone marrow); the endocrin glands show evident signs of hypersecretion; the liver and especially kidney show quite definite lesions."

The results of repeated injections of foreign proteins into the tissues and organs of guinea-pigs have recently been studied by W. T. Longcope[2] and by T. Harris Boughton[3] who found degenerative lesions of the small arteries in nearly all organs excepting the lungs. The lesion begins with edema of the endothelium, followed by granular degeneration and vacuolization of the cells with rupture of the intima. The nuclei may disappear (be expelled). Then comes a stage of regeneration with increase in the number of endothelial nuclei. The edema reaches the internal elastic layer which may rupture. This swelling and undermining may extend to the whole of the middle coat. There is no connective-tissue proliferation. The more serious lesions are found in the liver in the animals killed by shock or which died during the week following the last injection of protein. Longcope[4] also has described very important and interesting lesions consisting of round-cell infiltration, degeneration and finally necrosis with scar formation especially in the heart, kidneys and liver of rabbits repeatedly injected with egg-white.

In order to understand the nature and the pathogenicity of the morbid manifestations which an organism so treated may undergo, two phenomena must be taken into account:

1. The presence of the antibody in the blood and tissues.
2. The production of this antibody in excess by the cells of certain organs.

[1] Bull. Biolog. Soc., May 26, 1908, p. 869.

[2] The Relationship of Chronic Protein Intoxication in Animals to Anaphylaxis, Jour. Exper. Med., 1915, xxii, 793.

[3] Vascular Lesions in Chronic Intoxication by Proteins, Tr. Chicago Pathol. Soc., April, 1917, x, 156–157.

[4] Loc. cit.

The presence of an excess of antibody in the blood exposes the organism to a more or less violent anaphylactic shock whenever a new dose of antigen comes in contact with it.

Symptoms are explained by the formation of a precipitate which obstructs the capillaries and causes, in consequence, a sudden break in the nutritive equilibrium in the cells of various tissues, and especially in the cells of the nervous system.

The production of excess antibody results in hypertrophy and in lesions of nearly all the organs the reactions of which maintain the normal functions of the organism.

We saw above (A. Petit and G. Loiseau) that horses immunized against toxins or bacterial cultures show radical changes and lesions in liver, kidney, spleen, endocrin glands, hemolymphatic glands. Similar lesions are found in rabbits injected with horse serum.

These lesions of necessity depress the functions of these organs; and it is solely in these more or less pronounced depressions that the direct or indirect causes of the lesions of skin, digestive apparatus, joints, lungs (asthma, emphysema), nervous troubles (neurasthenia, cachexia, etc.) are to be found.

We are thus led quite naturally to assume that in all cases of chronic disease of unknown origin, the primary cause of the lesions and of the apparent symptoms must be looked for in the anaphylactic state brought about by the antigen.

Might it be possible to attribute the lesions observed at autopsy to a direct toxic action of culture fluid?

This is hardly probable since immediately after the first few small non-pathogenic injections, there is found in the blood of animals so treated a much greater quantity of antibodies than is needed to neutralize the injected doses of bacterial poison. There is even less probability in the case of rabbits injected with horse serum, which properly speaking, is not a poison.

A harmful action is certainly present since the organism sooner or later becomes ill. There is a breakdown of the physicochemical and therefore vital equilibrium of the affected cell; but this breakdown of equilibrium results not

from the direct combination of a foreign substance (poison) with the contents of the cell, but from the overproduction of a substance (antibody) which normally is produced by the cell in small quantities only.

Briefly: The overburdening of the cells entrusted with the production of antibodies causes the hypertrophy, the lesion and the insufficient functioning of the organ; and, consequently, the appearance of chronic disturbances.

ORIGIN OF CHRONIC NON-CONTAGIOUS DISEASES.

The lesions and the pathological states observed in animals intensively immunized or sensitized are caused by conditions which in nature occur only very rarely. They are sometimes observed in chronic infectious diseases of slow and very long evolution, particularly in tuberculosis, syphilis, malaria, the trypanosomiases, and it is impossible in these cases not to correlate the causes and results of the succession of crises, alternating with more or less long abatements in the chronic infections, on the one hand, with the repeated injections of living or dead antigens, on the other.

Preventive vaccinations as practised on man and domestic animals, usually do not lead to unpleasant consequences, because the doses are small and the injections not numerous. The immunity-anaphylaxis acquired by vaccinations is, however, in most cases of short duration.

Acute infectious diseases usually leave the recovered organism with a lasting immunity-anaphylaxis; but it has so far been impossible to establish with accuracy the relations which may exist, for instance, between an eruptive or typhoid fever contracted during childhood, with a dermatosis or arthralgia appearing in mature age. It is hardly possible to acquire accurate knowledge in these cases by experiment, because in order for the experiment to correspond exactly to any particular question, it would be necessary to consider entirely new and perfect organisms, which in all probability do not exist. On account of heredity and of the conditions of individual evolution each organism finds itself in a different

state of immunity-anaphylaxis; and even if these differences are not usually sufficiently pronounced to interfere with ordinary biological experiments, they do exert a decisive influence on secondary and distant reactions.

To these differences of "diathesis" must be attributed the different pathologic manifestations observed in the case of rabbits injected with horse serum. For the same reason injections of arsenobenzene will cause gastro-intestinal disturbances in certain individuals, dermatoses or arthritides or nervous disturbances in still others or perhaps all these symptoms at the same time; while in the majority of cases, there will be no apparent reaction.

It is solely by the state of previously acquired immunity-anaphylaxis that one can explain the idiosyncrasies, predispositions or hypersensitiveness of individuals to foreign proteins of all kinds, to drugs, to certain smells, to changes in temperature and to emotions. So that when one meets these same morbid states manifesting themselves chronically without any apparent immediate cause, the idea forces itself of its own accord that these diseases can have but one origin, a preëxisting state of immunity-anaphylaxis.

In order, therefore, to find a biological method of treating these diseases in conformity with the conception of the specificity of "sensitizing" and "shocking" antigens, it is necessary, above all, to search for the antigen which is the primary cause of the disease, and which may be different in each particular case.

That a definite susceptibility to foreign proteins existing in the form of dust and with which the patient comes in contact through the respiratory tract, as well as in the form of food which is ingested, may be responsible for a certain number of chronic states has recently been discovered.

The literature contains many reports of these cases and such diseases as hay fever, asthma, urticaria and eczema should always be studied with the possibility of such a foreign protein sensitiveness in mind. The studies of Goodale,[1] Long-

[1] Diagnosis and Management of Vasomotor Disturbances of the Upper Air Passage, British Med. and Surg. Jour., 1916, clxxv, 181.

cope,[1] Walker,[2] Schloss,[3] Cooke[4] and many others have brought out the fact that this hypersensitiveness depends upon an inherited tendency, the nature of which is unknown, that it can be demonstrated by applying some of the protein to a scratch in the patient's skin and observing the urticarial wheal which occurs locally within ten minutes and finally that this hypersensitiveness and the clinical conditions depending on it can be relieved by treatment either by removal of the offending protein or vaccination with an extract of it. In some of these cases the hypersensitiveness is to bacteria or their products.

The local reaction as well as the clinical conditions depend upon an excess of antibodies in the cells which at once combine with the foreign protein by virtue of their extraordinary affinity for it and form a product which is insoluble and poisonous for the cell and for the organism. Briefly, the method of treatment in chronic diseases is "vaccinotherapy" which has been so successfully studied and applied by Al. Wright in the treatment of certain acute infectious diseases; and it is in this direction that experiments were undertaken.

[1] The Susceptibility of Man to Foreign Proteins, Am. Jour. Med. Sc., 1916, No. 5, clii, 625.
[2] Studies in Asthma, Jour. Med. Research, 1917.
[3] Allergy in Infants, Am. Jour. Dis. of Children, 1920, xix, 433.
[4] Human Sensitization, Jour. Immunology, 1916, i, 3.

CHAPTER XI.

PRINCIPLES OF THE ANTI-ANAPHYLACTIC TREATMENT OF CHRONIC DISEASES BY ENTERO-ANTIGENS.

From Metchnikoff's work on intestinal flora it could be deduced that the digestive tract, and especially the large intestine must be considered as the principal source of all kinds of infections and of chronic intoxications. Metchnikoff thought that these intoxications were due to the development and to the secretions of certain bacilli, and that by modifying the reaction of the medium in which they lived, it would be possible to prevent their multiplication. He endeavored to obtain this result by causing in the intestine an acid reaction by means of the bacteria of curdled milk.

Allen,[1] S. Marbais,[2] A. Berthelot and D. Bertrand[3] and others tried to obtain the same result, *i. e.*, the destruction of poisonous intestinal bacilli, by bacteriotherapy based on the "vaccinotherapy" of Al. Wright.

Metchnikoff's idea of looking for the origin of gastro-intestinal disturbances in the normal intestinal flora is probably very sound, and the treatment of such troubles by the bacteria of curdled milk or by bacteriotherapy has often given very good results; but it was found, however, at the same time, that while the disease was cured, the intestinal flora was not appreciably changed.

Treatments by Bacillus bulgaricus or by intestinal bacilli were therefore efficient, although the mode of action was not in accordance with the theory.

[1] Vaccinotherapy, Levis, London.

[2] Bull. de la Soc. de Biol., February 20, 1915, p. 66.

[3] Vaccinotherapy in Chronic Enteritis, La Presse méd., 1917, Nos. 23 and 44.

Then again, we must not lose sight of the fact that the intestinal contents are not solely composed of bacteria, that they always contain more or less digested albuminous matter, and that the congested intestinal mucous membrane may allow this matter to pass into the blood.

We know that any heterologous albuminous substance which, undigested or incompletely digested, that is, in the form of albumose, peptone or polypeptid, has penetrated into the blood, will behave as an *antigen*, and we know that any ordinary occurrence, even a slight emotion, can make the intestinal mucous membrane permeable to these antigens, as well as to bacterial antigens.

An anaphylactic state, as well as the disturbances resulting from it, can thus be caused just as well by incompletely digested alimentary substances, as by intestinal bacteria or their secretions; but as it is easy to determine and to prove that the intestinal flora and the digestion of a normal man do not differ from those of a man affected by psoriasis or suffering from emphysema, the conclusion is necessary that the causes of these diseases must be looked for, not in the nature of the bacteria living in the intestine, nor in the nature of the albuminoid substances on which the organism feeds, but solely in the method by which it digests and assimilates both bacteria and albumin.

It often happens that of several thousand individuals living in the same surroundings and under the same conditions, only a few became ill with typhoid fever or cholera, and one wonders why the remainder escape infection: Why horses, rabbits, guinea-pigs, are not infected by the ingestion of the bacilli of these diseases, which are pathogenic for these animals, when injected into the peritoneum or into the blood.

In the case of man, we may assume a previous spontaneous immunization in certain cases, but in animals, this is very improbable. The only plausible answer to these questions is that the large majority of individuals who escape infection, and all animals who are never spontaneously infected, are refractory to these diseases.

And why are they refractory?

Simply because they either digest and completely destroy these bacilli, or they attack them not at all, in short, because these bacilli or their secretions do not penetrate into the blood as incompletely digested albumins or colloids.

Pathogenic bacteria differ from those which are not pathogenic principally because the first can live and multiply in blood and living tissue, while the others are destroyed by phagocytes or by proteolysis before having had the time to multiply; yet both the first and the second will by their albumins cause anaphylactic states.

Bacteria of the intestinal flora are thus not pathogenic, properly speaking, because they cannot multiply in the blood or in the tissues, but their albumins may penetrate into the blood through a congestion of the intestinal mucosa and cause an anaphylactic state in the same way as any other heterologous albumin.

From the whole of these conjectures and of the precise facts determined experimentally, one may therefore conclude that:

1. Chronic disturbances of nutrition which manifest themselves by different symptoms according to the affected organs or tissues, have for their common cause a state of anaphylaxis.

2. This state of anaphylaxis arises from the introduction into the blood of bacterial or of alimentary albuminoid substances.

3. The resulting illnesses may successfully be treated by antigens taken from the normal intestinal flora. This treatment is neither anti-infectious nor antibacterial but solely anti-anaphylactic.

Inspired by these considerations we undertook at random a series of attempts at anti-anaphylactic treatment, at first of some dermatoses, and later of all kinds of other chronic affections.

I. CASE REPORTS.

A. Dermatoses.—*Observation 1.—Indeterminate Dermatitis.*—M. F. W., aged forty-five years. For four years oozing red plaques varying in size from a pea to a fifty-cent piece

all over the body, and particularly on the legs. Insufferable itching. Sleepless nights, emaciation. General condition bad, attributed to insomnia. Transient gastro-intestinal disturbances.

The patient has consulted several specialists, and has tried several external treatments and changes in diet, without lasting success.

Examination of the Intestinal Flora.—No account was taken except of germs which grew in twenty-four hours' incubation on ordinary gelatin slants (meat-broth, peptone).

Found.—Colon bacilli 90 per cent., enterococci 5 per cent., indeterminate diplococci 3 to 4 per cent., very small streptococci 1 to 2 per cent.

Preparation to be Injected.—All the germs were mixed in 0.7 per cent. salt solution in the proportions in which they grew on the gelatin. The mixture was distributed in sealed ampoules, sterilized by heating to 70° C. for an hour.

Each ampoule contained about 1 c.c. of liquid with about 0.02 mg. of bacterial matter dried at 140° to constant weight.

Treatment.—First Series of Injections.—First injection at 2 P.M., 1 c.c. into the muscular tissue of the arm. Slight chills three or four hours after the injection. *No itching* at night, good sleep. Next day, slight general fatigue, slight pain and redness at the point of inoculation.

Second injection, twenty-four hours after the first, 0.5 c.c. followed every day for a week by injections, increasing the doses from 0.1 c.c. to the maximum of 1.0 c.c.

The patient no longer suffers from itching, the plaques have faded and are not so moist.

No treatment for the next month.

At the end of the month, the plaques are clearly on the road to recovery. There is no more itching, sleep is good, general condition much improved.

New Examination of the Intestinal Flora.—The same germs are found in the same proportions.

Serum Diagnosis.—The serum of the patient does not agglutinate any of the germs in a 1 to 40 dilution.

Second series of injections under the same conditions as the first, with this difference that at the beginning the dose was very small, 0.1 c.c.

Results.—At the end of the second series of injections, the plaques have completely disappeared.

For five years the patient has been in very good health, from every point of view.

Observation 2.—Urticaria with Phlyctenules.—M. L., aged forty-two years. General condition fair. Declared "fit" for active service at the beginning of the war. Discharged after three months for incurable skin disease.

The patient has lived for fourteen years in central Africa, where beginning with the first year of his residence there, he contracted a skin disease characterized by the appearance on the whole surface of the body, but especially on the back, of small, red phlyctenules with a small yellowish center. This center exuded a small amount of pinkish liquid which dried, leaving a red crust. Insufferable itching after the least fatigue together with sweating.

The patient has consulted many dermatologists, and has followed without success all the treatments recommended, among others, he has received several injections of his own serum. One of the dermatologists he consulted told him that his dermatosis was very similar to scabies.

The bacteriologic examination of the patient's stools gave approximately the same results as in the preceding case, and the same treatment was applied with exactly the same result.

The patient has never had a relapse, and has been in very good health for four years.

The second examination of his intestinal flora showed the same germs as the first.

These two observations taken at random among many other similar ones suggest the following reflections:

While the supposition was that one of the germs living in the large intestine and contained in the fecal matter of our patients must be the cause of their illnesses, we could not assume *a priori* that all the germs seen by the microscope in fresh or stained preparations of fecal matter, could share in the cause to an equal degree. On the other hand, as we had

no guide which could have suggested the choice of one germ rather than of another, we chose, to begin with, the germs whose cultivation was easiest and simplest: surface growths on gelatin slants, therefore, the commonest aërobes.

In order to recognize their morphologic characters, their biochemical and pathogenic properties, each germ was isolated in a pure culture, then cultivated in different media, and lastly injected, either mixed or separately, into mice.

It is to be noted here at once that the mice so treated never contracted a fatally infectious disease in spite of the relatively strong doses (0.1 c.c. of a twenty-four-hour broth culture). We were thus handling only innocuous germs.

Another patient was treated with a heterogeneous preparation and encouraged by the result obtained we entrusted the same material to Dr. Labonnette for the treatment of a serious case of eczema.

Observation 4.[1]—This patient had a long history of gastro-intestinal disturbances with abdominal and rheumatic pain at various times. In April, 1919, a seborrheic eczema of the trunk and scalp plus an oozing eczema of the perineum and scrotum appeared. The patient was given dead heterogeneous bacteria of which he took by mouth 2 mg. as an emulsion daily. Disappearance of the pains and of the eczema was almost instantaneous.

Observation 5.—Another patient was treated in a similar manner except that the development of pustules indicated additional treatment with a staphylococcic autovaccine obtained by culture of these pustules which was given.

Observations 6 and 7.—Two cases of psoriasis were also much relieved by the injection of entero-antigens. In one of these, a second course of treatment was begun ten days after the end of the first course but the local reactions were not more severe than the first—the patient was therefore not sensitized by the first course.

Case 7 received during his psoriasis and independently the Pasteur treatment for rabies—as a sequel to which the skin lesions healed.

[1] Observation 3 omitted in English translation.

Two facts are important: 1. The nearly complete disappearance of the cutaneous lesions in no case resulted in other morbid manifestations, such as asthma or acute articular rheumatism, which are quite frequent when one tries to "stifle" the evolution of cutaneous psoriasis by ointments.

We must therefore suppose that, in this case, the antigen treatment acted not only on the apparent symptom, but on the cause of the lesions as well.

2. Different antigens are not equally active. In one case the addition of an anaërobic bacillus, although in very small quantity to the vaccine, had a curative action which was evidently greater than that of all the other bacteria previously injected.

We shall see further on what may be the nature of this action. In this manner 25 cases of more or less serious psoriasis were treated. The most interesting cases were given us by Dr. Sabouraud whom I wish to thank here for his kindly assistance.

In all these cases, the antigen treatment gave far better results from the point of view of the disappearance of the lesions, of its harmlessness, and of the duration of cure, than all the other treatments previously advocated. One case only, treated for two months by an autogenous preparation taken by mouth (the patient refusing to be injected), showed no apparent improvement.

Struck by the particular activity of the anaërobic bacillus (Case 6), we wished to determine the importance of searching in each particular case, for the most active antigen. Convinced of the harmlessness of our preparations, we varied their composition, and even tried non-bacterial antigens.

Thus, of 25 cases of psoriasis, 12 were treated by autogenous bacterial preparations, 9 by heterogeneous preparations, 3 by intravenous injections of luargol.[1] The results obtained in all cases were about identical, and we can add that a psoriatic patient, bitten by a mad dog, was cured of psoriasis by antirabies treatment.

[1] Dr. Dalimier has treated 5 cases of psoriasis with luargol. Three were completely cured; in the other two luargol produced no results.

Observation 9.[1]—*Recurrent Psoriasis Caused by Iodine.*—One of these cases was of special interest. Treated in 1915, for the first time with an autogenous preparation, for psoriasis in small plaques spread all over the body, and completely relieved, the young woman returned in 1917 with the same plaques, this time localized exclusively on the back of the thorax. She stated that these plaques appeared some time after painting this region with tincture of iodine.

Relieved anew, but this time by means of a heterogeneous preparation containing a mixture of colon bacilli and of a small non-motile bacillus, she returned in 1918 covered from head to foot with a multitude of plaques which caused intolerable itching and which had appeared after the ingestion of an iodized preparation "taken on the advice of a friend," which was supposed to cure her of a little general fatigue. This time a series of ten injections of a mixture prepared especially with heterogeneous diplo-, strepto- and enterococci, conquered the eruption under the same conditions as previously.

The observed persistence of hypersensibility to iodine in this case, makes one believe that the treatment by the different antigens was *simply symptomatic*, and that it had not attacked the fundamental cause of the evil.

From all these observations it seems that, though the treatment of psoriasis is practically very simple, the theoretical explanation of it appears to be rather complex.

The identity of the results obtained in the majority of cases by autogenous and heterogeneous preparations, but of very similar composition, would lead one to think that the disappearance of psoriatic lesions results from a reaction caused by the same antigens or by closely allied antigens.

Observation 6 indicates the predominating action of an anaërobic germ which we did not use in any other case, while Observation 7, as well as the results from the cases treated with rabbit-marrow and luargol, seem to prove that the same results may be obtained by any antigen.

One must, however, take into account the difference in

[1] Observation 8 omitted in English translation.

doses of the different antigens which it was necessary to use to obtain similar results.

The total quantity of bacterial bodies used in from twenty to sixty injections, varied from 0.4 mg. to 2 mg., while the total quantity of marrow injected in fifteen injections and of luargol injected in ten injections can be estimated at from 1.5 to 2 gr., that is to say, a quantity a thousand times greater than that of the bacteria.

The same can be said of the action of the anaërobic bacillus (Observation 6) which seems to be at least 100 times as pronounced as that of all other bacteria put together.

The antigenic action on psoriatic lesions could thus be explained as follows:

1. Recovery is determined by reactions in the organism caused by antigens.

2. These reactions are all of the same kind, or at least very similar.

3. The same results can be obtained by different antigens in very different doses, which can also be explained by saying that antigens are mixtures in which the proportions of the active substance, always causing the same reaction, are very different.

The practical suggestion arising from the above would, therefore, be that in order to obtain the maximum curative result with the minimum harmful result, one must search for the proper antigen.

B. Asthma.—*Observation 10.*—M. M., aged forty-seven years, has suffered for five years from dyspnea which grows worse every year, and shows itself particularly in the evening after sunset, and lasts all night until 10 A.M. or 11 A.M. Cold and rainy days are usually much worse than good weather. Dyspnea is then accompanied by coughing with very difficult expectoration. During and since the war, this condition of asthma has become sensibly aggravated on account of the open air life of the patient who had to dig trenches.

The patient received in a total period of eighteen days two series of eight hypodermic injections of an autogenous bacterial preparation isolated from his own intestinal flora

and sterilized by heat. This was a mixture of colon bacilli, of Gram-positive diplococci and of Micrococcus tetragenus.

Several minutes after the first injection into the left arm, the patient felt "like a trembling," followed by a tingling and itching in the whole left side of the body and immediately afterward his respiration became easier.

Improvement continued during the course of the treatment. The patient can now (eighteen months after) go out and work in bad weather without suffering therefrom, sleep is normal, cough has completely disappeared. The general state is better than it has been for a long time, the patient feels younger. The attacks of asthma have not recurred for the last eighteen months. Gastro-intestinal functions, often disturbed previously have at the same time become completely normal.

Observation 11 (*Dr. Dalimier*).— *Hay Asthma.*—Mr. J. L., navy engineer.

Family History.—Mother died from cardiac rheumatism; father died at seventy-nine from arteriosclerosis. Neither parent suffered from asthma. Brother has slight and temporary hay fever. Both maternal grandparents suffered from hay asthma.

Personal History.—Scarlatina and whooping-cough. At twelve years, first attack of hay asthma. Since then, every year without exception, in the second fortnight of May, had an attack.

The minutest contact of a particle of hay is sufficient to bring on asthma. Wheat and barley have the same action, as also grapevine, but to a lesser degree. Flowers of any kind have no influence. Honey, however, it must be noted, sometimes produces some respiratory and gastro-intestinal disturbances. Never any attack on the ocean.

The attack is characterized by a very pronounced oculonasal catarrh, coryza and headache; then, after some days, dyspnea appears, asthmatic in type, very troublesome, especially at night. The attack lasts two to three months, with alternate increases and decreases, and leaves behind it an early morning dyspnea until the autumn.

Apart from this hay fever, this patient enjoys good health.

During the last twenty-five years, he has undergone all known treatments. Locally he has had his adenoids removed, he has taken nasal douches of hot air, and of various antiseptic or analgesic liquids. He has undergone several thermal cures: Luchon, La Bourboule, Le Mont-Dore, where he spent several consecutive seasons. He has tried ozone, which produced a notable and constant increase of the trouble: carbonic acid, and pollantin, without any benefit. The only measures causing relief have been arsenic by mouth, and "Doctor Tucker" applied direct.

Physical examination, April 15, 1919, normal.

Bacteriologic examination of the feces shows colon bacilli, diplococci.

Treatment.—As the patient, at this date (April 15, 1919) showed no morbid symptom, treatment was given from a preventive point of view. Autogenous entero-antigen, 8 subcutaneous injections, every fourth day. Very slight local reactions.

Patient seen again June 6. Has been in frequent contact with hay, in Paris and during his travels in England, beginning about May 15. It was only in the first days of June that oculonasal catarrh occurred to a very slight degree, without coryza or headaches. There is no trace of asthma. The patient, very pleased with his condition, states that this is the first time in twenty-five years that he has been so well at this time of the year, and he judges it useless to undergo the slightest treatment for the slight cough which still persists.

Observation 12 (*Dr. Dalimier*).—*Emphysematic Asthma.*—M. F., aged forty-one years, printing compositor.

Family History.—Mother rheumatic; father died at seventy-eight; no asthma.

Personal History.—Articular rheumatism in 1900, scarlatina in 1902, appendectomy in 1903, bronchitis in 1911, slight chronic lead poisoning. Two nervous crises during the last ten years, corresponding to lead intoxications. No children. His wife has had no miscarriages.

Permanent dyspnea since 1911, aggravated by attacks of asthma. Difficulty in breathing becomes considerable every

year from May to October, and the patient has found that it is increased by the inhalation of dusts.

He has tried codein, bromide, caffein, and iodide, and the only soothing liquid he now uses is "Doctor Tucker's Asthma Cure."

Classed as unfit for active service on account of asthma and emphysema.

Examination.—An obese man, heavy eater, evident signs of very pronounced pulmonary emphysema. Heart normal, blood-pressure 160/90. Urine: Neither sugar nor albumin. Slight pupillary inequality. Dyspnea on exertion with inspiratory spasm.

Diagnosis.—Chronic pulmonary emphysema, with intercurrent crises of asthma.

Fecal Examination.—Bacterial flora: Colon bacilli, diplococci, enterococci.

Treatment.—Autogenous entero-antigen. Ten subcutaneous injections, one every fourth day. Violent reaction at each injection consisting of local pain with inflammatory halo the next day, definite, even painful exaggeration of the respiration for twenty-four hours. After the end of this reaction, the patient feels each time much improved. After the termination of the series of injections, he has no more dyspnea; he gives as illustration of his improvement the fact that "he can now climb the Sorbonne hill by the rue St. Jacques without effort or trouble," whereas during the last ten years he was unable to do so.

C. Other Cases.—Detailed case reports of 32 additional cases comprising a wide variety of chronic morbid states have been omitted in this English translation.

The reports picture the remarkable results following the use of dead bacteria in the form of an emulsion (a vaccine) and administered either by mouth or by subcutaneous injection. In most cases, improvement is immediate. Practically complete relief of symptoms is experienced by the majority of the patients after at most fifteen treatments at one- to three-day intervals.

These cases include those with such diagnoses as the following: Neurasthenia, scleroderma, dysmenorrhea, meno-

pause, a large number of gastro-intestinal disturbances including several forms of enteritis and chronic diarrhea, gastroptosis, neuro-arthritis, rheumatism and the gastro-intestinal symptoms of tuberculosis.

SUMMARY OF OBSERVATIONS.

Two hundred and sixty cases of chronic disease, similar to those quoted were treated in this manner (with the collaboration of Drs. Cazin, Dalimier, Delettré, Dominici, Labonnette, Raspali, Richard, Smiechowska, and others).

In analyzing these cases, one finds from the first that the treatment by antigens prepared from the germs of intestinal flora, showed itself efficient, not only in cases of digestive disturbance and in urticaria, but also in many other cases, which appear to have no direct relation with the functions of the digestive apparatus. We must, therefore, conclude that, even if the primary causes of these diseases differ, *the reactions determining the pathologic symptoms must always be of the same nature.*

On the other hand, the minuteness of the curative doses (2 to 3 mg. by mouth and a few hundredths of a milligram in hypodermic injections) and the rapidity of the reactions caused by these doses, suggest that the bacterial antigens contain a much greater proportion of the active substance than peptone, animal proteins, milk or any serum which in certain cases of urticaria, asthma (Widal, Nolf, Paignez and Vallery-Radot Pasteur, and others), give similar curative results in doses a hundred or a thousand times greater.

The action of the bacterial preparations which were used in the cases quoted above were probably not "specific," in the sense of the antigens used in the vaccinotherapy of Wright, but their actions are *remarkably selective.*

GENERAL AND LOCAL REACTIONS CAUSED IN THE ORGANISM BY ENTERO-ANTIGENS.

Action on the Intestinal Flora.—We have already seen that the injections or the ingestion of our preparations, at the

doses used, do not appreciably modify the intestinal flora of the patients. A decrease of one bacterial species or another is sometimes observed in the stools after a fortnight's or a month's treatment; but the same changes are observed in normal non-treated persons; so that these passing decreases cannot be attributed to the action of the treatment.

We have never found a complete disappearance of any bacterial species living normally in fecal matter; on the other hand, we have found that certain pathogenic bacteria such as the paratyphoids or certain strains of colon bacilli completely disappeared after treatment by injection or ingestion of such dead bacteria.

We have never observed any marked agglutination reaction with any species of injected bacteria in the serum of treated patients fifteen, thirty or sixty days after the end of the treatment. The conclusion is therefore that the treatment, as applied, did not cause the formation of "antibodies in excess" in appreciable quantity.

General Reactions.—The first striking phenomenon after the first, or the first few injections or ingestions of an autogenous or heterogeneous preparation, is the rapid change of the patient's general condition. A direct action on the nervous system is nearly always observed which is shown by lassitude, a need for sleep, relaxation and rest, a general lull which is in no wise disagreeable, which may last several hours, rarely two or three days, and is usually followed by a long period (several weeks or months) of surprising exhilaration. The patient feels himself "being born again," he feels a surprising need for physical and mental activity, and can undertake without fatigue work, which a few days before would have seemed beyond his strength. Sometimes the period of lassitude is so short and slight, that the period of exhilaration seems to appear all at once. In other, less frequent cases, the first doses of the preparation are followed by headaches which may last for several hours, by chills or by a slight rise in temperature. Still more rarely, the symptoms of the disease are seen to increase slightly. Asthmatics may have a more violent crisis, the itching in dermatoses increases, psoriasis plaques become darker; but these aggravations

never last long, are not a contra-indication to further treatment, and are always followed by appreciable and rapid improvement. At the most, it may sometimes be necessary to diminish the dose. If this is necessary only one-tenth or even one-hundredth is given.

Local Reactions.—When the treatment is applied in the form of injections, the reactions at the point of inoculation vary considerably. Sometimes redness, and a more or less painful zone may persist for one to three days: at other times the injection leaves no other trace than the small needle point.

If the treatment is by ingestion, one often notes, on the first and second days a slight pain in the epigastrium. This pain is only slight and manifests itself only on pressure in the epigastrium.

Whether the treatment is applied by injection or by ingestion, palpation discloses a sensitiveness over the gall-bladder and over the posterior part of the liver between the eleventh and twelfth ribs, near the upper edge of the right kidney.

The kidney is never tender, but undergoes important functional modifications. A phenomenon is observed similar to that which often characterizes the terminal period of acute infections (typhoid fever, influenza), namely, polyuria.

The reaction on the gastro-intestinal functions is quite remarkable. No matter what the preparation, autogenous or heterogeneous, or whether administered by injection or by ingestion, it acts as a regulator of the digestion and of evacuations.

In those cases where gastro-intestinal functions are normal, for instance in psoriasis, the beginning of the treatment is characterized by a tendency toward constipation, which may last several days and recovers spontaneously without medication.

The circulation is also influenced by the action of the entero-antigens. In the cases of either increased or decreased blood-pressure, one often sees hypertension diminish by 10, 20 or 30 mm. and hypotension increase by 10 or 20 mm. after the treatment.

THEORY OF CURATIVE REACTIONS. KENDALL'S EXPERIMENT.

How then may we explain the nature as well as the mechanism of these curative reactions?

In order to answer these questions we must remember that:

1. Every normal or abnormal function of an organ, a gland or a tissue depends on the central nervous system, so that all the modifications of the physiological equilibrium of a cell may be caused or arrested by the direct or reflex action of the nervous centers.

2. Whatever be the cause of a lesion or of a functional disturbance of an organism, the pathologic symptom will be always caused by a nervous reaction.

3. Each functional disturbance of a cell can be but the rupture of the nutritive and respiratory equilibrium of this cell.

In this way, an emotion causes in certain people enteritis, dermatosis or an attack of asthma. This means that certain psychic centers have reacted on the trophic centers of the bulb, that their excitation has interfered with the capillary circulation of the intestinal or pulmonary mucosa or of the skin.

It is therefore in the excitation of the nervous centers that the initial cause of the disease must be looked for; it is likewise the nervous centers which prepare the lesions and which set off pathologic symptoms through the reflex action of the lesions.

In many other more numerous cases, the initial cause of the disease is an agent which is exterior to the organism: a poison, an antigen or a traumatism. It is this agent which disturbs the nutritive equilibrium of the cells and which thus prepares the lesions; but the maintenance of these lesions and the reactions causative of pathologic symptoms are still governed by the nerve centers.

To make this argument more plain let us suppose the presence of a stone in the gall-duct. The stone manifests itself by violent pains, because the walls of the canal contract

before and behind the stone and prevent it from passing. Morphine or atropine will relieve these pains by relaxing the walls of the canal so that the stone continues on its way without causing the slightest harm. The primary cause of the evil here is therefore the formation of the stone and its entry into the canal. It is likewise the stone which *prepares* the traumatic lesion of the walls of the canal, but it is the reflex reaction of the nerve centers which *maintains* the lesion and the pain. To abolish the sensitiveness of the nerve centers is to end the contractions and the pain.

In the same order of ideas, an anaphylactic state is created by preparatory injections of an antigen, and a fatal crisis is precipitated by the second injection of the same antigen, but this crisis can be avoided by the absorption of a sufficient dose of alcohol or ether (Roux and Besredka), or also by an injection of adrenalin (Milian). Here the primary, initial cause of the pathologic state is the preparatory injection of the antigen which causes the formation of the antibody by certain cells. The resulting lesion is localized in these cells; there is no symptom. The anaphylactic crisis is caused by the action on the nerve centers of the precipitate which results from the combination in the blood of the excess antibody with the antigen of the second injection, suddenly disturbing the general nutritive equilibrium and more especially that of the nerve centers. A sufficient dose of alcohol or ether anesthetizes the nerve centers, while adrenalin contracts the capillaries and prevents the precipitate from reacting in them.

As in the case of stone, so in the case of the antigen, it is through the nerve centers that the pathologic manifestations may be relieved or prevented.

It is interesting to quote here, on this subject, an accurate experiment of E. C. Kendall, inspired by the work of Crile on the rôle of the suprarenal capsules in Barlow's disease. This experiment as reviewed in the *Presse Médicale*[1] deserves to be quoted *in toto:*

"Operating on dogs, Kendall slowly injected intravenously

[1] Kendall, Edward C.: Experimental Hyperthyroidism, Jour. Am. Med. Assn., lix, 612. From the *Presse Médicale*, 1917, No. 59, p. 612.

amino-acids. The animals had been previously thyro-parathyroidectomized, and into some of them there was injected, before or during the introduction of amino-acids, the active principle of the thyroid (Kendall).

"The observed results allow of the classification of the animals into two groups: Some had abundant diuresis and their temperature increased, sometimes reaching 113°. Their respiration became accelerated, and deep; their pulse became rapid. Nervous excitability was increased, and there were rigors accompanied by spasms which suggested the contractions of tetany.

"Other animals showed quite different manifestations: urine was scarce, temperature remained normal, pulse was small and regular, respiration feeble and superficial, nervous system greatly depressed.

"Between these two types intermediate forms could be observed, and sometimes tetanus was seen to develop after a period of depression.

"Among the conditions intervening to modify these symptom-complexes, the influence of food is important. The depressive form is observed with digesting animals, the tetanic form with those fasting for twenty-four or forty-eight hours.

"The effects of thyroid extract are quite varied. If thyroid extract is introduced before the injection of the amino-acids, the depressive phenomena predominate.

"Since amino-acids determine under experimental conditions, results diametrically opposed, one is led to suppose that they undergo in the organism changes which modify their properties. It has long been known that they are transformed, at least in part, into ammonia and urea. It was therefore interesting to determine the proportions of these substances in the urine excreted by these experimental animals.

"When the symptoms of nervous excitation predominate the quantity of urine is often considerably increased. A dog weighing twenty-four pounds, in one hour excreted 1760 c.c. of urine. Before the experiment, urea formed 80 per cent. of the total nitrogen in the urine but during the experi-

ment, urea fell to 15 per cent. As the ammonia did not increase, the conclusion is that the urine contains a new substance. This new substance (X) deserves the name of *preurea*, because if the urine stands for twenty-four hours, the quantity of urea increases up to a double amount.

"In making the same analyses of the urine of these dogs affected with depressive manifestations, an increase of ammonia is observed, but no substance X is found. The conclusion was therefore arrived at, that if the ammonia from the amino-acids is transformed rapidly into X, phenomena of excitation appear; if it is transformed only slowly, depressive manifestations predominate.

"The substance X, which might be the cause of tetany, is normally transformed into urea by the parathyroid glands, and this fact explains perfectly the rôle of these glands in the development of nervous manifestations. But in which organ is the ammonia transformed into X (preurea)? Kendall supposes that it is in the suprarenals, because the removal of these glands results in depressive phenomena.

"To verify this hypothesis, he made the following experiment: He removed the cortical layer of the suprarenal of an etherized cat, and submitted it to digestion with ammonium carbonate. This salt was transformed into a special substance different from urea. In repeating the experiment with suprarenals taken from cattle or from other cats, the result was absolutely negative; the ammonium carbonate remained intact.

"For a time Kendall was unable to understand the cause of these contradictions. Suddenly he remembered that before being etherized, the first cat had been for some time in the presence of two dogs which had terrorized it. This was a flash of light. The ferment which transforms the ammonia into preurea must be produced by the influence of nervous excitation. He resumed his experiments on cats previously frightened, and found again in the cortex of the suprarenal the ferment he was looking for. He also obtained a positive result, not however constantly, by submitting the suprarenals to the action of an electric current.

"Besides nervous influences, one must always consider

the action of hormones in the blood. As the suprarenal cortex acts on ammonium carbonate and changes it to preurea, it is probable that this salt stimulates the functions of the gland, at least under certain conditions. It was therefore of interest to resume the study of the effects produced by intravenous injections of the ammonium salt.

"As with amino-acids, both depression and excitation are observed. In the first case the animal was feeble and its respiration remained light and superficial; in the second, the animal was strong, and its respiration became deep. A process of oxidation must therefore take place to activate the suprarenal cortex.

"These two reaction-types are accompanied by absolutely characteristic urinary modifications. When the depression phenomena predominate, the urine contains ammonia; when the tetanus manifestations predominate, the ammonia decreases. Thus by analyzing the urine, all the unseen phases of the experiment are followed.

"These facts all demonstrate the rôle of the suprarenal in the development of the nervous excitations attributed to the thyroid, and, it must be added, also demonstrate the rôle of the nervous excitation on the functioning of the suprarenals.

"The main thing to remember is that this experiment brings out with accuracy the nature of the functional and chemical reactions caused by emotion. It was fright that caused the formation in the cortical layer of the cat's suprarenals of the substance X, the *preurea* which is not normally formed there, but which also appears after the injections of large doses of amino-acids into the veins of parathyroidectomized animals. Here the injection of amino-acids causes a big nervous excitation which determines in the cortex the same reaction as emotion: the formation of *preurea*."

THE INFLUENCE OF THE NERVOUS SYSTEM.

We have seen above how all kinds of morbid states may be cured by injections or ingestions of antigens, and we have pointed out that it is difficult, in these cases, to admit

a direct action of the medicine on the intestinal germs or on the lesions. We have definitely shown that, in general, the pathologic manifestations of a lesion can be caused only by nervous reactions, and we have also seen that, in preventing the nerve centers from acting, it is possible to prevent or to cure a hepatic or nephritic colic; we could therefore deduce that our bacterial preparations were curative only on account of their action on the nerve centers.

A confirmation of this hypothesis can be found in the results sometimes obtained by a method applied in China from time immemorial, called "cha-chin," from which "reflexotherapy" is derived, as practised during these last years by several European doctors, and propagated in France particularly by Peter Bonnier.

We have not been able to obtain definite information about "cha-chin." According to several European doctors, who have sojourned in China, the "cha-chin" method consists in pricking the patients with long needles at different parts of the body, and particularly at the joints, which must be pierced right through. Chinese doctors obtain by this method, and apparently often, rapid cures, even in serious cases of acute infectious diseases, and more particularly in cholera.

Peter Bonnier treated all kinds of infirmity and chronic disease (deafness, nervous ticks, asthma, certain dermatoses, gastro-intestinal disturbances) by touching certain points of the nasal mucosa with a galvano-cautery. According to his idea, by cauterizing the termination of the trigeminal nerve, he caused a reaction in the bulbar centers, which then acted to restore the peripheral cellular functions.

Whatever the explanation, there are cases of asthma and of serous mucomembranous enteritis which have resisted all other known treatments and have been undoubtedly and radically cured by Bonnier. In several of these cases the cure has lasted for over ten years.

Is it possible to attribute today the curative results of reflexotherapy—it appears that this method has proved itself of certain efficacy only in the ratio of 1 case in 10—to reactions of a kind differing from nervous shock?

When we consider the infinitely small quantities of our bacterial antigens which proved active in our trials (200 to 300 mg., and even less in Observation 6), we might assume that the tissues destroyed by cauterization or by injections, and later resorbed, act as antigens; but even then we would still have to explain the nature of the reactions caused by these antigens. The problem would be shifted, but not solved.

We have seen above, in the section on anesthesia, in the experiment of Roux and Besredka, in Kendall's experiment, how predominating the rôle of the nerve centers is in all preventive, curative or pathologic reactions.

In these cases, the action of the nerve centers on the symptoms, and sometimes on the deeper causes of lesions is indisputable, and as it must be admitted in comparing the results obtained by bacterio- and reflexotherapy, that in both methods the nature as well as the mechanism of the curative reactions must be the same.

The injections of antigens, as well as the cauterization of the terminations of the trigeminal, cause local curative reactions by the excitation and the reflex action of certain nerve centers.

In the cases treated in our laboratory and by our collaborators, nearly identical results have been obtained by autogenous or heterogeneous preparations.

Diseases apparently as different as psoriasis, eczema, enteritis, asthma, jaundice or chronic appendicitis have been treated with equal success by the same heterogeneous preparation.

From the point of view of the theories of immunity and anaphylaxis, as well as from that of the therapeutic indication which may result, it is therefore very important to note that in the diseases considered (and probably in many others): the curative reactions are not determined by the chemical affinities which may exist between the curative substance, the pathogenic agent and the diseased tissue or the antibody produced, but by an elective action of the curative product on the nerve centers.

If the anatomy and the physiology of the nerve cells were

known down to their intimate details, if we knew which nerve termination had to be pricked, burned or excited in order to affect a given nerve center and produce the desired general or local reaction, it is certain that on this knowledge one might base a method of treatment as efficient as it would be easy to apply; but as long as our ideas on this subject are as inexact as they are today, the results of this treatment will depend much more on chance than on the knowledge of the operator.

We are much better equipped today to fight chronic disease efficiently and intelligently by antigens.

The bacteriotherapy and the choice of the most efficient curative antigen in each particular case are not dictated by a chance discovery. This method is the result of logical deductions based on a long series of experimental researches, and confirmed by other experiments which allow us all to appreciate its value.

CHAPTER XII.

GENERAL SUMMARY: THEORETICAL DEDUCTIONS.

1. The work of Pasteur, of his pupils, and successors on pure cultures and on the specificity of germs in infectious diseases have led to the practice of *specific preventive vaccination* with bacterial cultures of attenuated virulence or with sterilized bacterial bodies.

2. The work of Roux and Yersin and of Behring and Kitasato (1889–93) on bacterial toxins and antitoxic sera has resulted in the practice of *specific serum therapy* in illnesses caused by toxins (diphtheria, tetanus, certain kinds of pneumonias, of dysenteries, etc.).

3. The work of Hayem (1885–1890), Kraus (1897), Belfanti and Carbone (1898), J. Bordet (1898), Ehrlich (1899), and others, on the reactions caused in the animal organism by repeated injections of blood serum, bacterial cultures and of other heterogeneous albuminoid liquids, have resulted in:

(*a*) The conception and application in medical practice of Wright's specific *vaccinotherapy* in the treatment of acute infectious diseases.

(*b*) The discovery of Charles Richet's anaphylaxis (1902) and the practical application of the *specific anaphylaxis* of Besredka and Steinhardt (1907).

4. At the same time the researches of Schmidt Mulheim (1880) on peptones of Roger and Josué, Delezenne and Beso (1893–1895), Gley and Le Bas, Ancel and Bouin (1897-1907), and others on organ extracts have led to *non-specific tachyphylaxis;* the researches of Widal and his collaborators, Abrami, Brissaud, Lermoyez, and others, on paroxysmal hemoglobinuria; of Nolf, James W. Jobling, Pagnez and

Vallery-Radot-Pasteur, and others (1910–1917), on the curative properties of peptones, autogenous sera or heterogeneous sera, of heterogeneous bacterial antigens in the treatment of acute, chronic or infectious diseases, have resulted in *non-specific sero-* or *proteosotherapy.*

5. Our researches (1912–1919) on the properties and the action of the organism of the colloidal substances obtained by synthesis, and particularly of arsenobenzenes proved to us that all the phenomena of immunity anaphylaxis and of tachyphylaxis, and the methods of preventive vaccination of vaccinotherapy, of anti-anaphylaxis, of serobacteriotherapy and of proteosotherapy, specific or non-specific derived from such phenomena are caused by reactions which, in principle, are of the same kind.

6. Our researches in the etiology and nature of chronic diseases, inspired by the whole of the preceding work, have resulted in the application in practice of *non-specific but selective bacteriotherapy.*

The application of this last method is based on the following considerations:

1. Any congestion of the gastro-intestinal mucous membrane may be the cause of the passage into the blood of incompletely digested albumins (bacterial or alimentary) which act as antigens.

2. Every antigen, heterogeneous to the organism, will cause in this organism a state of immunity and of anaphylaxis; it will be therefore more or less harmful.

3. Every specific curative or preventive antigen (vaccinotherapy, anti-anaphylaxis) will prevent or cure disease, but will at the same time reinforce the specific condition of immunity-anaphylaxis.

4. If a certain number of different antigens can give, in a given disease, the same preventive or curative result; if, for example, typhoid fever can be treated with equal success by specific bacteriotherapy or by peptone (Nolf), an attack of asthma or urticaria by the injection of a serum, by an autogenous or heterogeneous bacterial preparation or by peptone; syphilis or trypanosomiasis by atoxyl, arsenobenzene or luargol; these results will be obtained by very

different doses. Where several grams of serum or of peptone will be needed, a few hundredths of a milligram of bacterial bodies will suffice; several grams of atoxyl or of arsenophenylglycin will produce the same effect as a few decigrams of luargol.

In order to cause a minimum of harmful result and at the same time a maximum of curative result, we must therefore look for the most selective products for each particular case, or rather groups of antigens for those groups of diseases which present a group of characteristics in common.

It would thus be very important to prefer heterogeneous curative antigens to specific antigens whenever possible on condition that they be very selective, because in this way we will avoid the reinforcement of the existing state of immunity-anaphylaxis, and the small doses of heterogeneous antigen will not cause the formation of a new immunity-anaphylaxis.

THEORETICAL DEDUCTIONS.

1. Disease, no matter what its nature and its manifestations is always the result of the breaking-down of the normal nutritive equilibrium of certain cells. This breakdown of equilibrium, resulting in characteristic lesions and symptoms for each disease may have as origin:

(*a*) Either crystalloid chemical poisons which fix themselves directly on the cellular matter and modify its composition and its reactions.

(*b*) Or antigens which bring about the passage into the blood of antibodies in excess and oblige certain cells to perform greater work to the detriment of their normal functions;

(*c*) A direct excitation of certain nerve centers by a poison, an antigen or an emotion.

Pathologic manifestations will always result from the reflex reactions of the nerve centers.

2. Most, if not all, non-contagious chronic diseases, as well as idiosyncrasies, have as primary cause antigens of intestinal origin; as determining cause, the anaphylactic state of certain tissues; as "exciting" causes, the reflexes of the nerve centers.

3. All and any medicines or methods of local or general application which have shown themselves to be in any degree efficacious in the treatment of these diseases, act fundamentally through the nerve centers. The degree of their efficacy depends on their greater or less selective action on a given nerve center, or portion of nerve center.

THE THEORIES OF IMMUNITY, OF ANAPHYLAXIS AND OF ANTI-ANAPHYLAXIS.

In order to understand the cause and the nature of the reactions which an organism may or must undergo under the influence of external agents, as well as the possible effect of these reactions on its evolution, it is necessary to consider the following:

1. The essential physicochemical properties of living matter.
2. The structure of a living being.
3. The general rules determining the nutrition of the organism and of its component cells, or, in other words, the conditions under which an organism can assimilate the substances which it needs in order to keep its tissues living and multiplying and to furnish energy to perform its work.

Without going into too great detail our knowledge today may be summarized as follows:

Living matter as found in the cells of all living beings, is made of albuminoid substances of which the composition and the physicochemical properties are very uniform.

Albumins are combinations of four elements (C, H, O, N) in fairly constant proportions, and of a dozen other elements in varying proportions. They form colloidal complexes, or "micelles," of which the constitution and intimate structure are unknown.

All that one does know at the present time on this point is that living albuminous "micelles" are complexes maintaining themselves at a certain constant state of physicochemical equilibrium, by drawing from their surrounding medium the substances of which they are composed and which they assimilate; and by eliminating the useless waste

from these transformating reactions, and by utilizing other substances the transformations of which furnish the energy needed for the work so performed.

An albuminous "micelle" thus may be compared to a moving engine, which, thanks to special affinities, draws from the medium through which it passes the fuel necessary to produce its working energy, and at the same time matter identical to its own in order to keep its parts in good repair and even to strengthen them.

Albuminous "micelles" are the nutritive units of living matter, and all "micelles" of similar albumin have the same physicochemical equilibrium. "Micelles" of different albumins are distinguished among each other by differences in physicochemical equilibrium and it has been determined that the albumins of all beings belonging to the same plant or animal species are the same.

The albumins of different species have a different physicochemical equilibrium. Thus the white of egg from a hen has not the same properties as the white of egg from other birds, the casein of cow's milk is different from that of goat's milk; the blood, the muscular or nervous substances of the horse are different from the same substances from all other animals; whereas the salts and the crystalloids entering into the composition of the tissues of different plants and animals and which are derived from the albumins are always identical.

The specific differences between the "micelles" and the albumins which they form are therefore determined solely by differences in the proportions of the component elements, by the arrangement of these elements and by the different physicochemical equilibria resulting.

We do not know of any living being that might be constituted by a single free albuminous "micelle."

The *biological unit* of living matter is a *cell*, and a cell is an arrangement of a certain number of albuminous "micelles" of different structures, physicochemical equilibria and therefore functions which form a harmonious structural and functional whole.

At least three kinds of "micelles" can be distinguished in a cell: those forming the plasma, the nucleus and the external

membrane. All these particles form more or less dense agglomerations, are immersed in a clear liquid composed of salts and crystalloids. The cells themselves are immersed in a liquid which is composed of the same salts and crystalloids, and which in addition contains colloidal particles (plasma, lymph, etc.).

From the point of view of the nutrition of intracellular particles, we distinguish in the organism three zones or media through which nutritive substances must pass.

These zones or media are separated from each other by dialysing membranes which function by virtue of their density, and by virtue of the differences in tonicity of the liquids on either side of the membrane, and especially by virtue of the chemical affinities between the components of the membrane and of these liquids.

The organism as a whole begins by making a first choice of the substances needed for its nutrition from the first external medium. A second choice is made by the membranes of the digestive tract which allow to pass into the blood only certain selected substances which have been transformed into simple compounds. A third choice is made by the cell-membranes which absorb certain substances and allow the remainder to be eliminated by the kidneys and the intestines.

In this way, the alimentary substances absorbed by the mouth undergo a series of successive fragmentations and selective passages through the membranes before they, in a crystalloid state, reach the intracellular "micelles," that is the *nutrition units.*

A cell may allow certain colloids made up of small "micelles" to penetrate into its interior. If these "micelles" are homogeneous, that is to say, have the same physico-chemical equilibrium as those which compose the plasma of the cell, the cell may assimilate a certain number without undergoing appreciable change in its own general nutritive equilibrium; but in the case of "micelles" having physico-chemical equilibria differing from those of the cell "micelles," the nutrition equilibrium of the invaded cell and of the new "micelles" will be disturbed to a greater or less extent.

An *albuminous micelle,* considered as a unit of specific function can no more assimilate entire "micelles," whether homogeneous or specifically different than a house or a machine could be constructed from other complete houses or machines.

In either case, the first step must be to demolish, isolate and separate the individual materials, which will then possess no specificity and with which new units can be reconstructed according to the plans and specifications.

The differentiated superior organism is guided in its choice of food by its organs of sensation and by its intelligence; the second and third degree units are guided by positive or negative chemotaxis which is but the non-differentiated combination of feeling and intelligence; and it is likewise affinities or chemotaxis which determine the formation of antibodies as well as the action of these latter on their antigens.

In order to well understand the mechanism of the results which these reactions may have for the entire organism, we must always remember that:

1. The work of demolition or of digestion for each nutritive unit must take place outside of its interior. The particle, the cell, and the entire organism, expel from their interior beyond their protecting membranes, the substances (antibodies) or, more generally speaking the energy which is needed for the digestion or transformation of foreign substances (antigens). This is done by that chemotaxis which by sensation, intelligence and memory can act at a distance. Thus it is that the sight of food causes the sensation of appetite and the secretion of gastric juice, and that the sight or odor of individuals of opposite sex causes amorous feelings and corresponding reactions of the reproductive organs.

2. In differentiated organisms each functional unit, while its reactions obey its own chemotaxis, must also conform to the chemotaxis of the whole. The "micelle" is influenced by the chemotaxis of the whole cell, the cell by the chemotaxis of the organism, the organism by the surroundings and the society in which it lives, and so on; and the history of the greatest organization of units, the society of nations is

reëchoed inversely by the same routes back again to the "micelles."

In order to understand in its entirety, the mechanism by which the animal organism can live normally, become ill and recover, we must also take into account the fact that the individual reactions of "micelles" and of cells, determined by specific chemotaxis are influenced also by the reactions of the central nervous system which dominates the functions of all the units of the organism, and can by itself disturb or readjust the nutritive equilibrium of these units.

It is always the central nervous system which, in the last resort, reëstablishes normal equilibrium; or, more accurately, which *establishes a new general equilibrium* in an organism which has been influenced more or less seriously by a heterogeneous substance; and the influence of the central nervous system will be all the greater, as it will have attained a higher degree of development.

All these considerations lead us to conclude therefore that an organism is absolutely incapable of assimilating colloid particles which are specifically different from its own without digesting them. This results not from a defensive biological law, but simply from the physicochemical properties of its structural and functional units.

This having been stated, the theory of immunity and of anaphylaxis may be formulated as follows:

Every bacterium, every substance which penetrates in a colloid state, into the blood or the tissues, or in other words, into the interior of an animal organism must be transformed into salts and crystalloids, that is, must be digested in order to be assimilated or eliminated.

Every organism, by its cells, glands or organs normally produces a certain quantity of the substance, or more exactly of a series of substances which carry on this digestion.

When an organism has once been obliged to perform this operation, it continues to produce digestive substances in quantity greater than normal. It is then immunized and anaphylactized.

All the substances which the organism is obliged to digest in its interior are *antigens*.

The digestive substances normally produced by the organism are *normal antibodies.*

The *excess antibody* found in the blood and in the fluids of an immunized anaphylactized organism, is the excess of *one of the digestive substances* of which the whole constitutes the normal antibody. The excess antibody found in the serum of immunized animals is a substance which *contributes* to the digestion of the corresponding antigen, without being able in itself to finish this operation.

Reactions between antibodies and antigens are specific, but are not always exclusively so.

Thanks to the antibodies in excess, the organism will digest more easily and more rapidly antigens which have determined the excess of these antibodies and the results will be:

1. A certain degree of anti-infectious or antitoxic immunity in those cases where the antigen is a germ which is pathogenic by its albumin or by its toxin.

2. A certain chronic morbid state determined by the functional insufficiency of the organs assigned to the production of the excess antibodies, and lasting as long as the overproduction of the antibodies.

3. Anaphylactic crises more or less acute and serious, whenever a new and sufficient dose of antigen will suddenly combine with the excess antibody and form a precipitate.

Thus acquired anti-infectious immunity consists in the ability to digest a certain dose of infectious germs before these germs have had time to multiply so as to become pathogenic; and the organism acquires this property by producing a series of intracellular and extracellular digestive ferments. One of these ferments is the excess antibody.

The first phase of this digestion, that is, the combination between the antigen and the excess antibody, occurs therefore outside the cells, in the fluids of the organism. If the quantity as well as the quality of the antigen is such as to form an abundant precipitate with the antibody, the defensive act of the organism, the neutralization of the infectious agent, will be accompanied by pathologic manifestations which constitute the anaphylactic crisis.

The mechanism of *anti-* or *tachyphylaxis* must therefore be considered and explained in two different ways:

1. As a specific neutralization of the antigen by the excess antibody.

2. As a reflex reaction of the nervous centers on the intracellular metabolism caused by the selective action of certain antigens on the nerve centers regulating cellular nutrition. In this case, the reciprocal specificity of antigens and antibodies does not come into play, or plays only a secondary rôle.