workers, who have banded themselves together to protect pharmacy, under the respected and revered banner of the American Pharmaceutical Association.

The moral effect of a large membership is well known to all thinking men; hence if the effort of the present members and workers should be reinforced by your co-operation, even greater results could be obtained; therefore why delay doing your part to increase the effectiveness and stability of the protection you enjoy as a member of a respected profession.

Come, join our ranks and help to protect pharmacy against those who would destroy it.

Let me call your attention to the words of Lowell: "No man is born into the world whose work is not born with him; there is always work and tools to work withal; for those who will and blessed are the horny hands of toil."

THEORIES UNDERLYING THE USE OF ANTITOXINS AND VACCINES.*

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The action of antitoxins has so definitely passed beyond the stage of pure speculation that I think there will be little difficulty in expounding the theories underlying their use. With regard to vaccines, likewise, we have come to describe more clearly their mode of action without the use of a terminology recognized only by the initiated few.

Out of studies in immunology—the science dealing with the mechanism of contagious diseases—have developed methods by which the body may be assisted either to prevent disease-producing germs from gaining a foothold, or to eliminate them after they have become established.

The disease-producing bacteria are classified in various ways according to their functions. For our present purpose, the classification of most interest is that which considers the bacteria according to their manner of causing disease. Thus we find that one group of bacteria produces definite, soluble, and diffusible poisons and that all the symptoms of the disease are dependent on the action of these poisons upon the tissues for which they have an affinity. The second group of bacteria, on the contrary, do not produce soluble and diffusible toxins in appreciable quantity—their effect is brought about by a much more complicated process. We believe the production of disease by this class of bacteria is not a function in which they alone participate, but is the result of their interaction with the body cells.

Belonging to the first class of bacteria, the only organisms of interest to us are the *diphtheria* bacillus and the *tetanus* bacillus. These produce soluble and diffusible poisons—*toxins;* and spontaneous recovery from these diseases depends upon the generation by the tissues of a substance which will neutralize the toxins —*anti*-toxins. The requisite antitoxins can be easily produced in animals and

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transferred to the bodies of patients by administering the blood serum of the treated animals.

For obvious reasons, horses are generally selected for the production of antitoxin. The germs in question are developed upon a fluid artificial culture medium, veal broth. After the bacteria are removed from the full-grown culture, the sterile filtrate, containing the specific toxins, is injected subcutaneously into the horses. The horses react by the production of antitoxin. Enormous quantities of toxin are administered, and consequently enormous quantities of antitoxin are generated and stored in the blood serum of the animal. The antitoxins on the market then, consist of this blood serum either native or chemically treated so that the pseudo-globulin constituent of horse serum which carries with it the antitoxin principle is removed and furnished, in solution, in as pure a state as possible.

The strength of the antitoxin is determined by titrating it against toxin, the guinea pig being used as indicator. In defining a unit at present, there is no more reason to say that it is the amount that will neutralize 200 fatal guinea pig doses of a theoretically pure toxin, than there is, in defining an inch, to say that it has a definite relation to the circumference of the earth. Twelve inches make 1 foot, 36 inches 1 yard; 1000 units of diphtheria antitoxin constitute the immunizing dose, 5000 units the average initial curative dose; 1500 units is the official immunizing dose of tetanus antitoxin.

The action of diphtheria antitoxin may be clearly illustrated by imagining the disease to be due to a mineral acid generated within the body and poured into the circulation in constantly increasing quantities. According to the urgency of the case, let us inject a corresponding quantity of a harmless alkali. The acid is neutralized, the disease is controlled, and the fate of the patient now depends only upon the amount of damage done to the tissues before the alkali was administered.

In tetanus the case is slightly different. Tetanus toxin has a strong affinity for the nerve tissues, and the compound formed by this union cannot be split up by antitoxin. After symptoms of the disease have developed, there is but one hope in treating tetanus with antitoxin. If the treatment has begun before the lethal quantity of toxin has been fixed by the nervous tissue, and if the amount of antitoxin then administered be sufficient to neutralize the free toxin in the blood, there is a chance that recovery may ensue.

Bacterial Vaccines. For a clear understanding of the action of bacterial vaccines, it may be helpful to consider this subject from the standpoint of our knowledge of anaphylaxis. Anaphylaxis, in its derivation, means a lack of resistance—it is the opposite of prophylaxis. Richet, in his investigation of certain poisons derived from sea urchins, noted that an injection of these poisons into a dog, instead of rendering the animal immune to a second dose, actually made him more susceptible. The work of Rosenau and Anderson showed still more clearly the operation of this phenomenon.

Anaphylaxis concerns the effect of proteins or albuminous substances upon animals; it concerns *all* proteins whether they are poisonous in themselves or not; for instance, egg white and normal horse serum act precisely as the proteins of the plague bacillus or of the typhoid bacillus. And furthermore, the proteins of

dead bacteria act practically in the same way as the proteins of living bacteria. It must be remembered, however, that anaphylactic symptoms can be produced only by proteins foreign to the animal; that is, anaphylaxis cannot occur in a guinea pig from the repeated injection of guinea pig serum, nor can the symptoms be produced in a horse by the injection of horse serum.

If we inject a normal guinea pig with a dose of protein parenterally—that is, by any route except by the gastro-intestinal canal—it does not appear to suffer the slightest inconvenience. If, however, we inject this animal two or more weeks later, with the same protein, it will die within one or two minutes and with very definite symptoms accompanying death. This is a manifestation of anaphylaxis.

For an explanation of this phenomenon we must go back to the work of Prof. Victor V. Vaughan upon the chemistry of the protein molecule. Vaughan has shown that a protein, treated chemically according to his method, is split into two parts—the one poisonous, the other non-poisonous. The *poisonous* part obtained from all proteins is the same whether it results from the splitting of egg white or from the splitting of typhoid bacilli, the symptoms leading to death in the guinea pig are identical. This poisonous part then is a poison and has no other function nor effect; one dose has no bearing upon the effect of a subsequent dose, no hyper-susceptibility is produced, and no tolerance, even by repeated administration.

The *non-poisonous* part, on the other hand, is specific in its action. The non-poisonous part of typhoid bacillus protein will immunize an animal against typhoid infection, but not against infection with colon bacilli; the non-poisonous part of horse serum will sensitize a guinea pig to horse serum, but not to goat or sheep serum.

These results of Vaughan's work upon the chemistry of proteins suggest an explanation of the mechanism of anaphylaxis; they show us that instead of being the opposite of immunity, anaphylaxis is merely one of its manifestations; and furthermore they give us a clearer understanding of immunity itself.

When foreign proteins are injected into the tissues of an animal, the body cells at once set to work to remove this protein. They prepare a ferment capable of splitting the protein molecule, which possibly because of its size is not diffusible, into smaller fractions able to pass into the circulatory system and be thence eliminated. These fractions of the protein molecule are similar to those obtained by Vaughan in his chemical splitting; that is, a *poisonous* part which, after the first injection, is liberated slowly and is therefore harmless in its effect, and a *non-poisonous* specific part which stimulates the body cells to produce a specific ferment-like substance. About two weeks after injection, the protein has been entirely removed from the tissues, the poisonous part has been eliminated so gradually that no symptoms have resulted, and the non-poisonous part has stimulated the tissues to generate a large amount of specific protein-splitting ferment.

At this point we must pause to note that according to Vaughan, the protein-splitting ferment includes the anti-bodies so difficult to understand in the theories of the German and French schools of immunity. This theory of the American school does not contradict the fact established by Metchnikoff, and further eluci-

dated by Wright, that the white blood corpuscles play an active part in the removal of foreign proteins whether they be cells or fluids; nor is it out of harmony with the theory of Ehrlich, who gives to the group of anti-bodies—collectively the "ferment" by Vaughan—different names according to their functions.

The guinea pig, then, at the end of two weeks after the first injection of, let us say, horse serum, contains in his tissues no trace of horse serum; but he does have within his body a large quantity of protein-splitting ferment, which may remain in the tissues for a long time; and even if it disappears, the power to generate this ferment upon demand may remain permanently. If we now inject into this guinea pig a second dose of horse serum the proteins contained therein are at once attacked by the specific ferment; digestion occurs almost immediately, resulting in the liberation of a large quantity of the poisonous part of the protein molecule; the animal is overwhelmed by it and dies, usually in less than five minutes. A dose sufficiently large to cause death depends upon the method of injection; if injected into the circulation or into the brain 1/20 cc. is sufficient; if injected subcutaneously, however, at least 5 cc. is usually necessary.

Now as to the bearing of this phenomenon upon infectious disease—Vaughan has used typhoid fever as a typical illustration. Infection results from the entrance of a few typhoid bacilli into the tissues under circumstances which permit their growth and multiplication. There is normally present in the body a small amount of a non-specific protein-splitting ferment which attacks the typhoid bacilli, liberating the non-poisonous part which in turn begins to stimulate the tissues to the production of a specific anti-typhoid ferment. We know that in guinea pigs it takes from 8 to 14 days to produce enough ferment to cause serious symptoms of intoxication upon the injection of a second dose of the protein. Now this period corresponds exactly to the incubation period in typhoid fever. It is during this time that the typhoid protein-splitting ferment is produced in increasing quantities while the typhoid bacilli are rapidly growing in numbers. The ferment sets free the poisonous part in gradually increasing quantities with the appearance and progressive increase of fever and the other symptoms of the disease. This process continues up to the point where the number of typhoid bacilli destroyed each day equals the number reproduced in the lesion. This balance is maintained for a time until the number of bacilli destroyed exceeds those reproduced.

A patient recovered from typhoid fever, has remaining in his tissues a large amount of typhoid protein-splitting ferment, so that when typhoid bacilli again gain entrance to his tissues, they are at once attacked and destroyed before they have a chance to develop. Obviously there is no intoxication because the amount of typhoid proteins is infinitesimal compared to the amount necessary to result in anaphylactic shock.

It is now easy to understand the action of typhoid vaccine. When we inject beneath the skin a number of typhoid bacilli, their disintegration is started by the normal proteolytic ferments in the body. A second and third dose given at intervals of about 10 days increases the quantity of specific typhoid protein-splitting ferment. The theory of typhoid immunity by means of bacterial vaccines applies equally to the production of immunity to other infecting bacteria. The theory underlying the use of bacterial vaccines in disease is based on the

fact that the tissues affected are unable to produce a sufficient quantity of the specific ferment to overcome the infection. The injection of bacterial proteins in a healthy part of the body leads to the production there of these anti-bodies which are conveyed to the focus of infection through the circulatory system and thus assist the local cells.

It will now be clear that the requisites to success in vaccine therapy are, (1) that the vaccine injected must contain bacterial proteins identical in kind with those causing the infection; (2) that the ferment produced locally must come in contact with the infecting bacteria. For one with proper training it is not hard to determine the kind of bacteria causing an infection; nor is it hard to obtain either a stock vaccine representing these bacteria or to prepare an autogenous vaccine identical with them; and it is a very simple matter to inject these bacterial suspensions beneath the skin of the patient.

If the patient is not in the last stages of disease, there is not one chance in many thousands that his tissues will fail to produce the proper anti-bodies or ferments. If the patient shows no improvement as result of the treatment, it behooves the physician to use means by which the ferments may be induced to perform their function.

In some infections, as in staphylococcic infection, accessory measures are seldom needed, while in streptococcic infections they are nearly always necessary. In gonococcic infections of the urethra and prostate, the mere injection of vaccines accomplishes but little; in gonococcic infections of the joints, however, the vaccine is apparently sufficient.

We are indebted to Besredka of the Pasteur Institute in Paris for an improvement upon bacterial vaccines which constitutes a real advance in vaccine therapy. As said above, when the bacterial vaccine is injected beneath the skin a small quantity of the protein is split up by natural ferments and the specific non-poisonous part thus liberated stimulates the production of ferments which continue the disintegration until the maximum effect of the vaccine is obtained.

The ferment itself is composed of at least two constituents; one is specific and by Ehrlich has been called *amboceptor;* (the *opsonin* of Wright is a similar anti-body). This substance has the power of fixing itself to the bacteria, thus preparing them for digestion by another substance which is not specific but is always present in the blood of healthy animals, and because the latter completes the ferment action, it is called *Complement.* Besredka proposed that amboceptor be utilized to prepare the bacteria for the immediate action of the complement. Bacteria thus prepared for the action of the complement were said to be "sensitized" and the suspensions of such bacteria were called by him "sensitized vaccines." The advantage they have over ordinary bacterial suspensions is that they eliminate the period during which the specific ferment is being formed. "Sensitized vaccines" have already been used extensively in France and also to a certain extent in England. The published reports amply attest their superiority.

Anti-bacterial Serums. The so-called "therapeutic or anti-bacterial serums" include anti-streptococcic, anti-pneumococcic, and anti-meningococcic serums. These are prepared by the injection of horses, first with dead, and then with living bacteria. In the case of anti-meningococcic serum, injections of autolysed bacteria are alternated with the cocci themselves. The autolysate contains a toxic

substance which causes the production of some antitoxin. This serum, like anti-dysenteric serum, partakes therefore of the nature of both an anti-toxic and an anti-bacterial serum.

These serums depend for their activity upon substances called ferments by Vaughan, but according to the nomenclature of Ehrlich, "Anti-bodies;" that is, substances antagonistic to the bacteria. Used in sufficiently large doses, anti-bacterial serums have undoubtedly great value. The chief difficulty lies in the fact that no method has so far been found by which anti-bacterial serums can be produced comparable in potency with diphtheria antitoxin.

It is well known that a much larger dose of any curative serum must be used if it is injected subcutaneously than if injected intravenously. Realizing this fact and the relative weakness of anti-bacterial serums, there is but little doubt that their use intravenously will be resorted to in the future with increasing frequency.

Summary. 1. There are two classes of bacteria with regard to their method of producing disease: (a) those that produce soluble and diffusible toxins, and (b) those that do not.

2. The toxin-producing bacteria are the diphtheria bacillus and the tetanus bacillus.

3. Antitoxins, produced by injecting horses with the specific toxins, are antagonistic to the specific toxic products of the bacilli in a manner very similar to the antagonism between acid and alkali.

4. To the second class belong the great majority of the disease-producing bacteria.

5. The symptoms in the diseases caused by the latter, are probably the result of the action of their specific metabolic products, combined with the effect of the liberated poisonous part of their protein molecule.

6. Recovery from such infectious diseases depends upon the production of sufficient specific protein-splitting ferment to remove their causative bacteria from the tissues.

7. The amount of this specific protein-splitting ferment may be increased by injecting bacteria of the same kind beneath the healthy skin.

8. Immunity from infectious disease depends upon the existence in the tissues of sufficient specific protein-splitting ferment to dissolve invading bacteria before they have a chance to develop.

9. The rational administration of bacterial vaccines presupposes accurate diagnosis and the administration of bacteria identical in kind with those causing the infection. It depends furthermore upon the ability of ferments and antibodies to come in contact with the infecting bacteria.

10. "Sensitized vaccines" are superior to ordinary vaccines because they reduce the preliminary period during which the injected bacteria are being split up so that the non-poisonous part may be available for the production of specific anti-bodies.

11. Anti-bacterial serums—anti-streptococcic and anti-pneumococcic—depend for their activity upon their content in specific anti-bodies or ferments.

12. The amount of these ferments in even the best serums is relatively small and the serums must therefore be used in larger doses than has been customary in the past.

13. Anti-meningococcic serum is both anti-bacterial and antitoxic.

14. Since the efficiency of curative serums is increased many fold when administered intravenously, this route will be used more frequently than has been the custom in the past.

A CONSIDERATION OF AUTOGENOUS VACCINES.*

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Empiricism is dying. Throughout the last century and particularly its latter decades, the searchlight of truth has lighted up many of the heretofore dark places in the study and practice of medicine. The discovery of the causation of many diseases through bacterial agencies was epoch-making and led the way naturally toward the introduction of measures able to cope with such a foe.

During the last thirty years scores of men have been at work on this problem and have each added their little to the sum total of our present knowledge and from the time of Jenner one startling etiologic and therapeutic discovery has followed another, so that among the names destined to live will always be found those of Pasteur, Koch, Pfeiffer, Ehrlich, Behring, Wassermann, Nogouchi and others.

Bacteria are divided into two classes, the good and the bad—Saprophytic and Pathogenic. The Saprophytic bacteria are scavengers; they thrive best on dead tissues and assist in freeing the body of many waste products. Pathogenic bacteria thrive best on the living tissues of the host in whom they are capable of producing disease. Their pathogenic action is due to the liberation of the toxins they contain or the elaboration of poisons in the tissues of the host.

Of these bacterial toxins there are two main types: The Exo-toxins, contained in bacteria whose poisonous principles are capable of being dissolved out of the bacterial cell. To this class belong the Bacillus of Diphtheria and the Bacillus of Tetanus. The great majority of bacteria, however, produce Endo-toxins, or poisons which are incapable of separation from the cell bodies by any of our known filtration methods. Examples of this are the Bacillus of Typhoid Fever and the Streptococcic and Staphylococcic groups.

While bacteria are capable of producing disease it is not through their mere presence *per se,* for as we know, our persons in health permit of the culturization of numerous pathogenic bacteria, therefore, other factors must enter in and these factors comprise the natural defensive mechanism of the body against disease.

Natural Resistance: This varies greatly with the individual and has a certain selective action, for why is it that one person can harbor in his mouth virulent Pneumococci and Streptococci and yet can go through life without a single attack

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