4. The growth of these gradually replaces the initial calcification, and at five months only a trace of the process remains. The probabilities are that after longer time there would be a true bony fusion.

The final conclusions reached by this paper are:

1. Defects of the human skull can be covered by bone.
2. The bone may be secured from a portion of skull adjoining the defect.

FIG. 10. Edges of graft and peripheral bone at five months. 1. Edge of bone. 2. Edge of graft. 3. Superior surface. 4. Inferior surface. 5. Calcified connective tissue. (Cam. luc., Leitz, oc. 4 obj. 3, $\times 100^3$. Formalin, hematoxylin and eosin.)

3. This bone graft represents essentially the outer table of the skull, with the periosteum covering it.

4. No pedicle need be preserved in order to insure the viability of the bone graft.

5. Experiments on dogs show the graft to be solid at three months.

6. Histological examination shows that the bone remains viable and grows into its new position.

The object of this paper is to show that defects of the skull should be repaired promptly in order to avoid the occurrence of epilepsy and allied conditions.

THE DEFENSIVE PROPERTIES OF THE ORGANISM.*

BY S. C. DICKERSON, B.S., M.D., NEW BEDFORD, MASS.

It is an incontrovertible fact that the progress and science of medicine and the therapeutical applications for the relief of pathological conditions incident to disease, are the results of epoch-like growths. Although we must candidly and freely admit, while there are many imper-

fections and false conclusions inevitable in a science so intricate and so broad, based as it is on so many theoretical premises, still if we are patient, earnest and honest seekers after truth, we cannot fail to gather here and there, valuable and helpful facts from these pure hypotheses.

As you know, the causative agents of disease were anticipated through hypothetical reasoning and deductions, long before their discovery. And since, through the valuable work of Devaine, Koch and others, the germ theory of disease has become an established fact.

No age, no epoch in the progressive evolution of medicine has been able to solve all the problems, or any considerable part of them; and hence the solution of one problem leads to the probability of others. No sooner, therefore, were the causative agents of certain diseases established, than that very important and perplexing problem, "In what way does the body protect itself from these invading foes, and what are the defensive elements concerned?" arose.

This theoretical explanation of the defensive properties of the organism or the theory of immunity is the subject we intend to discuss in this paper.

In order to explain the theories of immunity, it will probably be more interesting and clear to begin with the defensive properties of the organism against soluble toxins like those of diphtheria and tetanus. In this class of infectious diseases the microbes become localized, elaborate their poisons, which are carried to distant parts of the body. The question naturally arises, What is the nature of these protective elements? The answer to, and the elucidation of, this question will shed considerable light on the defensive power of the organism in this class of infection. To answer this question satisfactorily, Ehrlich's side-chain theory of immunity must be brought into requisition. Ehrlich's attempt at standardization of diphtheria toxin gradually led him to this conception of immunity. He claims that the cells have side-chains or receptors which will combine with toxins. When a poison, tetanus, for example, enters the body and is not sufficiently powerful or concentrated to destroy the cells, these cells are stimulated to reproduction of the receptors corresponding to the particular toxin. According to Weigert's Law of Hyper-compensation, the receptors are produced in excess, and are then thrust off into the blood stream, and are known as antitoxin. Now what happens when the toxic elements enter the blood? They come in contact with the circulating receptors or antitoxin and their affinity is satisfied.

By a series of experiments Wassermann has shown that there are three stages necessary for the production of antitoxins or antibodies.

First, a binding of the haptophorous group of the toxin to the receptor.

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Second, an increased production of the receptors following the binding.

Third, the thrusting off of these increased receptors into the blood stream.

Wassermann has recently demonstrated the existence of these three stages experimentally.

It is a well-known fact that if a powerful toxin is heated to 148° to 150° C., or is kept for a long time exposed to heat, light and oxygen, it loses its toxic power. But it still has the power of satisfying through its haptophorous group the corresponding receptor. This innocuous toxin is known as a toxoid, $H + (T) + X$.

Some tetanus toxin which Wassermann had kept since 1896, and which had lost its toxic property, was used in the following experiments:

He injected this tetanus toxoid into a guinea pig, and from one to two hours afterward some fresh tetanus toxin was injected. He found that the lethal dose would have to be increased, because a part of the receptors were occupied by the toxoid (according to Ehrlich's theory). When, however, he waited somewhat longer, one to three days before injecting the fresh toxin, less than the minimum lethal dose tetanized and killed the animal, for in this case Weigert's Law of Hypercompensation had come into play, producing an increased number of receptors, without any formation of antitoxin, that is, freely circulating receptors as no antitoxin was found in the blood after injecting the toxoid; therefore Wassermann claims that the toxoid brings about a (1) binding of the haptophorous group with the receptors of the cell, and (2) an increased production of these receptors which remain attached to the cell, or sessile, and hence the toxophorous group is needed to bring about the necessary stimulation for the thrusting off of the receptors into the blood stream or the formation of antitoxin. This is a very important observation as you can see, since so many investigators claim that antitoxin can be produced by the use of toxoids.

The nature of the neutralization of the toxins by the antitoxins has been and still is productive of a great deal of discussion, and a wide difference of opinion. Ehrlich maintains that the neutralization is the result of a chemical reaction, supporting his views on the following observations:

1. Antitoxin and toxin can be titrated like an acid and an alkali.

2. Their union is hastened by heat and delayed by cold.

3. That combination takes place more rapidly in a concentrated solution.

Equally capable observers, Buchner being the chief exponent, oppose the chemical nature of the reaction, and explain it on purely physiological grounds. He claims that there is no interaction between the toxin and antitoxin, but when both are present in the body of an animal, the antitoxin stimulates the cells to resist the toxin.

The limitations of this paper will not allow me to enter into this discussion, but the evidence based on experimental observations seems to

support Ehrlich's view. Permit me to call your attention to one experiment which seems to me conclusive proof of the chemical theory.

From the researches of Meyers and Ramson it has been shown that tetanus poison is not absorbed via the blood or lymph channel, but reaches the central nervous system via the nerves; but the tetanus antitoxin, unlike the toxin, is not a neuropathic substance but follows the blood and lymph channels. Adrenal, as you know, strongly contracts the capillaries and thus blocks a particular area. Wassermann using a neutral or innocuous mixture of tetanus toxin and antitoxin, if he injected the hind paw of a guinea pig no tetanus developed. But if he injected some adrenal in a similar sized guinea pig, and waited till the capillaries were contracted, and then injected his neutral mixture, tetanus developed. His explanation is as follows: The path of the antitoxin was blocked, while the neuropathic path for the toxin was open, and hence the toxin was torn loose from its combination with antitoxin and hence produced tetanus. Wassermann found, however, if he waited two or three hours before using the mixture, the combination was so firm that the substances could no longer be torn apart. He could hasten the firmness of this union by using an excess of antitoxin. As suggested by Wassermann, the possibility of increasing this affinity by means of large doses of antitoxin is a point of considerable practical value in serum-therapy.

In passing from toxic immunity to anti-microbial, or immunity against infectious agents, we find the problem more complex, and the evidence and explanations to justify conclusions based on hypothetical deductions greatly at variance. This phase of immunity, like the toxic, is largely dominated by Ehrlich's views. Pfeiffer's reaction gave the initial impulse to investigations which have played such an important rôle in anti-microbial immunity. If a guinea pig immunized against cholera virus be injected with a virulent culture of the same into the peritoneal cavity, a clumping, finally disintegration and dissolution take place. Bordet's work on hemolysis, together with a great number of experiments, have shed considerable light on Pfeiffer's phenomena, which is the basis of the modern theory of immunity.

Bordet injected a horse's with a rabbit's xanthocytes, and found that the horse's immunized serum produced lysis of the rabbit's red blood corpuscles. If, however, this serum be heated to 55° C. for one hour, the hemolytic power was destroyed. But hemolysis could be restored by adding some fresh normal serum. Therefore the presumption arose that there are two bodies concerned in hemolysis and bacteriolysis. Ehrlich has demonstrated, the body destroyed by heat is the complement, while to the more resistant body he has given the name of amboceptor, intermediary body, or immune body. Therefore, lysis, according to his theory takes place by the amboceptor combining through its haptophorous group with the bacterial

or other alien cells, after which the complement unites with the corresponding Haptophorous group of the amboceptor causing the disintegration and finally solution of the foreign cells.

$H + N + X = \text{Red blood corpuscles}$

$H + H + X = \text{Amboceptor}$

$H + (L) + X = \text{Complement}$

The lytic element (L) dissolves the red blood corpuscles.

Formation of amboceptor

$H + N + X = \text{Red blood corpuscles}$

$H + H + N + X = \text{Tissue cells} = H + H + X$

$H + L + X = \text{Complement.}$

Investigators differ widely with regard to specificity of the immunity agents in hemolysis and bacteriolysis. There is considerable unanimity of opinion as to the specific nature of the amboceptor, but even this Ritchie claims is not unquestionable, because, "on the broad view of the theory of immunity the conception of specificity of the amboceptor is questionable, especially when we consider that the immune bodies are derived from the receptors or mediators concerned in normal metabolism; therefore, the assumption that the affinities of these side chains may be satisfied by other cells than the red blood corpuscles and bacteria."

As to the specific nature of the complement opinions are extremely divergent. Ehrlich believes that each series of immune bodies has a corresponding complement, while Bordet maintains the non-specific nature of the complement. It would be interesting, if not profitable, to enter into this discussion, but the limitation of this paper will not permit.

Observations of Wechberg and Neisser seem to indicate the specific nature of the complement in bacteriolysis, for if below a certain number of immunity bodies, or a great increase over a certain number be used, no bacteriolysis. But any increase of immunity bodies over the normal number has no effect in hemolysis.

Also anti-complements seem to prove the specific nature of the complement.

Oppenheimer claims that the complement is non-specific with reference to its action on cells but is specific with reference to its affinity for amboceptors.

There is considerable dispute with regard to the nature of the reaction between the bacteria, immune bodies and complement. Ehrlich believes that the amboceptor has no injurious effect on the invading cells, but are merely mediators, or go-betweens for the complement. Buchner and Metchnikoff, however, believe the amboceptor not only is bound to cell, but influences it, and that the alexine, or complement, merely completes the process.

Another important phase of this question is the origin and source of formation of these defensive elements of the body. Metchnikoff and his followers maintain that the phagocytes are the

chief protective agents of the organism against infection. His general phagocystic theory is so well known that we need not enter here into its discussion. New facts based on experimental investigations have caused a considerable revision of his first theory. Recently he contended that the origin and source of these immunity agents are the protoplasm of the leucocytes which attracts, kills and then englobes the invading cells. As you can readily see, the virtue of this theory is based on chemiotaxis, the pathogenic effect of which depends on the fact whether the bacteria attract, do not attract, or repel the phagocytes. On this theory, natural immunity can only be accounted for on the ground that "the phagocystic reaction is very pronounced and so effective that an infecting agent is invariably destroyed. In artificial immunity the immunizing process produced by the administration of small doses of bacteria, or bacteria in a state of diminished virulence, enables the phagocytes to become accustomed to them so that they can ultimately endure and dispose of a dose fatal in another animal of the same species." Therefore, according to the phagocystic theory, the destruction of the morbid agent, if recovery takes place, occurs within the cell.

Metchnikoff claims, however, that the immunity body may escape into the body fluids, and there sensitizes the invading cell, but its destruction takes place chiefly through the action of the cytase which remains in the cell. This view is hardly consistent with the finding of both the complement and amboceptor in the body fluids. But here again, contending for his intracellular destruction of bacteria, he regards the presence of the immunity agents in the fluids of the body due to degeneration of the leucocytes, supporting his contention on the observation: When the peritoneal cavity is injured by injection of foreign substances, there is almost complete disappearance of the leucocytes, a process of phagolysis, which is soon followed by hyperleucocytosis, mainly macrocytes if the foreign cells are xanthocytes; microcytes if they are bacteria.

Pfeiffer, however, denies the freeing of the immunity agents through phagolysis, basing his opposition on the fact that exudates rich in leucocytes, his or Pfeiffer's reaction takes place more slowly than where it is poor in white blood corpuscles.

Bordet does not concur in Pfeiffer's observation, claiming that the Pfeiffer reaction does not occur where phagolysis does not take place, *e. g.*, anterior chamber of the eye, subcutaneous tissue and passive edema.

The experiments of Gengou seem to me to throw some light on this contention. Blood was drawn into paraffine tubes preventing coagulation; also into ordinary tubes allowing coagulation and then centrifugalized. The plasma exhibited little or no bacteriocidal power, while the serum had definite bacteriocidal power. If Gengou's experiments prove positive in a

large number of experiments in both normal and immunized animals, the inference would be that there is little or no bacteriocidal power in the circulating blood, thus making the white blood corpuscles the chief source of the protective or defensive elements. Still Wassermann's experiments seem contradictory to the above conclusion.

Guinea pig + typhoid + immunized serum = no typhoid.

Guinea pig + typhoid + immunized serum + anti-complement sufficient to neutralize the complement = death to the animal.

He concludes that the complement is not confined within the cell but naturally exists free in the guinea pig's blood.

Gentlemen, it would lead us too far into meshes and entanglements of the many theories proposed, to discuss them all, but the probability is in a problem so complex and perplexing, that there is a certain amount of justification in the contention of each. That in some infections; *e. g.*, pneumonia, septicemia, the leucocytes are the main defensive agents; remember, I say, the chief, because we cannot say that other cells are not brought into requisition. Hoekton in some recent investigation found that the serum of pneumonia patients has very slight if any bacteriocidal properties, but leucocytosis was very evident, and you know that leucocytosis is of considerable prognostic value in pneumonia. Still there are other factors probably concerned that future investigation will discover. Hoekton and Reudiger in some recent studies on the antilytic, action of salt solutions and other substances, conclude that those antilytic salts like CaCl_2 , BaCl_2 , $\text{K}_4\text{Fe}(\text{CN})_6$, "prevent hemolysis and probably bacteriolysis by virtue of their action on the complement:

"1. Because in nonlytic serum salt mixtures corpuscles freely take up amboceptors whose complementophile groups remain free.

"2. Because precipitation of the antisalts restores the lytic property of the complement.

"3. Because of the quantitative relationship between complement and antisalts."

These observations together with the additional discovery that disintegrated typhoid bacilli have anti-bacteriolytic properties, open the way for an explanation of many clinical and experimental facts not in harmony with the accepted theories of immunity.

It has always been difficult to reconcile relapses and reinfection to the prevailing theories of immunity, but these experiments of Hoekton and Reudiger on salt solutions and disintegrated typhoid bacilli indicate that it is possible for the disintegrated bacteria or other substances to occupy the complement and by the introduction of fresh germs, reinfection or relapse may occur.

Another important observation is that a normal salt solution enhances the value of the lytic properties of an immune serum. This is of great practical value in view of the fact that a normal salt solution is so freely used in septic cases and abdominal operations.

I cannot better serve you in closing this paper than in the final words of Ritchie: "The consideration of the theories advanced at the present day to account for the phenomena of immunity thus leads on to results which have a deep biological significance. If looked at from the clinical standpoint alone, they form a contribution to our understanding of the complex processes by which living matter manifests itself as active. Not only so, but they lead to the possibility of understanding functions of cells, the laws which govern their activity, and the way in which groups of cells in the complicated household of the animal body contribute to each other. Thus not only the pathologist but the biologist and physiologist are concerned in the solution of the problems which are opened up."

Like Moses, we have a mere glimpse into the Promised Land of medical problems whose complexity has baffled the most acute scientific minds in all ages. As the explanations and understanding of the fundamental factors underlying the absolute defensive properties of the body become more evident, this glimpse of the "Promised Land" will change into an occupation. Then, and not till then, will many of the biological questions incident to the pathology of the individual be solved—the solution of which will generate a newer and better therapeutical armamentarium of the physician. The light is dawning, and in order to reach the highest coefficient of medical service, there must be a hearty co-operation of the laboratory worker and the clinician.

Clinical Department.

A CASE OF LANDRY'S PARALYSIS.*

BY W. D. ALSEVER, M.D., SYRACUSE, N. Y.

Mr. M., forty-eight years of age, a resident of Syracuse and a native of New York state was by occupation a metal polisher, but he had been out of work for several months, because of a strike, until ten days before he called on me. He was then working at his trade and was handling only one metal, namely, iron. He confessed to being a light drinker and he surely did not exaggerate. He used tobacco freely and also tea and coffee. At twenty years he had a soft chancre removed by an abscess of the left groin. A careful physical examination and cross-questioning about his subsequent history did not lead me to doubt the accuracy of this diagnosis or to think that he had suffered from other venereal disease. At twenty-eight years he was in bed nineteen weeks with inflammatory rheumatism but he entirely recovered and had no recurrence of the trouble. He habitually rose once or twice at night to urinate but micturition was rarely painful. One brother died of alcoholism and rheumatism, one sister of heart disease at thirty-five years, and another sister died in infancy. His wife was well and vigorous excepting for a rarefying osteitis of the bones of the right ankle which was first noticed after the disappearance of swelling of the legs which accompanied pregnancy during the previous year. There were several healthy children.

This man first consulted me on Saturday afternoon

*Read before the Syracuse Academy of Medicine, Feb. 6, 1906.