CELLULAR TOXINS

OR THE

CHEMICAL FACTORS

IN THE

CAUSATION OF DISEASE

BY

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FOURTH EDITION, REVISED AND ENLARGED

LEA BROTHERS & COMPANY

PHILADELPHIA AND NEW YORK

TO

ALBERT B. PRESCOTT, M.D., LL.D.

DIRECTOR OF THE CHEMICAL LABORATORY IN THE UNIVERSITY OF MICHIGAN,

THIS LITTLE WORK

IS RESPECTFULLY DEDICATED

AS A SLIGHT TOKEN OF THE HIGH ESTEEM IN WHICH HE IS HELD BY HIS FORMER STUDENTS,

THE AUTHORS.

PREFACE TO FOURTH EDITION.

During the fourteen years which have elapsed since the appearance of the first edition of this book, the subject matter of which it treats has increased in importance, has modified our conceptions of disease, and has furnished facts which are now utilized in treatment. Quite naturally, during the growth and development of the chemistry of the infectious diseases, this science has from time to time changed the relative importance of different phenomena. When the first edition of this book was written it was believed by those most competent to speak on the subject, that the basic products of bacterial growth constituted the chief factors in the causation of the infectious diseases, but it has been shown by subsequent discoveries that this conception is erroneous, and we now look for the specific bodies among the synthetic substances formed within the cells of the microörganism. This advance in knowledge has rendered the chief title selected for former editions inappropriate, and accounts for the change which we have made therein. The text has for the most part been rewritten with the intention of curtailing the space given to subjects which advanced knowledge has shown to be less important, and also for the purpose of introducing new matter. We regret exceedingly that want of space has compelled us to omit altogether the bibliography found in previous editions. References to the literature employed in the older editions have been omitted, while those bearing upon investigations which have been made since the appearance of the last edition are given in footnotes. Those to whom the third edition is accessible will be able to look up every piece of work referred to in this volume and satisfy themselves concerning the interpretation which we have placed upon the original contributions. In order to abbreviate as much as possible, we have omitted many details given in the previous editions. This curtailment has of necessity not been uniform throughout the book; certain chapters having been cut down much more than others. In some instances the desire to take up less space has possibly led us to omit statements of considerable importance. Especially is this true of the chapter devoted to poisonous foods. Several new chapters have

been added, bringing into the volume subjects which were wholly unknown at the writing of the last edition. We have endeavored to present to our readers everything of importance done in the lines treated of down to the close of the year 1901. If this volume meets with the kind reception extended to its predecessors, its authors will feel themselves amply repaid for the labor that they have placed upon it.

UNIVERSITY OF MICHIGAN, JUNE 1, 1902.

CONTENTS.

CELLULAR TOXINS.

CHAPTER I.

THE ETIOLOGY OF THE BACTERIAL DISEASES.

THE bodies of the higher animals are made up of groups of specialized cells, which are mutually dependent, one upon the other, for their normal development and continued healthy existence. These groups of cells constitute the various organs and the framework by which they are held together and through which food is distributed to all, and the special products of one colony are carried to the others, or cast out from the whole as waste material. Each organ has its special functions, the healthy performance of which is necessary to the well-being of the whole. If the digestive cells of the alimentary canal fail to secrete active fluids, the cells of the brain, the heart, the lungs, and, in short, of every part of the body are impaired and disease results. If the food be properly digested and the absorption cells of the walls of the alimentary canal fail, a like disaster is brought upon the whole. If the kidneys, liver, skin, or lungs do not properly eliminate effete and poisonous products, these accumulate and interrupt the healthy activity of the cells of the body. Disease is the result of impaired or perverted cell action.

The animal body is often invaded by foreign cells, which may become, for a time at least, parasites, living at the expense of the host and elaborating their own special products, which may prove harmful to one or more of the colonies of cells constituting the healthy body, and thus the health, and even the existence of the whole, may be placed in jeopardy. These foreign cells find their way into the body with the food, drink, inhaled air, or through some break in the skin or mucous membrane. The harmful invaders may consist of microscopical, unicellular forms of vegetable life known as bacteria, and the action of their special products upon the cells of the body gives rise to the *bacterial* diseases.

Certain other vegetable forms of life, especially those belonging to the fungi, may live as parasites on the higher animals. These are not known to produce chemical poisons, but by their presence and encroachment on certain tissues they induce impaired or perverted action of the cells of the same. The skin is the favorite habitat of these parasites, and the disorders which they cause are known as *fungous* diseases.

Some species of single-celled animal organisms, known as protozoa, may invade the body and there live and reproduce themselves, modifying, impairing and destroying normal tissue. The disorders resulting from these causes are known as *protozoal* diseases.

Other more highly developed animals pass at least a portion of their lives as parasites, and we must recognize certain diseases as due to *animal parasites*.

The living cells of the animal body may be altered or destroyed by the action of poisons of mineral, vegetable or animal origin. The poisoning that results in this way may be acute or chronic; it may manifest itself in one case principally by its action on the nervous system, and in another the symptoms induced may be referred more especially to the digestive organs. Diseases due to the administration of poisons generated wholly outside the body are grouped together under the name of *intoxications*.

A given group of cells in the body may be so altered by mechanical violence that the continued performance of healthy function is no longer possible. A depression of the skull, as the result of a fall or blow, may induce epilepsy or insanity. Diseases induced in this manner are said to be *traumatic*.

Lastly, without outside interference, any group of cells in the body may, from having an excess of work thrown on it, or from other causes, many of which remain unknown, fail to do its duty, and, as a consequence, disaster may threaten the whole. These diseases may be denominated as *autogenous*.

This gives us a simple etiological classification of diseases into: (1) Bacterial, (2) fungous, (3) protozoal, (4) animal parasitic, (5) intoxications, (6) traumatic, (7) autogenous.

While the above given etiological classification of diseases is admissible, it must be understood that in many instances the cause is not single, but multiple, and for this reason sharp lines of classification cannot be drawn; for instance, the greatest danger in those traumatic affections in which the traumatism itself does not cause death, lies in infection. The wound has simply provided a suitable point of entrance for the infecting agent; indeed the break in the continuity of tissue may be so slight that it is of import and danger only on account of the coincident or subsequent infection, as is true in most cases of tetanus and septicemia. Furthermore, an infectious disease, whether it originates in a traumatism or not, is markedly influenced by what we are pleased to call the idiosyncrasy of the patient, and by this we mean the peculiarities of tissue metabolism taking place in the individual at the time. A dozen men may be alike exposed to the same infection, and the infecting agent may find a suitable soil for its growth and development in two of these, while in the other ten this same agent meets with such adverse influences that it dies without producing any appreciable effects; or all may be

infected, but with differences in degree, as is evidenced by variation in symptoms, in the length of time that the infecting agent continues to grow and develop in the body, and in the ultimate result. Every physician who has had experience in the treatment of any of the infectious diseases appreciates the importance of the personal equation in his patients. It is a fact, frequently observed clinically, and capable of experimental demonstration, that privation and exhaustion not only increase susceptibility to infectious diseases but also heighten mortality from the same.

That some neurotic affections originate from traumatism, has been abundantly demonstrated; that some are largely due to malnutrition accompanied by improper metabolism or insufficient elimination, or, in other words, are to some extent autogenous, all believe. With a clear understanding that the above classification does not attempt a sharp and marked differentiation of the causes of disease, we will give our attention to a consideration of the etiology of the infectious diseases, and of the traumatic and autogenous, in so far as these are influenced by infection.

Recognizing the fact that germs do bear a causal relation to some diseases, the question arises, how do these organisms act? Inasmuch as anthrax was the first disease demonstrated to be due to bacteria, attempts to answer this question have generally been made by reference to the microörganism of this affection, or, in other words, the question is changed so as to read, "In what way does the bacillus anthracis induce the symptoms of this disease and cause death?" Of the proposed solutions of this problem the following are the most important:

1. It was suggested by Bollinger that apoplectiform anthrax is due to deoxidation of the blood by the bacilli. These germs are aërobic, and it was thought that they might act by depriving the red blood corpuscles of their oxygen. This theory was rendered more tenable by the resemblance of the symptoms of anthrax to those of carbonic acid poisoning. The most prominent of these symptoms are dyspnœa, cyanosis, convulsions, dilated pupils, subnormal temperature, and, in general, the phenomena of asphyxia. Moreover, post-mortem examination reveals conditions similar to those observed after death by deprivation of oxygen; the veins are distended, the blood is dark and thick, the parenchymatous organs are cyanotic, and the lungs are hyperemic. Apoplectiform anthrax was compared to poisoning with hydrocyanic acid, which was at one time believed to produce fatal results by robbing the blood of its oxygen.

This theory presupposed a large number of bacilli in the blood, and this accorded with the estimate of Davaine, which placed the number at from eight to ten million in a single drop; but more extended and careful observation showed that the blood of animals dead from anthrax is often very poor in bacilli. Virchow reported

cases of this kind and Bollinger himself found the bacilli often confined to certain organs, and not abundant in the blood. Later, Siedamgrotzky counted the organisms in the blood in various cases and found not only that the estimate made by Davaine is too large, but that in many instances the number present in the blood is small, while Joffroy observed in some of his inoculation experiments that the animals died before any bacilli appeared in the blood. These and other investigations of similar character caused workers in this field of research to doubt the truth of the theory of Bollinger, and these doubts were soon converted into positive evidence against it; but for a while it was the subject of an interesting controversy. Pasteur, in support of the theory, reported that birds were not susceptible to anthrax, and he accounted for this by supposing that the blood corpuscles in birds do not part with their oxygen readily. However, it was shown by Oemler and Feser that the learned Frenchman had generalized from limited data, and that many birds are especially susceptible to this disease. Oemler found that the blood, even when rich in anthrax bacilli, still possesses the bright red color of oxyhemoglobin. Toepper and Roloff reported cases of apoplectiform anthrax in which there was no difficulty in respiration, and Toussaint caused animals which had been inoculated with the anthrax bacillus to breathe air containing a large volume of oxygen and found that this did not modify the symptoms or retard death. Finally, Nencki determined the amount of physiological oxidation going on in the bodies of animals sick with anthrax by estimating the amount of phenol excreted after the administration of one gram of benzol, and found that the oxidation of the benzol was not diminished by the disease. In short, the theory that germs destroy life by depriving the blood of its oxygen has been found not to be true for anthrax, and if not true for anthrax, certainly it cannot be for any other known disease. The bacillus anthracis is, as has been stated, aërobic, while many of the pathogenic bacteria are anaërobic —that is, they live in the absence of oxygen; this element is not necessary to their existence, and indeed, when present in large amount, it is fatal to them. Moreover, in many diseases the bacteria are not found in the blood at all, and, lastly, the symptoms of these diseases are not those of asphyxia. These facts have caused a complete abandonment of this theory.

2. If a properly stained section of a kidney taken from a guinea-pig, which has been inoculated with the bacillus anthracis, be examined under the microscope, the bacilli will be found to be present in such large numbers that they form emboli, which not only close, but actually distend the capillaries and even larger blood vessels, and interfere with the normal functions of the organ. A similar condition is sometimes found on microscopical examination of the liver, spleen and lungs. From these appearances it was in-

ferred by Bollinger that the bacilli produce the diseased condition by accumulating in large numbers in these important organs, and mechanically interrupting their functions. This is known as the mechanical interference theory.

If anthrax were the only infectious disease, or if in other infections the germs were as numerous in the blood as they are in anthrax, the mechanical interference theory would still have strong support, but to the majority of germ diseases it is not at all applicable.

3. Another answer given to this question, "How do germs cause disease?" is that they do so by consuming the proteids of the body, and thus depriving it of its sustenance. The proteids are known to be necessary for the building up of cells and it is also known that microörganisms feed upon proteids. However, this theory is untenable for several reasons: in the first place, many of the infectious diseases destroy life so quickly that the fatal effects cannot be supposed to be due to the consumption of any large amount of proteid; in the second place, the distribution of the microörganisms is such that they do not come in contact with any large proportion of the proteids of the body; in the third place, the symptoms of the majority of the bacterial diseases are not those which would be produced by withdrawing from the various organs their food. The symptoms are not those of starvation.

4. Still another theory, which has been offered, is that the bacteria destroy the blood corpuscles, or lead to their rapid disintegration. But in many of the infectious diseases, as has been stated, the microörganisms, although abundant in some organs, are not present in the blood. Moreover, the disintegration of the blood corpuscles is not confirmed by microscopical examination.

5. Seeing the vital deficiencies in the above theories, and being impressed by the results obtained by the chemical study of putrefaction, bacteriologists have been led to inquire into the possibility of the symptoms of the infectious diseases being due to chemical poisons. In investigating this theory, the following possibilities suggest themselves:

(*a*) The microörganisms may be intimately associated with, or may produce, a soluble chemical ferment, which by its action on the body produces the symptoms of the disease and death. At one time this theory had a number of ardent supporters, among whom might be mentioned the eminent scientist De Bary; but Pasteur proved the theory false when he filtered anthrax blood through earthen cylinders, inoculated animals with the filtrate and failed to produce any effect. Nencki made a similar demonstration when he inoculated a two per cent. gelatin preparation with the anthrax bacillus, which liquefied the gelatin, and on standing the bacilli settled to the bottom, after which the supernatant fluid which was,

clear and alkaline in reaction, was filtered and injected into animals without producing any effect.

It must not be inferred from the above statements that bacteria do not produce ferments. Many of them do form both diastatic and peptic ferments, which may retain their activity after the bacteria have been destroyed; but there is no proof in any case that these ferments have a causal relation to the disease. After the disease process has been inaugurated some of these ferments probably play an important part in the production of morphological changes, the nature of which will be indicated when the different diseases are discussed.

(*b*) The microörganisms may act either directly or indirectly as ferments, splitting up complex proteids in the tissue and producing among these split products the specific poisons which induce the characteristic symptoms of the disease, and may cause death. This theory, once quite generally held, has stimulated numerous investigations, some of which have led to important discoveries; but at present it is safe to say that among the bacterial split products formed either in artificial culture media or in the body, there is not found one which, on account of its intensity of action or from the nature of the symptoms which it produces, can be regarded as the specific cause of any one of the infectious diseases. Moreover, it has been shown that some of the most virulent germs, as for instance, the bacillus of tetanus, will grow and retain their virulence in artificial cultures made up principally of inorganic substances and containing only minute quantities of organic bodies of such simple construction that it must be admitted that the specific toxins of these microörganisms cannot result from their cleavage action.

While we are forced to conclude that no specific toxin has been found among the cleavage products of bacteria, it is well established that certain powerful poisons originate in this way, and it will come within the scope of this treatise to deal with all substances formed by the cleavage action of bacteria, both upon the constituents of artificial culture media and within the animal body.

(*c*) Poisons may be produced by the cellular activity of bacteria much in the same way as morphin is formed in the poppy. This theory supposes that the formation of bacterial toxins is a synthetical, rather than an analytical, process. It is now generally believed that most, if not all, of the pathogenic microörganisms consist of cell walls containing cell protoplasm, and that the specific toxin is a constituent of the protoplasm, and that its formation is one of the vital phenomena manifested by the organism in its processes of growth and multiplication. In some species the cell wall is not easily permeable and the toxin is found only within the cell; while in other species the toxin formed within the cell readily passes through the wall and diffuses through the culture media in artificial growths, or

through the tissues, when the germ is multiplying in the animal body. In at least some species the formation of a toxin is not a phenomenon which invariably accompanies growth and multiplication. This is shown to be true by the frequently observed fact that a highly virulent germ may under certain conditions wholly lose its toxicity while it continues to vegetate most luxuriantly. It seems to be evident that certain conditions of growth, as, for instance, the nature of the medium, the temperature, the supply of oxygen, and the presence or absence of certain chemical agents, determine the amount of specific toxin formed within the cell. Most pathogenic germs find the conditions suitable for the elaboration of poisons at their optimum in the animal body, and for this reason their virulence is increased by passing successively through a series of animals. However, this is not always true, and germs may decrease in virulence by being passed through certain animals; some observers have reported the finding of certain microörganisms that invariably decrease in virulence on being transferred from one animal to another. There are many interesting questions along this line which need to be investigated much more fully than has been done up to the present time before we can speak positively concerning them. They furnish the basis of problems that are of both scientific and practical interest. In many epidemics the specific microörganism, to which the epidemic disease is due, apparently increases for a while in virulence and then gradually seems to become less dangerous. However, a discussion of these questions would take us too far away from the subject matter just now in hand.

We will now give what appears to us, in the present state of our knowledge, a correct definition of an infectious disease:

An infectious disease arises when a specific, pathogenic microörganism, having gained admittance to the body and having found conditions favorable, grows and multiplies, and in so doing elaborates a chemical poison which induces its characteristic effects.

In the systemic infectious disease, such as anthrax, typhoid fever and cholera, the specific poison is undoubtedly taken into the general circulation, and may reach and influence every part of the body. In the local infectious diseases, such as gonorrhea and infectious ophthalmia, the first action of the poison seems to be confined to the place of its formation; although even in these, when of a specially virulent type, the effects may extend to the general health, or the poison may strongly act on some distant part of the body. It is probably true that in many of the infectious diseases the chemical poison has both a local and a systemic action; thus, it is by no means certain that the ulceration of typhoid fever is due directly to the living bacillus, for it is now an established fact that this disease may exist, run a typical course, and end in death, without anatomical changes in the intestine. In diphtheria and tetanus the toxin

formed within the bacterial cells readily diffuses through the cell walls and enters the circulation, while the organism itself is confined to relatively a small area and may not be found in the blood at all. Such diseases are properly called bacterial intoxications. In some other infectious diseases, such as anthrax and one form of the plague, the germ itself may be distributed by the blood and lymph to every part of the body; these diseases are designated as septicemias.

With the proof established that the deleterious effects wrought by germs are due to chemical poisons elaborated by them, let us inquire what properties a microörganism must possess before it can be said to be the *specific* cause of a disease. The four rules of Koch have been conceded to be sufficient to show that a given germ is the sole and efficient cause of the disease with which that germ is associated. Briefly these rules are as follows:

1. The germ must be present in all cases of that disease.
2. It must be isolated from other organisms and from all other matter found with it in the diseased animal.
3. The germs thus freed from all other foreign matter must, when properly introduced, produce the disease in healthy animals.
4. The microörganism must be found properly distributed in the animal in which the disease has been induced.

We will briefly discuss the applicability of these rules. When it is stated that the germ must be present in all cases of the disease, it need not be understood that an unlimited number of cases must be examined before the causal relation of a given organism to the disease may be reasonably suspected. This would require more than a life-time, and would demand facilities for the study of the special disease that do not and cannot exist. The number of cases in which the germ is constantly found should be reasonably large, and the larger this number the greater the probability that the organism is etiologically related to the disease. Moreover, the germ may be present in all cases, and yet it may not be found in all. To demand that it be found in all cases would be to presume that the methods of detecting and recognizing a given organism are perfect, and there is no ground for this assumption. Again, since the results of no one man's work can be accepted in science until they have been confirmed by others, the personal equation must be considered; what one man finds, another may fail to find. Diligence, skill and accuracy are not equally developed in all men, and, moreover, the methods employed may differ. To illustrate these points: Koch, after the most pains-taking study embracing twenty-nine cases of pulmonary tuberculosis, nineteen of miliary tuberculosis, twenty-one of tuberculous glands, thirteen of tuberculous joints, ten of tuberculosis of the bones, four of lupus, and seventeen of bovine tuberculosis, announced that he had discovered a bacillus which is constantly present in tubercular disease. Since this announcement thousands of physicians and bac-

teriologists, possessing different degrees of skill, and often by different methods of staining, with microscopes of all kinds, good and bad, have sought for this bacillus, and it is not strange that now and then some man fails to find the organism in a genuine case of tuberculosis.

Another most important point in this connection lies in the fact that the clinical and the bacteriological diagnoses do not always agree. The most skilful clinicians may differ concerning a case of membranous sore throat. One is sure that it is diphtheria; a second is in doubt and reports it as a suspicious or doubtful case; and a third is sure that it is not diphtheria. A bacteriological examination may reveal or fail to reveal the presence of the Loeffler bacillus. Again, it may be that any number of the most competent clinicians agree in saying that the case is or is not one of diphtheria, and yet a bacteriological examination may result in a contradictory diagnosis. This is exactly what has happened in the study of diphtheria. From statistics gathered by Novy, it appears that of 8,186 cases of clinical diphtheria, diagnosed as such by different men in Europe and America (to May, 1895), the Loeffler bacillus was found in 5,943, the bacteriological examinations also being made by different men. The clinical diagnosis was confirmed bacteriologically in 72.6 per cent. of these cases. On the other hand, of 333 cases diagnosed as diphtheria by Baginsky, 332 furnished the bacillus, and of 117 seen by Kossel, all were confirmed by the bacteriological examination. These figures are given to illustrate the factors of variation that may arise in the application of the first of Koch's rules.

Shall we accept the clinical or the bacteriological classification of disease? There can be no doubt that the latter is the more exact, and its adoption will lead to a more accurate and scientific study of disease. An etiological classification of the infectious diseases is one of the great desiderata of scientific medicine. Whether it will ultimately be made upon the morphological characters of the bacteria or on their poisonous products cannot yet be determined. There are certain objections to making the first of these the basis that seem well-nigh insuperable, and some of these will be discussed later.

The importance of the first of Koch's rules is self-evident; however, the invariable presence of any germ in a certain disease does not prove that the former is the cause of the latter. Indeed, so long as the investigation goes no further than this, we are justified in saying that the microörganism may be an accompaniment or a consequence of the disease; therefore, additional evidence is wanting, and is furnished by complying with the other rules of Koch.

The second rule is complied with by means of plate and other cultures, a description of which would be out of place here.

The third and fourth rules are difficult of application, because the lower animals are often immune to many of the diseases to which man is susceptible.