BIOLOGICAL LECTURES DELIVERED AT THE MARINE BIOLOGICAL LABORATORY OF WOOD'S HOLE, IN THE SUMMER SESSION OF 1895

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VARIOUS

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Trieste

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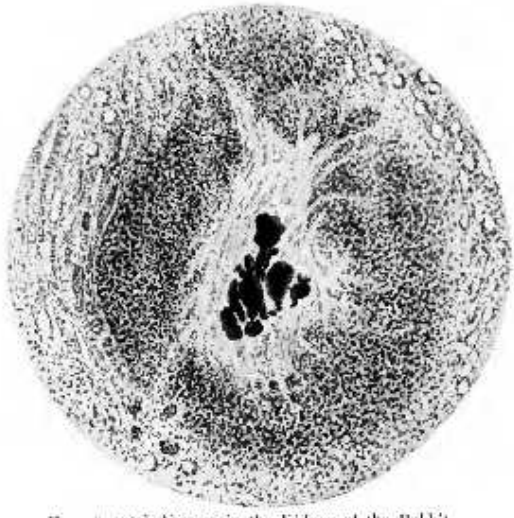
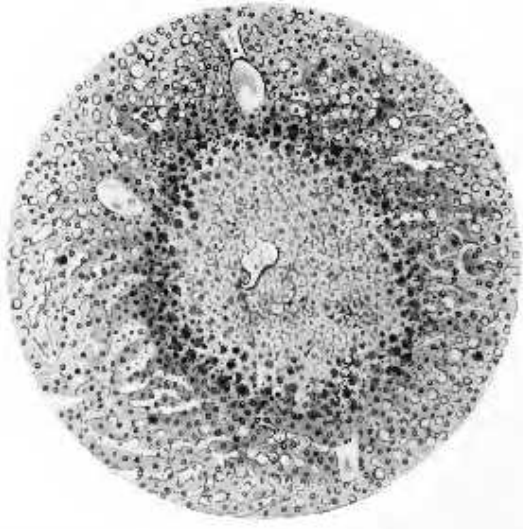
FIG. I.



Experimental Abscess in the Kidney of the Rabbit.
Staphylococcus pyogenes aureus infection.

FIG. II.



Experimental focal cell necrosis in the liver of the Guinea pig. Ricin intoxication.

FIRST LECTURE.

INFECTION AND INTOXICATION.

SIMON FLEXNER, M.D.

(Associate Professor of Pathology, Johns Hopkins University.)

The science of biology in its widest sense comprises the study of life in all its forms and activities, both normal and abnormal. For this reason I shall not apologize for bringing before you a subject closely related to pathology, a branch which is concerned only with the abnormal forms and activities of life.

The underlying principles, which are to-day the subjects of thought and research in the branches usually classed as the biological sciences, are not essentially different from those which are also found in the field of work which more peculiarly belongs to pathology. Nor is pathology any longer a study, the subject matter of which is limited to man and the higher animals. Its application to the lower animals, and even to plants, has been so successful that we are now justified in looking to the comparative study of disease processes for the solution of some of the many still obscure problems in human pathology.

Manifestly it would be neither possible nor profitable to attempt to compass in so brief a time the entire field of pathological research. It becomes necessary, therefore, to restrict our attention to a single one of its problems; and as there is at the present time none which is attracting more attention than that relating to the causation and effects of infectious diseases, I have chosen for this hour the discussion of one aspect of this subject. My remarks will be prefaced with a few general statements concerning the parasitic agents of disease. Some

of these belong to the vegetable, others to the animal kingdom. They are found in the former, among the fungi and bacteria, and in the latter, among the protozoa, vermes, and arthropods. While, however, the term pathogenic micro-organisms is arbitrarily applied to all the vegetable parasites, among the animal parasites only the protozoa should properly come under this category.

Infectious diseases, then, are such as are caused by pathogenic micro-organisms, *i.e.* by fungi, bacteria, and protozoa. In speaking of the bacterial origin of diseases many writers apply the term bacteria to micro-organisms of animal as well as of vegetable origin; but it must be remembered that protozoa are not bacteria, although the term pathogenic micro-organisms can be properly applied to both. I wish, therefore, to emphasize the fact, that besides the diseases of bacterial origin, there are also others which are caused by organisms belonging to the animal kingdom. Typical examples of this class are found in the different forms of malarial fever which are caused by the invasion of the blood and organs by organisms belonging to the group of protozoa.

It must, however, be admitted that the diseases caused by vegetable parasites are best understood. This fact is easily explained by our present successful methods employed for the propagation of these parasites outside the body, whereas as yet the pathogenic protozoa have not been obtained in the form of pure cultures outside the bodies of infected animals. The growth and multiplication of the pathogenic micro-organisms are associated in many instances with the production of certain substances of a toxic nature, these poisons, or toxins as they are called, playing a great rôle in the causation of disease. Certain non-pathogenic or saprophytic micro-organisms in the course of their growth are also capable of producing poisonous products. There is, however, this marked difference between these two classes of agents, namely, that whereas the former are capable of living and of manufacturing the toxins within the living body, the latter can subsist only in the presence of dead material. Examples of poisoning by the products developed by saprophytic bacteria are found in the accounts,

which we so often read, of epidemics occurring suddenly to large numbers of persons from the ingestion of partly decomposed meat, fish, sausage, milk, etc. Infection is therefore to be distinguished from intoxication, inasmuch as the first presupposes the existence of a living agent which enters the body and survives there, while the second is to be attributed to the effects of any toxic agent which may be present in the body in sufficient amount to produce more or less marked symptoms of disease. The relation of intoxication to infection cannot be better expressed than in the following paragraph. "It is impossible to draw any sharp dividing line between intoxication and infection; but it is believed to conduce to precision and clearness to regard as agents of infection only such as are capable of reproduction, that is, such as are living organisms and not include among these agents chemical poisons whether produced by bacteria or other vegetable cells or by animal cells" (Welch).

There is perhaps a tendency at the present time to minimize the importance of the living agents themselves in the production of the phenomena of infectious disease, and to ascribe these entirely to the action of the toxic agents manufactured by the micro-organisms. But in view of the fact that in several typical infectious diseases, among which may be mentioned anthrax, asiatic cholera, and typhoid fever, it has been found quite impossible to separate in an active form the toxic products from the bacteria which produce them, the latter cannot be regarded as less essential to the production of the disease than the former. Indeed there are few diseases at present known in which all the symptoms can be ascribed to the toxic products of the micro-organisms alone. To quote another paragraph from Dr. Welch's writings: "In the case of most infectious diseases we can no more separate the actual presence, multiplication, and specific vital activities of the bacteria within the body from the disease than we can substitute any chemical substance for the actual presence and growth of the yeast fungi in the production of alcohol from sugar."

Yet the rôle played by the chemical substances developed from certain bacteria in the production of the phenomena of

disease is not inconsiderable, and we may safely say that only with such bacteria as produce toxins of great potency, which are easily yielded by the cells to the surrounding medium, would it be possible in a given disease for the toxic chemical substances by themselves to give rise to the same phenomena as those which are due to the action of the living bacteria.

The study of the nature and action of these toxins, or, as they are now generally called toxalbumins, has added not a few interesting facts to our knowledge of poisons in general; but, at the same time, it must be understood that the forms with which we are dealing have not at this time been isolated in a state of absolute purity, although they have been obtained in a condition of great potency. Their exact nature is not as yet well understood. They are believed by most bacteriologists and chemists to be of an albuminous nature, many authorities claiming them as enzymes. They are amorphous bodies and differ essentially from the crystallizable ptomaines, with which substances they are sometimes confused. Perhaps the one best studied, certainly the one possessing the greatest potency, is the toxalbumin produced by the tetanus bacillus. In the still impure state in which it has been obtained, its activity has been found to be simply appalling. A single dose of 0.000.000.05 grm. suffices to produce death after tetanic convulsions in a mouse weighing 15 grams, and it is estimated that the fatal dose for an adult human being does not exceed 0.23 mg. You will appreciate this fact better if you remember that the fatal dose of atropine is 130 mg., and of strychnia from 30 to 100 mg. It should further be mentioned that this toxalbumin, unlike many of the others, is capable of giving rise to the same symptoms as the bacillus which produces it.

Another extremely virulent, although less active, toxalbumin is that obtained from the cultures of the diphtheria bacillus. Of this 0.4 mg. suffices to kill eight guinea pigs, each weighing 400 grams.

In contradistinction to the tetanus toxin, that produced by the diphtheria bacillus does not reproduce the entire series of phenomena of the disease to which it belongs, since the injection of it does not produce at the point of inoculation an