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THE SPECIFIC IMMUNITY OF THE TISSUES AND ITS BEARING ON TREATMENT[1]

AT the present time, in this day of rapidly increasing knowledge in all lines of human endeavor, we accept at first as wonders and then more or less as commonplaces the marvels that have been accomplished even during the past fifty years. We tacitly predict the future by the accomplishments of the past, and this has given us an almost unlimited optimism, even to a greater extent than previous generations have ever had. The various lines of study have been brought into closer contact with each other than ever before and have become interdependent.

The above applies equally as well to medical work as to other fields. Advances have been tremendous, and yet it seems that we have only begun to get into very close contact with what we do not know. Advances in surgery have not exceeded those in internal medicine, and the wonderful work done in the field of infection and immunity can be appreciated only by the trained student.

Advances in medicine have been made by improvement in existing theories and methods, and also by the introduction of new theories and methods. The latter has always been due to the utilization of previously existing knowledge, and could not have been possible without it. Modern scientific work abounds with instances of this, of which research in diabetes over the past forty years is a very good one. New ideas are readily tested by research work and the good separated from the worthless. This is putting the scientific imagination to its best use. Improvement in clinical results, even though slight, would be relatively considerable, as it would be in diseases that had previously offered special resistance to our efforts.

There is no more interesting or important subject in the whole field of medicine than that of infection and immunity. Cases of infection comprise most of those with which the practicing physician comes in contact. I mean by that the primary and secondary results of infection, whether they be specific diseases, infection of tissues by organisms that do not cause specific diseases or the general results of the absorption of bacterial toxines. By far the greatest part

[1] Address of the president of the Southwestern Division of the American Association for the Advancement of Science, Boulder, Colorado, June 8, 1925.

of human mortality is due to diseases that are caused by living organisms, and even in many cases that are not of such origin, the factor of infection must sooner or later be taken into account. This subject of infectious diseases constitutes our most important medical problem, and includes, of course, that of our natural and acquired immunity to them.

I will deal especially with the resistance of the tissues to the invasion of living organisms, which in clinical medical work are usually bacteria, but do not wish to be understood as minimizing the importance of the immune bodies that are present in the blood serum, either before infection takes place, or which develop as the result of our resistance to infection.

Every species of animal and plant has special preferences of habitat and food. These factors vary within extremely wide limits, in fact, to very nearly the same extent as living organisms do in structure and physiology. The same applies to bacteria, whether living outside of the body or in it.

The differences in the species of infecting organisms, the food required by each, the toxines formed and all the other factors concerned explain the wide variation in the human diseases caused by them. This constitutes the basis of human infectious diseases.

I will refer to bacteria as the infecting organisms, as they are the ones that most frequently cause human infectious diseases.

The problem presented by the growth of bacteria in the human body may be compared with the growth of a vegetable seed. The seed represents the infecting agent. It is well known that the seeds of different species grow with varying rapidity, that some are much hardier than others and also that different individual seeds of the same species do not have the same ability to grow, some producing small and others large and healthy plants. This corresponds with the virulence of the various infecting organisms, and the differences in individuals and strains. The seed can grow and reproduce only within definite limits of temperature, but can live above and below these limits. The gases with which it comes in contact are important, as are also the amount and character of the light. The water, and the chemicals dissolved in it, represent the body fluids, and the soil represents the tissues.

In agriculture one of the most important factors that is considered is the character of the soil. Does it contain the proper nutriment for the seed, are there present in it injurious chemicals and what is its biological content? The agriculturist wishes to know definitely about these points. The composition of the soil should be altered, when advisable and possible, to meet the varied requirements of the different seeds. Also, if the seed does not grow well, he wants to know why and always takes into consideration as a possible explanation the composition of the soil used.

In cases of human infection there must be good reasons why the bacteria do or do not grow on the tissues, that is, infect them. The changes in the tissues resulting from infection have been very carefully studied, but we have not given sufficient attention to the character of the tissues as far as it relates to their ability to resist infection. It is possible, and indeed probable, that this immunity of the tissues is the most important single factor in the institution of an infectious process.

The factors governing the growth of the seed in the ground and the bacteria in the human tissues are very complex. The total result in either case may depend upon only slight changes in any one factor. Bacteria in human infections must meet favorable conditions if they are to survive or grow actively on the tissues. Unfavorable conditions are quickly reflected in the results. This applies to variations in all the factors concerned.

Only a comparatively few of the organisms that get on or into the human body meet with sufficiently favorable conditions to grow on the tissues enough to injure them or produce a definite disease. Many bacteria and microscopic animal organisms enter the body, in one way or another, and are either killed quickly, die for lack of favorable conditions or are eliminated without growing on the tissues, but some may find a lodging and either do not injure them at all or so slightly as to be negligent. These are known as non-pathogenic organisms. However, others grow on account of meeting with conditions that are especially favorable to them; there is the kind of nourishment desired in the tissues affected and an absence of unfavorable chemicals in them and the fluids supplying them, or both. On the other hand, the tissues that are not affected either do not contain the food necessary for the infecting organisms or contain substances injurious to them which prevent or inhibit their growth, or both.

In the case of some diseases, like typhoid fever, the infecting organism gets into the general circulation and goes to all the tissues of the body, but only a few of these are infected, that is, permit the bacteria to multiply actively in them. Why are not all the tissues infected equally? The only possible explanation of this is that the tissues themselves in some, at present, unknown way resist invasion. This is a very important biological fact and is universal, as can be readily understood by a study of other infectious diseases. There are very important reasons for it which are not well understood, and the subject has received very little attention from bacteriologists and pathologists.

With regard to the influence of the blood serum, it may be said that the immune substances in it are too frequently not enough to prevent infection, but they develop sufficiently in time after infection has taken place to be a very important factor in killing the infecting agent. The composition of the serum is evidently not responsible for the resistance of certain tissues, and the inability of others to resist. The determining factor must be the chemical composition of the tissue itself.

After an injury to the tissues, whether it be mechanical, chemical or bacterial, the white blood cells exert a powerful protecting influence by collecting there in large numbers, but are not concerned in the incidence of infection of healthy tissues by bacteria.

As we may refer to the ability of certain organisms to grow on certain tissues as specific infection, so we may refer to the special ability of certain tissues to resist certain organisms as the specific immunity of the tissues.

Kolmer, in referring to the causes of this tissue immunity, states that "in general, we must conclude that either (1) microorganisms tend to be destroyed in every tissue or organ except those that are poor in defensive forces and are susceptible or (2) microorganisms or their products circulate passively through a tissue and do not lodge because they possess no affinity for these cells."[2]

The relative influence of the food supply needed by bacteria and the presence of chemicals poisonous to them could be determined by the addition of tissues to various bacterial cultures, using different media. A number of tissues have been used in the preparation of culture media, but they have been added for the purpose of encouraging the growth of bacteria and not to discover what power they have to prevent it.

If the cause of this immunity of the tissues were due equally to the lack of food supply and the presence of a poisonous substance, it would warrant the formulation of a natural law, as follows: *The human body contains preformed within itself a natural defense against, and a possible cure of, all infections to which it is liable.*

This infers that if the chemicals in the tissues that are poisonous to the infecting organisms could be isolated and made in sufficient quantities, they could be used not only in the treatment of these infections, but possibly also in prevention in special instances. This would be making use of one of the most important causes of our inherent resistance, which is certainly effectual and also probably the best that can be found.

The presence of these substances is only hypothetical, but the same may be said of numerous others commonly referred to in medical work and whose presence we do not doubt. I refer especially to the various immune chemicals present in the blood developing as the result of infection. The latter vary with the nature of the infection and the composition of the toxine produced by the infecting agent, and are entirely hypothetical. This subject, which we may term hypothetical chemistry, is a large and important one.

The vitamines will, no doubt, be isolated and identified before long. This will lead to their manufacture for therapeutic purposes. They are at present hypothetical, but we do not question either their presence or what they do.

The isolation of these protective chemicals present in the tissues will, of course, be a question of time and careful work, but should be as possible as the other successes of physiological chemists.

I will now review briefly the essential features of some infectious diseases that illustrate the points mentioned above. Hookworm infection is a good example. The life cycle of this parasite is as follows: Let us start with the worms adhering to the mucous membrane of the upper part of the human small intestine. The eggs are thrown off in large numbers and are discharged with the feces. They then develop only under favorable conditions of soil, moisture and heat, when they form motile larvæ. When these come into contact with human skin, generally on the hands or feet, they adhere to it, gradually work their way through it and enter the circulation. They are carried to the lungs, pass through the tissues, enter the air cells, pass up through the bronchioles, bronchi and trachea, and are then coughed up through the larynx. Most of them are probably then expectorated by the patient, but some are swallowed. On entering the stomach they are not killed by the gastric contents, but leave the stomach and attach themselves to the mucous membrane of the small intestine. They seem to know just what tissues in the human body to make use of in passage, and do not take up a permanent residence anywhere except in the small intestine. They do not attempt to go to any other tissues in the body, which they could no doubt do if they tried to, as other similar parasites do.

In trichiniasis the trichina spiralis is ingested in infected meat, and in the gastro-intestinal tract the larvae are set free from their enveloping sheaths, grow to maturity and produce numerous eggs, from which larvae develop. These pass through the intestinal mucosa and find their way to the muscles. Other tissues are not infected. The parasite seems to know instinctively where to go and how to get there.

The amoeba histolytica is also highly selective and finds its most suitable location for growth in the hu-

[2] Kolmer, "Infection, immunity and specific therapy," 1915.

man body in the mucous membrane of the colon and in the liver, and it occasionally, but seldom, infects the ileum. The path of infection is by mouth, the organism being usually ingested in the food and drink. It is not killed by the hydrochloric acid in the stomach, and does not attach itself to the oesophagus or stomach. Infection of the liver is through the portal circulation, and these organisms could easily get into the general circulation if they did not find the liver tissues especially favorable. The latest work seems to indicate that amoebae sometimes do enter the general circulation and infect other tissues, but this is unusual.

In typhoid fever the bacillus typhosus infects only certain tissues, the order of preference being about as follows: The lymphoid tissues of the intestinal mucosa, mesenteric lymphs glands, blood, spleen, liver and gall-bladder. The organisms are found in the circulation shortly after the time symptoms begin, and the isolation of them from the blood constitutes one of the methods of early diagnosis. Several tissues other than the above are occasionally involved, but the rest, constituting the great majority of all the tissues of the body, are not affected at all. This is clearly not due to the character of the blood serum, but must be due to the composition of the tissues themselves.

In diphtheria the Klebs-Löffler bacillus has special preferences of growth in the human body. It affects the pharynx, back of the nose, larynx and trachea. It will much less frequently grow in the bronchi and farther forward in the nose and mouth. The bacilli, of course, must be swallowed in large numbers, but the stomach and intestines are rarely involved. A number of cases of diphtheritic peritonitis have been reported, but they are rare, especially in view of the frequency of this disease. The rest of the tissues of the body are seldom infected.

The micrococcus lanceolatus, which causes lobar pneumonia, also has special preferences. The bases of the lungs are much more frequently involved than the apices. It has been found in pure culture in the pleura, pericardium, endocardium, meninges, joints and abscesses. It is frequently found in the sputum of tuberculosis patients in the absence of pneumonia, and may also be recovered from cultures made from the pharynx and back of the nose. Here also the bacteria are swallowed in large numbers and do not infect the stomach and intestines, but cases of pneumococcus peritonitis are occasionally reported. Other tissues are very rarely affected.

Tuberculosis is one of the best examples of specific infection and immunity that we have and is of universal interest to the residents of the southwest. It infects by preference the tissues of the body in about the following order: The apices of the lungs, bases of the lungs, pleurae, mediastinal glands, larynx, lymphoid tissues of the intestines and related lymphoid glands, peritoneum, urogenital organs, brain and the bones and serous surfaces connected with them. The tissue that is least often infected, in fact, that is practically never infected, is that of the muscles. The tubercle bacillus gets into the general circulation and goes to all parts of the body, after which time all the tissues have an equal opportunity to be infected, at least, as far as this factor is concerned. The protection against infection is evidently not in the blood serum, but is inherent in the character of the tissues themselves.

The therapeutic application of these principles is very broad, and if only partially successful should permit a great reduction in the mortality from diseases that are either incurable at present, or whose ravages are enormous.

It would not be necessary for a chemical that is given for therapeutic purposes to kill the infecting organism. All that would be needed, in many cases at least, would be to moderately reduce its vitality. In most cases of infection the difference between the ability of the organisms to infect and all the forces of the body to resist must be rather small; otherwise these cases would not only be fatal, but rapidly so, especially in the acute infectious diseases. The more acute and fatal the infectious disease the larger will be this margin of infectivity, as it may be called, while it is proportionately less in the milder and more chronic diseases. In the instance of such a chronic disease as tuberculosis this margin of infectivity must be very small, owing to the long duration of the disease and its slow clinical course.

The composition of the tissues of the various animals used in research and for making biological preparations is not exactly the same as that of the human tissues, but corresponds closely enough for therapeutic purposes, as is proved by the variety and importance of the preparations that are already in use. The field from which to choose is almost unlimited.

Some animals are not susceptible, and others only slightly so, to the organisms causing many human infections. It is possible that this species immunity may be made use of, in fact, it should be of considerable practical advantage.

We may use tuberculosis to illustrate the therapeutic aspect of this problem. The muscles are not infected in spite of the facts that the tubercle bacilli get into the general circulation and that the resistance of the patient in most chronic pulmonary cases is at a low ebb for a considerable time before death. The patients frequently become exhausted and emaciated to the last degree. The muscles are greatly atrophied, and would certainly contain tubercles if they did not possess some very special resistance. Presuming that this immunity is due in part to the presence of a definite chemical, several conclusions would then seem warranted. This chemical is not soluble in water, as then it would always be in the circulation in sufficient amounts to prevent and cure the disease. It is destroyed in the process of emaciating, as otherwise, when the muscles atrophy, it would be thrown into the circulation in sufficient amounts to either cure the disease, or by killing the bacteria in large numbers to set free enough endotoxines to kill the patient. Research with the various chemical solvents at our disposal would be indicated.

During the years 1912 to 1915 Dr. R. E. McBride, of Las Cruces, New Mexico, and I did some research work in tuberculosis along the lines indicated above. We inoculated, both subcutaneously and intraperitoneally, guinea pigs with sputum containing tubercle bacilli obtained from human cases. The muscle tissue used was obtained from Angora goats. This animal is readily obtainable in southern New Mexico and was selected on account of the high species immunity to tuberculosis. The muscles of the flank were used, and pieces were placed in a 1 per cent. solution of tricresol, which is strong enough for purposes of sterilization.

In preparing the material for injection a piece was placed in a stone mortar, of course under aseptic conditions, and thoroughly ground up. The connective tissue was discarded. A syringe with a rubber plunger was used, and the mixture readily passed through a 20 gauge needle. The mixture was made fresh each time before using.

At first we injected 1 cc at a time. The injections were made two or three times a week, and were given subcutaneously. Infected animals that did not receive injections of muscle tissue were used as controls. Sometimes the treated animals developed tuberculosis and died in the same period of time that the controls did. Occasionally the onset of tuberculosis was delayed for varying periods, and several times it was prevented. Several instances occurred in which lesions that were apparently tuberculous healed on continued treatment with this preparation.

No local abscesses developed as a result of these injections. Lumps formed which lasted for ten days or two weeks, but these were finally absorbed. There was no general reaction, and at no time was there any evidence of anaphylaxis.

We then decided to make clinical use of the method. The first point to determine was the danger of anaphylaxis in human cases. Dr. McBride injected subcutaneously into me 3 to 5 cc of this preparation once a week for six weeks. In each instance a small lump formed which was only slightly sore, and which was completely absorbed in from two and one half to three weeks. There was no general reaction.

Dr. McBride then treated three tuberculosis patients who were under his care, of course explaining to them the nature of the treatment, and obtaining their consent in writing. Injections were given twice a week over a period of three months.

I treated a patient in El Paso for five months. A total of forty-eight injections were given, at first every day, and later about every five days. The amount of the mixture injected ranged between one and one half to six cc. The lumps produced were only slightly sore and usually disappeared in three weeks. There was no general reaction.

All these patients were in an advanced stage of the disease, with cavity formation and were not doing satisfactorily.

The results obtained were not conclusive, but were sufficiently suggestive to warrant the statement that improvement resulted from the injections. Other patients under observation, in about the same condition, who did not receive the injections, served as controls.

The resistance of the tissues is no doubt an important factor in other diseases than those of infectious origin. This is suggested in cases of cancer or epithelial malignancy. Our knowledge of cancer has increased very greatly in the past twenty-five years, especially as the result of modern research methods, but the problem is far from solved. There is one point that may throw light upon one phase of our resistance to this condition, and also possibly upon its treatment. It is well known that epithelial malignancy is common in the esophagus, stomach and large intestine and is rare in the small intestine, especially in the duodenum, and also that it is frequently associated with gastric ulcer and very seldom with duodenal ulcer. The study of the causes of these phenomena may develop some very important facts regarding the nature of malignancy and our resistance to it and is well worthy of research. The epithelial cells of the small intestine must have some defensive factor against malignancy that is not present in the other organs mentioned above, and I suspect that secretin is the protecting chemical.

In conclusion I wish to emphasize the facts that the importance of the resistance of the tissues to infection has never received the attention that it deserves and that this is a promising field for research.

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