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VACCINE THERAPY: ITS PRACTICAL APPLICATION.

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What is vaccine therapy? It is the only rational treatment for certain classes of infections and, I might add, in some it is the only form of therapy that brings results. To be more specific, however, it is the treatment of an infection by the hypodermic injection of a suspension of skilled bacteria of the species causing the infection. Such a suspension of bacteria is known as a vaccine, and we speak of streptococcus vaccines, staphylococcus vaccines, etc., according to the organism in the vaccine. A certain manufacturing house is putting on the market stock vaccines which they call "Bacterins." The name is, perhaps, more applicable to the preparations than the term vaccine, but the latter is the one in almost universal use, has undoubtedly come to

stay, and is therefore the one that should be used. We recognize two kinds of vaccines—those made from the organism isolated from the individual himself and which is called an autogenous vaccine, and that made from laboratory cultures of the organism or a mixture of several strains of the same organism to which the name stock vaccine is given. The question of the relative value of stock and autogenous vaccines will form a part of the discussion of this paper.

Although attempts at immunization against and cure of disease by inoculation with bacteria or their products have been carried on for years, it remained for Sir A. E. Wright of England, to place the subject on a scientific basis, and to advance an explanation of how a vaccine acts and why it does good. Some years before Wright worked out the proof of how the body overcomes certain bacterial infections and how it is stimulated by the use of a vaccine, he was treating successfully with vaccines cases of acne, furunculosis, etc., which had resisted all other forms of treatment, but he was working in the dark. It was empirical therapy and he could not guage the proper size of dose and the proper interval of dosage. As a result, he did not have the uniformly brilliant results that now attend his treatment.

That the control of infection depends to a great extent upon the phenomenon of phagocytosis by the leucocytes has been granted almost universal credence since Metchnikoff first gave to the world his theory that all infections, when cured, are overcome by the leucocytes engulfing and destroying the invading microbes. He placed all the initiative, so to speak, in the leucocytes. He thought that all that was necessary for a leucocyte to ingest bacteria was for it to get near enough to them. He regarded the leucocytes as scavengers with a limitless appetite, that traveled around in the blood stream, ready to clean up any germs with which they came in contact. It remained for Wright to prove that the leucocyte by itself does not possess the power to ingest bacteria, that it will not ingest a germ unless that germ has been made palatable for it by the action of a certain substance in the blood. To this substance Wright gave the name "Opsonin," from the Latin verb "opsono," meaning, "I prepare food for."

Interesting as are the experiments by which Wright came to his conclusions regarding the nature of opsonins, it is not in the scope of this paper to describe them, but it will suffice to give merely the conclusion which he has reached:

1. There is present in the blood serum a substance which, by its action on bacteria, so alters them that the leucocytes may ingest them. This substance is the opsonin.

2. Without having been acted upon by the opsonins, the bacteria cannot be ingested by the leucocytes.

3. The opsonin exerts no influence upon the leucocytes.

4. Opsonins are thermolabile substances, i. e., they are destroyed by heating to 60 degrees Centigrade.

5. There is probably a specific opsonin for each organism.

These observations of Wright's are certainly of scientific interest. Are they of any practical value? The answer is unequivocally "yes." When one stops to consider that it is through the agency of the opsonins that the leucocytes are able to overcome many of the bacterial infections, the value of a thorough knowledge of opsonins is readily seen, providing we are able to measure the amount of opsonin present in a given case and then to increase it if there is not enough already present. As we are indebted to Wright for the discovery of opsonins, so also are we indebted to him for devising a means of estimating quantitatively the opsonic content of the blood and for giving us a means of increasing the amount of opsonin when deficient. As we are unable to isolate the opsonins by any chemical means, it is obviously impossible for us to measure the opsonins as such, but we can determine the effect that the serum of a normal individual and that of a person suffering from some infection has upon the bacteria producing the disease, and then by comparing the two find the relation that the opsonic content of the diseased person's blood bears to that of the normal blood. Very briefly, the method is as follows: In one pipette mix equal volumes of the patient's blood serum, a suspension of leucocytes and an emulsion of the bacteria causing the disease. In another pipette mix equal volumes of the same suspension of leucocytes, the same emulsion of bacteria and normal blood serum. Incubate the two

pipettes at body temperature for a certain length of time, and then smear a drop of the mixture from each pipette on a slide, stain them and count 100 leucocytes, noting the number of bacteria in them. Let us suppose the patient to be suffering with a chronic furunculosis due to the staphylococcus aureus. Also let us suppose that in counting 100 leucocytes on the slide from the patient's serum we find 300 cocci ingested by the leucocytes, while on the slide from the normal we find 600 cocci in 100 leucocytes. Then the average number of cocci ingested by each leucocyte after being acted upon by the patient's serum is 3, while the average number per leucocyte after being acted upon by the normal serum is 6. Therefore, as the suspension of leucocytes and the emulsion of bacteria were constant in both mixtures, the conclusion is that, under similar conditions, the serum of the patient in question can prepare only 3 staphylococci for ingestion by the leucocytes, while the normal can prepare 6. If we divide 3 by 6, we get .5. This quotient, obtained by dividing the average number of bacteria ingested by the leucocytes in the smear from the patient's serum by the average number ingested by the leucocytes in the smear from the normal, is spoken of as the Opsonic Index. In this case the opsonic index is .5, that is, the patient's blood contains only one-half as much opsonin as normal, or, to put it in simpler terms, that individual has only one-half as much resisting power toward the staphylococcus aureus as the normal individual possesses. Therefore, if we can do something to increase that patient's opsonic content or, in other words, to increase his resisting power against the staphylococcus, it stands to reason that his chances of overcoming the infection are greatly augmented.

This is accomplished by the use of the vaccine. Wright found that, when he injected an individual with a vaccine, he obtained a characteristic effect upon the opsonic index. At first there was a slight fall—the negative phase—which passed off in 24 to 48 hours, and was followed by a rise beyond the original and sometimes far beyond the normal. This is the positive phase and indicates increased resistance toward the organism as long as it lasts, which varies with the organism used, and also with the size

of the dose. After a period of days, the index again returns to approximately its original level. This change in the opsonic index following an inoculation with a vaccine may be spoken of as the curve or opsonic reaction. Wright also showed that by repeated inoculations with the proper size dose and at the proper intervals he could maintain an increased resistance against that organism. From this it is evident what course should be pursued in case of an infection which we wish to treat by a vaccine. Absolutely essential first is the determination of the infecting organism. This can be done only by the bacteriologist. After the organism is determined, the patient's opsonic index toward that organism should be taken. A vaccine is made from the organism and, if the index is found to be low, the patient receives an inoculation—the size of the dose depending upon the organism in question, the opsonic index and the general condition of the patient. The index is then taken every two days in order to see if the inoculation has had the desired effect. If it has, it is repeated when the index reaches or approaches normal. This is the outline of our method of undertaking the treatment of a case with a vaccine.

Naturally several questions arise in the minds of the practitioner. Can I apply the method in my practice? Must I have the organism identified? Is it necessary to have the index taken throughout the course of the treatment? Must I have my vaccine made from the organism isolated from the patient, i. e., an autogenous vaccine—or can I use a stock vaccine of that organism?

The first question may be answered in the affirmative. It is possible for any practitioner to carry out vaccine therapy as successfully as the specialist, providing he obtains the proper vaccine and knows the dose and interval of dosage best suited to his patient.

Must the organism be identified? Naturally one cannot make use of a vaccine until he knows with what organism his patient is infected. In a few infections, furunculosis, for example, we know that in almost every case the staphylococcus aureus is the infecting organism and we can make use of a stock vaccine if we so

desire, and the chances are that we shall have good success. However, even in furunculosis and abscesses, the infecting organism may be the staphylococcus albus or the streptococcus, or even a mixed infection of two organisms, and, in such a case, the necessity of a determination of the infecting organism would be all-important for the success of the treatment. It is not necessary, however, to wait for the actual identification of the organism before beginning vaccine inoculation, when autogenous vaccines are being used. Having isolated the organism, made the vaccine, taken the index and found it low, we can begin the inoculations and leave the actual identification of the organism to be worked out subsequently, as it means considerable delay if we wait for complete bacteriological proof of identity of the organism before beginning treatment. The time required to isolate the infecting organism and make and standardize the vaccine from it will vary from 48 hours to several days, depending upon the organism present and whether it is in pure culture or not.

Must the opsonic index be taken throughout the whole course of the treatment? Most certainly not. Fortunately, we find that in the same individual the curves of opsonic reaction obtained from the same size doses of vaccine are of practically the same duration, so that all that is necessary is to take the index throughout one reaction or two at the most in order to determine the optimum dose and correct interval of dosage for that individual, and then repeat that dose at the intervals determined. I am aware that this method is contrary to the teachings of Wright and many others, who believe in increasing the dose with each inoculation, but I believe that better results are obtained by simply trying to maintain a resistance slightly above normal instead of an abnormally high resistance, because, as with other tissues of the body, overstimulation of the opsonogenic structures probably leads in the end to a state of collapse, when they will fail to respond to the stimulus of the vaccine. Also, I am taking a position different from some when I hold that it is necessary to take the index at all; but I maintain that without taking the index for one curve at least time may be lost, as we have no other guide as to the dose or interval of dosage. That I am correct in this position is

shown, I think, by the fact that the advocates of vaccine therapy without the index run to cover, so to speak, by taking the index if the patient fails to show signs of improvement after the first few inoculations. In other words, they prefer to grope around in the dark until they fall into a hole and then turn on the light so as to be able to crawl out of it, instead of turning on the light first by taking the index and thereby avoid falling into the hole, with the resultant loss of time in the improvement of the patient. In cases of mixed infection, as in many cases of cystitis and sinuses, it is always essential to take the opsonic index toward the different organisms in order to determine which is the one responsible for the pathological condition.

Must we use autogenous vaccines? For all infections except those due to the tubercle bacillus, the gonococcus and the staphylococcus aureus, I believe that autogenous vaccines are essential. In tuberculosis, autogenous vaccines are practically out of the question, owing to the time required to grow the tubercle bacilli. In gonorrhœal affections, too, I think that a stock vaccine must be used in most cases, owing to the difficulty in growing the gonococcus, although it has been shown that autogenous vaccines here are to be preferred when it is possible to obtain them. In staphylococcus aureus infections, I believe that autogenous vaccines will result in much more rapid cures than the stock vaccines, and consequently are to be preferred, but the latter may be used with a considerable degree of success.

I shall not weary you with statistics as to cases treated which have been reported, for they are tiresome at best and, when all is said and done, the fact still remains that they are only statistics. I shall merely enumerate the infections which in the majority of cases yield to this form of treatment, and then give very briefly the results of some of my own observations—mostly in cases treated by myself, but a few of them in cases treated by Ross at the Toronto General Hospital. Good results may be expected in the application of vaccine therapy to all forms of staphyloccocus aureus and albus infections, cystitis due to bacillus coli and streptococcus, local infections due to bacillus coli and streptococcus, acute gonorrhœa, gonorrhœal urethritis, chronic ure-