***"Vaccine Therapy",* Encyclopædia Britannica, The Encyclopædia Britannica Company, 1922, New York, Vol. XV, pp. 319-321**

VACCINE THERAPY. – Since the discoveries of Pasteur it has become recognized that a very large number of the diseases from which human beings suffer are due to infection of the tissues by living micro-organisms, most of which belong to the simpler forms of plant life.

Immunity from such infections may be natural or may be acquired. By natural immunity we understand a natural resistance to infection by certain micro-organisms which are known to have pathogenic properties for other species of animals. It is know, for instance, that microbes which produce a rapidly fatal disease in one kind of animal are quite innocuous when introduced even in enormous numbers into another kind.

As an example of an acquired immunity may be taken the immunity conferred as a rule for a lifetime by an attack of measles or chicken-pox. The individual who has once overcome such an infection is usually immune from a further attack, even though exposed to infection.

It is this fact which led Jenner to try to confer immunity against smallpox by producing a modified mild "attack" by vaccination with calf lymph. It is now admitted that such vaccination does confer immunity, and that even should infection occur the disease runs a mild course.

Since the discovery of bacteria as causative agents of disease, much study has been devoted to the part played by cells and fluids of the tissues in recovering from bacterial infections. Evidence has been sought for response on the part of the body to the bacterial invasion. It is Metchnikoff that we owe the knowledge that the white blood corpuscles and other cells of the body react to the introduction of bacteria into the tissues. Enormous number of these cells congregate at the site of invasion and engulf the microbes (phagocytosis). As Sir John Burdon Anderson aptly put it, the white blood corpuscles act as the policemen of the body.

It was soon learnt, however, that this is not the only way in which the body reacts to microbic infection. Buchner was able to show that the tissue fluids and the blood serum in particular acquire new properties as a result of bacterial infection, properties which render them highly injurious to the invading microbes. It was shown, for instance, that if actively mobile typhoid bacilli are brought into contact with the blood serum of a normal individual the bacilli are but little affected by the serum. On the contrary, if the bacilli are brought into contact with the serum of an individual convalescent from typhoid fever their mobility ceases, they are massed into clumps (agglutination) and finally killed (bactericidal action) and dissolved (bacteriolytic action). Sir Almroth Wright was able to demonstrate that a further property is acquired by the serum, namely an increased power to render the bacteria more readily ingestible by the phagocytic cells (opsonic action). Exactly how and where these new properties are acquired is not yet known, but one of the most striking facts emerging from the study of these reactions is that they are directed against the particular micro-organism which has invaded the tissues the reactions are said to be specific. Thus the blood serum of a patient convalescent from typhoid fever, which is strongly bactericidal for typhoid bacillus, behaves like a normal serum when brought into contact with any other kinds of bacteria. Similarly, while an attack of typhoid fever confers immunity against a second infection by the typhoid bacillus, it confers no immunity from infection by other bacteria, even those so closely related as the para-typhoid bacilli.

It must be admitted that recent work goes to confirm the opinion that there is a concomitant non-specific response common to the reaction against all microbic infections, but this does not detract from the importance of recognizing the highly specific nature of these immunity reactions.

A very important step forward was taken when it was demonstrated that the body responds to the introduction into the tissues of dead bacteria in the same was as it does when living bacteria invade the tissues, for this made possible artificial immunization. To attempt to confer immunity against any microbic disease by the introduction of very small numbers of even attenuated living bacteria is fraught with manifest dangers, for the bacteria are capable of multiplication in the tissues and are no longer under control. To attempt to confer immunity

against disease by the introduction of dead microbes into the tissues is a different matter, for the dosage can be regulated and the bacteria cannot multiply in the tissues.

Thus it was Sir Almroth Wright proposed to confer immunity from typhoid infection by inoculation into the healthy tissues of a standardized suspension of dead typhoid bacilli in physiological salt solution (typhoid vaccine). The immense benefit derived from such inoculations was fully demonstrated during the World War 1914-8. Wright's studies in immunization had demonstrated that it was possible to confer immunity against microbic infections by the inoculation of bacterial vaccines into healthy individuals. It seemed at first that nothing but harm could result from the inoculation of such vaccines once the tissues had become infected. It appeared, indeed, as if to do so were merely to add more poison to a system already being poisoned. Such, however, is not the case. Pasteur was the first to show, in connexion with rabies, that beneficial results could be obtained by inoculating vaccine during the incubation period of the disease. But it was discovered by Wright that the rapidity with which a specific response to the inoculation of a vaccine occurs depends on the dose of the vaccine given, and that this response occurs very rapidly if the dose is an appropriate one, which opened up the whole field of vaccine therapy. Wright showed that the inoculation of too large a dose of vaccine can lead to a state of lessened resistance and that no immunizing response follows. But this so-called negative phase can be modified as regard severity and duration by the adjustment of the dose, even to the point of its virtual disappearance, and nevertheless a good immunizing response follows. And such a satisfactory response occurs when vaccines are inoculated into an already infected individual. This means that, if the gravest generalized infections be expected, there is not in microbic diseases a wholesale poisoning of the tissues of the body. There is infection of certain tissues and others remain healthy or, at all events, capable of immunizing response. And it is to the power of these healthy tissues to respond that we turn in vaccine therapy. Just as the tissues of a healthy individual inoculated with an appropriate vaccine response by elaborating protective substances against the microbe or microbes contained in that vaccine, and such response confers immunity of the individual, so do the healthy tissues of an infected individual respond to a vaccine containing the infecting microbe, and such a response raises the resisting power of the individual to the infection.

Now infections by microbes can broadly be divided into two classes: (a) generalized, and (b) localized. By a generalized infection we mean that the microbes and their products have ready access to the blood, and lymph stream, and thus exert their baneful influence not only locally but at a distance on various tissues of the body. In a localized infection, on the other hand, the microbes affect a particular region of the body only and the remaining regions are not at all or only quite secondarily affected. From what has been said before, it is obvious that in the first class vaccine therapy has but a limited sphere of application; in the second class it has a very wide one. For it is on the satisfactory response of tissues that the success of vaccine therapy depends and this will bear definite relationship to the healthiness of the tissues; further, the gravity of the infection must necessarily enter into account, just as a small war calls for but a small effort, whiles a great war, in which the life of a nation is at stake, calls for a maximal and sustained effort.

When it is borne in mind that the substances elaborated in response to the inoculation of a vaccine are largely carried to the site of infection by the blood stream, it will be realized that the success or failure of vaccine therapy depends largely on the blood supply of the affected area. So long as the newly elaborated antibacterial substances can come into contact with the bacteria, success may be anticipated, but when barriers to their arrival exist, success is limited or denied by the extent or completeness of the barriers. Thus in acute lobar pneumonia the affected area of the lung is occupied by an impenetrable clot of blood; little good can therefore be expected from vaccine therapy once this clot has formed and as long as it remains. But this does not preclude the exploitation of vaccine therapy in pneumonia in the earliest stages of the disease or after resorption of the clot has begun. Fortunately, in the majority of infections there is not such general disturbance of the blood supply to the infected area; in such case it surely follows that a supply of blood rich in protective substances must constitute an advantage, as against a supply of blood poorer in such substances. It will be realized from these remarks that the utmost care is needed in the accurate bacteriological diagnosis of each infection before vaccine therapy is employed, and the vaccine must be prepared with care as to sterility and specificity.

The administration of the vaccine needs the knowledge not only of general medicine but of bacteriology and the principles of active immunization against microbic infections.

The Encyclopedia Britannica (1922) – Vaccine Therapy

The Vaccine. – For practical purposes bacterial vaccine may be defined as sterilized and enumerated suspensions of bacteria, the liquid medium being either physiological salt solution or dilute nutrient broth. The bacteria must be isolated in pure culture and strictly indentified by the usual tests. The microbes thus indentified are usually inoculated on to the surface of a solid medium (e.g. agar-agar) and, after growth has occurred, the bacterial colonies are floated doff into sterile physiological salt solution. The suspension thus obtained is placed in a hermetically sealed tube and thoroughly shaken, if necessary by mechanical means, so as to break up the colonies and obtain an even suspension. A small sample of the suspension is then removed for enumeration, the tube once more hermetically sealed and the whole placed in a water bath at 60° C. for one hour. This temperature has been found to be sufficient to kill most of the pathogenic bacteria without profoundly altering their chemical composition. Sterility of the vaccine is not, however, presumed and each one is subjected to cultural control before being certified sterile.

The enumeration of the suspension may be carried out in various ways. The original method of Wright is as follows:

	Autogenous vaccine advisable	Stock vaccine adequate	Effective doses	
			Minimal (million)	Maximal (million)
Acne bacillus	In some cases	Generally	5	500
Staphylococcus	..	Generally	50	1000
Streptococcus	In most cases		1	50
Pneumococcus	Generally		5	50
Influenza bac.	Generally	If polyvalent	10	500
B. of Friedlander	Generally	..	5	100
B. coli	Generally	..	1	100
M. catarrhalis	Generally	..	5	100
Bordet's bac.	..	Generally	50	500
Diphtheria bac.	Often	Often	10	50
Gonococcus	..	Generally	1	50
Antinomyces	..	Generally	1	25
Meningococcus	..	Polyvalent	50	1000
M. melitensis	..	Generally	30	100
B. tyhposus	..	Yes	10	100
B. paratyphosus A	..	Yes	10	100
B. paratyphosus B	..	Yes	10	100
Tubercle bac.	(?)	Nearly always used	1/500,000 mg	1/1000 mg

It has been the practice for some 25 years to enumerate the corpuscles of the blood in a counting chamber of known depth and ruled with squares of known size. Wright, therefore, mixed an equal quantity of blood and the

bacterial suspension. Films of the mixture are made and appropriately stained for microscopic examination. An adequate number, about 500 usually suffices, of red blood corpuscles are counted in a series of fields of the microscope and at the same time the number of bacteria seen is noted. The number of red blood corpuscles per cub. mm. has previously been determined in a counting chamber, so that all that remains to be done is to work out the proportion of bacteria to red cells and so to arrive at the number of bacteria per cub. mm. or cm. of the suspension. There are technical difficulties in the way of enumerating certain bacteria, e.g. the tubercle bacilli; in these cases the bacterial growth is weighed, and the dosage, instead of being expressed in millions of microbes per cub. cm., is given in milligrammes of their fractions, e.g. a usual dose of staphylococcus vaccine will be 250,000,000 cocci, whilst that of the tubercle vaccine would be 0.0001 milligrammes.

A vaccine made from cultures obtained directly from the patient to be treated is said to be an autogenous vaccine. A vaccine made not directly from cultures obtained from the patient but from cultures of the same species of microbe as that which is infecting him is termed a stock vaccine. In general it may be affirmed that autogenous vaccines are nearly invariably to be preferred to stock vaccines, whilst in the case of certain microbes they are indispensable. Stock vaccines, however, are usually effective, save time and expense and have very wide application. Latterly attempts have been made to reduce the toxic action of the bacterial suspensions and so-called sensitized and detoxicated vaccines have been recommended, but it is doubtful whether these procedures constitute a useful advance.

The accompanying table gives a summary of the microbes from which vaccines are commonly prepared, together with the minimal and maximal effective doses in which they are administered.

Vaccines are administered by hypodermic injection and the inoculations are painless.

Where the minimal effective dose is employed the inoculation is not followed by any local or constitutional disturbance. If there is any sensible constitutional change, that change is in the direction of increased well-being. When a medium dose is inoculated there may be a small amount of local tenderness and a transient aggravation of the patient's symptoms, or slight constitutional disturbance, malaise, headache and possibly a slight rise in temperature. But none of these negative phase effects are at all marked except where an excessive dose has been employed.

It is outside the sphere of this article to enumerate the various disease in which vaccine therapy finds application, but a few in which vaccines have proved of exceptional value may be mentioned.

Boils, carbuncles and other staphylococcal infections usually yield readily to treatment by staphylococcal vaccine. Erysipelas, puerperal septicæmia, acute surgical septicæmia and septic wounds are conditions benefited by treatment with streptococcus vaccine. Certain forms of rheumatism, arthritis and fibrositis are relieved and the progress of the disease is arrested by treatment with an appropriate vaccine, and the same may be said in the case of certain cases of bronchial asthma, chronic bronchitis and recurrent colds.

The distressing symptoms of inflammation of the bladder due to infection by the bacillus coli are relieved and may entirely disappear under the treatment with an autogenous vaccine.

Tuberculous disease of the glands, skin and joints is amenable to treatment with a tubercle vaccine, and in rigidly selected cases the same holds good for tuberculosis of the lung.

It may be confidently asserted that, with the increasing knowledge vaccine therapy will find wider application and will become recognized as a valuable weapon in the combating of microbic diseases. (A. C. I.)