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RECENT ADVANCES IN VACCINE THERAPY*

BY

ALEXANDER FLEMING, F.R.C.S.

Assistant Director, Inoculation Department, St. Mary's Hospital; Professor of Bacteriology in the University of London

In an address on recent advances in vaccine therapy it is permissible for a moment to consider the history of this form of treatment. If we except Jennerian vaccination we find ourselves with Pasteur. He discovered that fowls could be protected against chicken cholera by the injection of attenuated cultures of the infecting organism. Then he turned his attention to anthrax, and after the famous experiment on sheep at Pouilly le Fort, which no one who has seen the film *Louis Pasteur* can forget, there could be no doubt that vaccines could protect animals against bacterial disease. Differences of opinion still exist as to the best way of preparing vaccines and as to the best methods of using them, but this one experiment of Louis Pasteur established for all time the principle of active immunity by means of bacterial vaccines.

Pasteur's work was carried on entirely with living vaccines and, except for rabies, was concerned only with animal diseases. Living vaccines have certain fairly obvious drawbacks in human medicine, and the next advance was the use of prophylactic vaccines made from killed cultures. This step was intimately associated with the name of our great countryman and my own master, Sir Almroth Wright, who has advanced science in many ways, not the least of which was the introduction of anti-typhoid vaccine, still universally applied. The next step, the vaccine treatment of established infections, was entirely due to Wright's initiative. It began with the treatment of local staphylococcal infections of the skin, but has now spread to many others.

When first I started working at bacteriology in Wright's laboratory at St. Mary's Hospital in 1906* vaccine therapy was in its infancy, and there were great hopes that by its means all bacterial infections could be controlled. Now, some thirty-three years afterwards, we can look back and congratulate ourselves that, although all these hopes have not been completely fulfilled, and although we are far off finality in our knowledge and practice of active immunization, in many types of infection a great measure of relief can be given to patients by the intelligent use of vaccines. At the present moment vaccine therapy is, in practice, having something of a setback in that medical practitioners have become chemically minded because of the sensational results obtained in certain infections by sulph-anilamide and its allies. These drugs have an extraordinary effect on a small number of bacteria which infect the human body, and they are being used to treat all manner of bacterial infections whether or not there is any

substantial evidence that there is likelihood of their being successful. However, it is certain that before long the limits of the new chemotherapy will be better understood, and I hope later to produce evidence indicating that the best results in the treatment of certain bacterial infections will be obtained by a combination of vaccine therapy with the new chemotherapy.

Method of Administration of Vaccines

The ordinary method of administration is by hypodermic injection. You are all familiar with this method, but there are certain technical details in the administration which I hope you will forgive me for mentioning. They are not "recent advances," but they are useful, and they make for the popularity of vaccine therapy.

Sterilization of the Syringe.—At the inoculation department of St. Mary's Hospital we have used hot-oil sterilization for over thirty years, and we have no intention of giving it up. An oil bath with a small gas-jet underneath stands in a corner of the laboratory, and the gas is adjusted so that the temperature of the oil is from 120° to 140° C. There need be no regulator. These oil baths can be purchased from laboratory outfitters or they can be improvised for a shilling or two from a small gas-burner, an enamelled cup, a suitable stand, and a thermometer. To sterilize the syringe the needle is removed, hot oil is drawn into the barrel and expelled two or three times; then the needle is replaced and is immersed in the oil, which is drawn through it into the syringe and again expelled. The needle and the inside of the syringe are now sterile. During the last thirty years millions of hypodermic injections of vaccines have been given to outpatients in our inoculation department without any septic complication developing.

For the busy practitioner this method is really very suitable, but it entails a capital outlay for as many syringes and needles as he would be likely to use on any one round of his practice. These are sterilized in oil as described above and are then put in their fountain-pen-like metal cases and carried with the other implements in the bag. The used ones are resterilized in oil on return to the consulting-room. One great advantage of this method is the saving in the needle bill. A hypodermic needle that is being used frequently every day will last for months; as it is kept oily it does not rust or get rough, and if one has a suitable needle sharpener (these can be obtained at a cost of about half a crown) an occasional rub will keep it sharp—much sharper than any new needle I have ever used.

* An Address delivered to the Nottingham Medico-Chirurgical Society.

It has been recommended, however, that vaccines be introduced in other ways than by hypodermic injection, and in recent years a certain prominence has been given to oral vaccination. The idea of administering vaccines by the mouth is not new, for as long ago as 1902 Almroth Wright and his colleagues in the Army experimented with typhoid vaccine given this way, and concluded that, while it was not without effect, it was too uncertain to be of practical utility. Before the great war several reports had been made, but the first large field experiment was that in 1915 by Dubarry, who maintained that considerable protection resulted from the oral administration of typhoid vaccine. Since the war oral vaccination against intestinal diseases received a great stimulus from the researches of Besredka, but his work is still very far from being generally accepted. Recently I have had the opportunity of reviewing much of the work done on oral vaccination against the enteric fevers. From this study certain conclusions emerge: (1) on the evidence at present available it is very difficult to maintain that oral vaccination can be seriously considered as an alternative to vaccination by the subcutaneous route; (2) oral vaccination may, however, be regarded as worth trying when the choice is between that and nothing.

In the past few years oral vaccines have been issued for protection against colds. We have experimented in connexion with the administration by the mouth of vaccines of the respiratory tract organism, and have found that after the ingestion of these vaccines antibodies cannot be detected in the serum of individuals who have not previously been inoculated subcutaneously.

This is not entirely unreasonable in view of Glenny's elucidation of what he has called the "primary" and "secondary" stimuli. This was worked out with toxin and antitoxin, but it is a general phenomenon which applies to all antigens and antibodies.

The first injection of a toxin, toxoid, or vaccine does not usually produce a high and lasting titre of antibodies demonstrable in the blood of the inoculated animal. This primary stimulus, although it produces very little apparent effect, in some way sensitizes the cells of the animals so that if a second injection of the same antigen is given after an interval of one or more months there is a very rapid and complete rise in the antibody content of the blood. The dose of antigen necessary to produce this secondary stimulus need not be a large one: in the case of the "anti-catarrh" vaccines the primary stimulus conferred by the injection of a vaccine so sensitized the individual that even a small amount of antigen absorbed through the alimentary tract might give the effective secondary stimulus.

Nature of the Vaccine

It is impossible to enter into the intricacies of this question, but it might be useful to deal briefly with the important practical problem of antigenic dissociation. A vaccine is a suspension or preparation of killed bacteria that is used to stimulate the production of antibodies in the animal to which it is administered. Vaccines contain the antigens of the bacteria—that is, the substances which stimulate the production of specific antibodies. These antigens are chemical substances, upon the character of which the chemists have in the last ten years thrown much light. Small changes have been made in the structure of an antigenic molecule, resulting in striking alterations in the antibody response. But these changes in the antigenic molecules of bacteria need not be made by chemists in the laboratory; they can result naturally during the growth

of bacteria. Thus a bacterial culture which has been grown on an artificial medium for a long time may change its antigenic structure, and in a most important way. The "rough" or "R" degeneration was first recorded by Arkwright, who noticed that certain colonies in stock cultures of the *Salmonella* group of bacteria had a rough appearance, and when the change was fully advanced would not make even suspensions in salt solution as the normal culture did. These physical changes might of themselves be of no moment, but it was shown that they were accompanied by chemical changes and that some of the original antigens of the bacteria had been lost; especially was it found that vaccines made of these degenerate cultures were unable to protect animals against infections of the ordinary virulent bacteria.

In the United States for a long time all the typhoid vaccine was produced from one strain of typhoid bacillus, "Rawlings," which was isolated by Wright in 1900 and which was used to make the early typhoid vaccine for the British Army. For over thirty years, therefore, it had been grown in artificial media. In 1932 Grinnell collected cultures of this Rawlings strain of typhoid from a number of laboratories in America which produced typhoid vaccine. He found that these cultures were all more or less degenerate, and that none of the vaccines made from them would efficiently protect mice infected with a virulent culture, although a vaccine made from a recently isolated culture did so. We can assume, therefore, that for a time most of the typhoid vaccine used in the United States outside of the Services was not very effective, and these observations bring home to us the importance, when preparing stock vaccines, of using cultures in which the antigens have not degenerated.

Nowadays in the best vaccine laboratories care is taken that stock vaccines are not made from degenerate cultures. In the laboratory at St. Mary's Hospital, to which I have been attached during the whole of my working life, we have been fortunate in always having had an ample supply of fresh cultures from the hospital patients, so there was little chance of our vaccines being made from degenerate cultures; but until this "R" variation was properly appreciated many stock vaccines must have contained a large proportion of degenerate cultures.

Active Immunization with Toxoids

The production of an antitoxic immunity by the injection of toxoids is a method of treatment which will be extended as bacterial toxins become better known. A toxoid is an exotoxin that has been acted on by formalin, by which process it loses its toxic properties but retains its antigenic power. This means that it can with safety be injected into the animal body, and the animal will respond with the production of antitoxins just as if the unaltered toxin has been given. The introduction of toxoid therapy has made it possible with ease and safety to produce in man an active antitoxic immunity which can be accurately measured. The most common application in medicine of the use of toxoids is in diphtheria prophylaxis, but so much has been written about it that it is unnecessary here to do more than state that it is extremely effective.

Tetanus

Tetanus toxin has been known for many years, and tetanus antitoxin is universally used as a prophylactic measure in cases of accident. This antitoxin is prepared by injecting horses with tetanus toxoid. Ramon, in Paris, suggested that it would be of value to actively immunize

men with this toxoid, and he showed that the procedure was safe and caused no untoward reactions. He also showed that it could be combined with T.A.B. inoculations, and that in fact the yield of antitoxin was greater when it was so combined. This active antitoxic immunity to tetanus induced by tetanus toxoid is lasting, and an increased antitoxic content can be detected in the serum years afterwards, in marked contrast to the passive immunity following the administration of tetanus antitoxin, which has disappeared in a week or two.

Active immunization with tetanus toxoid has been extensively used in the Services in France, and is being employed to some extent in this country. Now all medical practitioners drive cars, and all drivers of cars are liable to serious accident. I suggest, therefore, that it might be a wise precaution to be actively immunized with one or two doses of tetanus toxoid. In this way the antitoxic content of the blood would be considerably increased, and even if tetanus antitoxin were not administered the chance of fatal tetanus would be greatly lessened. It is difficult to say whether this active immunity would, after a lapse of a year or more, be sufficient to prevent all tetanus, but there is not a doubt that the increased amount of antitoxin in the blood would neutralize a moderate dose of toxin; it would also provide the primary stimulus, so that the body would react to the production of tetanus toxin in a wound, with a further rapid production of antitoxin.

Staphylococcus

In recent years much attention has been paid to staphylococcus toxins. It has been clearly demonstrated that a staphylococcus such as can be isolated from any boil produces a true exotoxin which can be toxoided by formalin, and these toxoids have been extensively used in the treatment of boils and other staphylococcus infections. Dolman, an old St. Mary's student, first published the result of treating such conditions with toxoid, and since then many enthusiastic articles have appeared. For the last six or seven years we have been treating in our outpatient department large numbers of localized staphylococcus infections with toxoid, and certain interesting facts have emerged. The antitoxic response to staphylococcal toxoid can readily be measured with great accuracy (with much greater accuracy than the response to any other staphylococcal antigen), and by studying the antitoxic response of different patients throughout a course of toxoid treatment useful information has been gained.

CURVE OF ANTITOXIC RESPONSE

The antitoxic content of the serum of a normal healthy man is from 1/2 to 1 unit per c.cm., and this does not differ materially from the reading obtained in most of the patients who come to us for treatment of recurrent furunculosis. This means that recurrent attacks of boils have not provided an immunizing stimulus. It has often been urged against vaccine therapy of established infections that when the patient already has so many living bacteria in his body it would be useless injecting some more dead ones in the shape of a vaccine. In these cases of recurrent boils we find that although the patient may have been suffering at intervals for years from infections of a toxigenic staphylococcus he has not made any antitoxic response. It is not that he cannot make such a response, because if a few doses of from 0.1 to 0.5 c.cm. of toxoid are administered the antitoxic content of his serum promptly rises. The extent of the rise varies with the individual, and for each individual there seems to be a limit beyond which it will not go, no matter how much

toxoid is administered. This maximum figure is usually from 6 to 12 units, but it may with certain individuals be as low as 1.5 units per c.cm. (see Table I).

TABLE I.—*Variation in the Antitoxic Response to Toxoid in Different Patients*

Case	Antitoxic Content per c.cm. before Treatment	Toxoid Treatment	Antitoxic Content per c.cm. after Treatment
1	0.5 unit	0.1 c.cm. in 1 dose	1 unit
		1.5 " " 7 doses	1.4 units
		1.1 " " 3 " "	1.5 " "
2	2 units	1.9 " " 4 " "	1.5 " "
		1.0 " " 4 " "	6 " "
		2.6 " " 4 " "	6 " "
		2.0 " " 2 " "	6 " "
3	<1 unit	1.0 " " 4 " "	8 " "
4	3 units	0.7 " " 3 " "	13 " "
		2.5 " " 4 " "	13 " "

There is thus a great variation in the response of different patients to the same antigen, and in general it has been noticed that the clinical results obtained are better when there is a good response, although this is by no means invariable. While it is easy to measure the antitoxic power of the blood it is very difficult to measure accurately the antibacterial response. It may well be that some of these patients respond badly to any antigen, and this would explain the differences in the results obtained in different patients with any form of active immunity, be it toxoid or vaccine.

DIFFERENT FORMS OF TOXOID

Staphylococcal toxoid may, like diphtheria toxoid, be used either as the simple toxoid or as toxoid-antitoxin floccules. To obtain these latter the toxoid is mixed with an equivalent amount of antitoxic serum, a precipitate from which is separated and resuspended in saline. This precipitate contains the antigens of the toxoid and is useful where the crude toxoid gives rise to severe local reactions. The antitoxic response to the crude toxoid, to toxoid-antitoxin floccules, and to toxoid mixed with vaccine is of about the same order, as is shown in Table II, which indicates the response obtained to these antigens in different patients.

TABLE II.—*Antitoxic Response obtained with Different Forms of Toxoid*

Treatment	Antitoxic Titre	
	Before	After
0.8 c.cm. simple toxoid in 2 doses	1	6
0.8 c.cm. vaccine (toxoid + vaccine) in 3 doses	1	10
1.7 c.cm. toxoid-antitoxin floccules in 3 doses	1	8

PERSISTENCE OF ANTITOXIN IN THE BLOOD OF PATIENTS AFTER CESSATION OF TREATMENT

Observations were made on the blood of patients for various periods after treatment was stopped, when it was found that there was a gradual reduction in the antitoxic titre, so that after one year it had dropped to 57 per cent. of its titre at the time of the cessation of treatment. This is brought out in Table III.

TABLE III.—*Persistence of Antitoxin after Cessation of Treatment*

Interval since Toxoid administered	Number of Cases	Average Reduction in Antitoxin
2 months	9	18%
3-4 " "	18	27%
6 " "	13	41%
7-12 " "	9	41%
14 " "	1	4 units to 3
15 " "	1	6 " " 3
17 " "	1	6 " " 4
4 years	1	4 " " 2

MAINTENANCE OF THE ANTITOXIC TITRE BY OCCASIONAL
DOSES OF TOXOID

In one or two cases it was attempted to maintain the antitoxic titre at its height by occasional doses of toxoid. A record of one such case is given in Table IV, where the maximum titre was maintained for fifteen months by a dose of 0.5 c.cm. of toxoid every three months.

TABLE IV.—*Maintenance of Antitoxic Titre by Occasional Doses of Toxoid (Antitoxic Titre before Treatment = 3 Units per c.cm.)*

Treatment	Antitoxic Titre
0.1, 0.2, 0.3 c.cm. toxoid	6 units
0.3, 0.4, 0.5, 0.5 c.cm. toxoid	6 "
Interval of 3 months	6 "
0.5 c.cm., then interval of 3 months	6 "
0.5 " " "	6 "
0.5 " " "	6 "
0.5 " " "	6 "
0.5 " " "	6 "

With the staphylococcus, however, the antitoxic power of the blood is only one part of the immunity, and we have seen a number of recurrences of boils in patients who at the time of the recurrence had a high antitoxic content in their blood. In Table V are recorded a number of patients whose boils recurred when the antitoxic power of their serum was from 5 to 6 units per c.cm.

TABLE V.—*Recurrences with High Antitoxic Power*

Recurrence after :	Antitoxic Power
2 months	6 units per c.cm.
4 "	5 " "
4 "	5 " "
9 "	6 " "
10 "	5.5 " "

We have been using staphylococcus toxoid in the treatment of local infections for the last six or seven years, and we have employed vaccines on similar cases for over thirty years. On looking up the records certain interesting facts emerge. (1) It is very difficult over a large series to say whether vaccines or toxoids were the more effective in recurrent furunculosis. (2) Some patients whose attacks of boils recurred in spite of vaccine treatment were promptly "cured" when toxoid treatment was given. (3) Some patients in whom toxoid apparently failed were rapidly "cured" with vaccine.

It is quite reasonable to find that toxoid therapy will cure some vaccine failures and that vaccine therapy will likewise cure some toxoid failures, as the two methods are complementary. Each represents an immunizing process with a different antigen of the staphylococcus, and one gives an antitoxic and the other an antibacterial immunity. It is now our custom either to administer toxoid and vaccine mixed together or to give alternate doses of the two antigens at weekly intervals. In this way it appears that the best results can be obtained.

Influenza

The question whether or not an individual can be protected against epidemic influenza by means of a vaccine is one which is of the greatest importance in medical

practice. This question leads to another, What is epidemic influenza? Before the great war we were quite content to think that it was an infection by the influenza bacillus of Pfeiffer, and there is no doubt that in the 1918-19 pandemic this bacillus was present in practically 100 per cent. of cases in England and France, and that it was responsible for much of the mortality. However, more recent work, especially at the Medical Research Council laboratories, has definitely established that the primary infective agent in epidemic influenza is a virus. This virus can be passed on in ferrets and mice, and can be cultivated in the incubator in chicken embryos still in the shell. It appears likely that mild influenza, such as the first wave of 1918 or the more recent epidemics, is to all intents and purposes a pure infection of the virus and that the serious and deadly epidemic of 1918-19 was due to a combination of this virus with a bacterium, especially the influenza bacillus.

A very interesting influenza story comes from America. During and following the 1918 pandemic an epidemic of swine influenza appeared among the pigs in that country. This swine influenza is a serious and fatal disease, and has been investigated by Shope (1937) more thoroughly than was possible in any human disease. Shope discovered that swine influenza was due to a combined infection with a virus and a bacillus practically identical with the influenza bacillus of Pfeiffer. If he infected pigs with a pure virus without the bacillus a transient fever resulted and all the pigs recovered; if he infected them with the bacillus alone practically nothing happened; but if he infected pigs with both the virus and the bacillus typical swine influenza resulted and the pigs died with pneumonia. Shope found that the pigs which had been given the pure virus and had recovered from the trifling infection that resulted were completely immune to fresh infection with the virus. He also found that inoculation of the pigs with vaccines made from the influenza bacillus gave some degree of protection against swine influenza, although it was not so complete as the protection with the virus. Table VI, which

TABLE VI.—*Effect of Influenza Bacillus Vaccine on Swine Influenza (from Shope)*

Pig No.	Time between Vaccination and Test (Days)	Clinical Illness	Presence of	
			Virus	Bacillus
1	9	Mild influenza	+	-
2	9	2-day fever	+	+
3	9	Not definitely ill	+	-
4	Control (no vaccine)	"Filtrate disease"*	+	+
5	14	Typical swine influenza	+	+
6	14	Mild influenza	+	+
7	14	4-day fever. Mildly ill	+	+
8	14	" "	+	+
9	14	" "	+	-
10 } 11 }	Controls (no vaccine) {	Typical swine influenza	+	+

* "Filtrate disease" is the name given by Shope to the disease resulting from a pure virus infection.

is adapted from Shope, shows the protection which he obtained in pigs with heat-killed vaccines of the influenza bacillus. The animals received three doses of vaccine, and then after nine or fourteen days they were infected intranasally with a combination of virus and influenza bacillus.

Here it will be seen that all the animals receiving the vaccine of the influenza bacillus suffered from a much milder disease than the controls, which had not been protected. This observation is of the greatest interest in view of the attempts made to prevent influenza in man with bacterial vaccines, especially those of the influenza bacillus. After the 1918 pandemic many papers appeared stating that such vaccines had conferred a degree of protection against influenza, but none of the figures given have satisfied statisticians. In view, however, of Shope's experimental results with pigs it appears that these claims were justified and that protection can be obtained by such bacterial vaccines.

Attempts are at present being made to protect man against influenza by means of a vaccine of the influenza virus. The results on experimental animals have been successful, but the opportunity has not yet arisen for the final proof that it can protect man during an epidemic. It seems likely that in the near future it will be possible to obtain a virus vaccine which will give, either alone or in combination with the older bacterial vaccine, complete protection against epidemic influenza in the majority of the inoculated individuals.

Prevention of the Common Cold

This problem has much in common with that of influenza. Attempts have been made to prove that all "colds" are due to virus infections, but even the best workers have not succeeded in demonstrating a virus in the majority of colds in any series. A "cold" is the clinical reaction to any acute irritation of the upper respiratory tract, and bacteriological investigations make it certain that many colds are purely bacterial in origin and are probably often exacerbations of a chronic infection. Even if in some cases the primary infective agent is a virus, much of the discomfort experienced by the patient is due to superadded bacterial infection. What has been said about influenza probably applies equally to colds. No virus vaccine is at present available, but in susceptible people, who often apply to their medical practitioners for protection against recurrent colds, much good can be done by bacterial vaccines such as have been in use for many years.

Synergic Action of Vaccine Therapy and Chemotherapy

The latest development in connexion with vaccine therapy is its association with the new chemotherapy—that is, treatment by means of sulphanilamide, M & B 693, and similar chemicals. I have shown that the action of M & B 693 on pneumococci in human blood is bacteriostatic and not bactericidal. This means that the chemical interferes only with the growth of the infecting bacteria; the natural defensive mechanism has to complete their destruction. It follows that the more powerful these defences are the more rapid and complete will be the killing of the bacteria. In other words, the higher the degree of immunity of the patient the better will be the apparent result of treatment by M & B 693. It is thus incumbent on the physician to use any possible means of increasing the immunity as well as to give a drug like M & B 693.

I have shown *in vitro* that the addition of antipneumococcal serum to a mixture of blood and M & B 693 greatly enhances the antibacterial power of the mixture. Several workers have shown that an antiserum used in conjunction with sulphanilamide saves animals which would have died if treated with antiserum or sulphanilamide alone: probably the most striking communication on this subject is that by Loewenthal (1939).

Nothing has yet appeared in connexion with the combination of vaccine therapy with these new chemicals, except the suggestion by Cokkinis and McElligott (1938) that in gonococcal infections better results are obtained if the treatment is delayed for a time to allow an increased immunity to develop as a result of the infection, or if immunity is artificially induced by a vaccine. Recently Maclean, Rogers, and I (1939) have made experiments which show that vaccine therapy can with advantage be combined in pneumococcal infections with treatment with M & B 693. Mice were inoculated with a single dose of vaccine containing 25,000,000 pneumococci. After six days these, together with uninoculated mice, were infected with a virulent culture of the same pneumococcus. Some of these mice were treated with M & B 693 and some were not. The results obtained are shown graphically in the accompanying table. It seems quite clear from these that a single dose of vaccine saved the animals, which would inevitably have died if treated with M & B 693 alone.

Table showing Synergic Action of Pneumococcus Vaccine and M & B 693

Infecting Dose of Pneumococci	Number of Mice	Treatment
1 m.l.d.	● ● ● ●	Control mice untreated
100 m.l.d.	● ● ● ●	25 million vaccine; no M & B 693
100 m.l.d.	● ● ● ●	No vaccine; 5 daily doses of 25 mg. M & B 693
100 m.l.d.	○ ○ ○ ○ ○	25 million vaccine and 5 daily doses of 25 mg. M & B 693
1,000 m.l.d.	● ○ ○ ○ ○	

● = Mouse died. ○ = Mouse survived.

A confirmatory experiment was done with rabbits, except that these were infected with the virulent pneumococcus intradermally instead of intraperitoneally, as in the case of the mice. Here again the vaccinated rabbit not treated with M & B 693 died; the uninoculated rabbit treated with M & B 693 lived, but had a very serious illness for four days, when pneumococci could be recovered from the blood; the vaccinated rabbit treated with M & B 693 had only a trifling illness, and pneumococci were never recovered from the blood stream. The temperature charts of the two rabbits (vaccinated and unvaccinated) treated with M & B 693 are of interest.

Chart showing the synergic action of pneumococcal vaccine and M & B 693. The continuous line = unvaccinated rabbit; the broken line = vaccinated rabbit: both were treated with M & B 693. The arrow indicates the time of infection with pneumococci. Blood cultures: vaccinated, always negative; unvaccinated, + (indicated above).

It would be well to consider the application of these results to the treatment of pneumonia in man. This is a serious disease, and from the communications which have already appeared there is no doubt that M & B 693

has a profound influence on the infection. There is no doubt also that the simple administration of this drug does not save all the patients, and it is necessary, therefore, to consider whether we can supplement its beneficial action. It has been shown that a specific antiserum acts synergically with sulphanilamide in streptococcal infections, and that *in vitro* pneumococcal serum acts in the same way with M & B 693. No reports have yet been made regarding the united action of pneumococcal serum and M & B 693, but there is little doubt that this will be a good combination. However, pneumococcal serum is not available in all types, it is expensive, and it is not always easy to administer in general practice.

It would seem that there is more hope in vaccine therapy. Vaccines are available for every type of pneumococci, or a polyvalent vaccine can be used which contains all of them. Vaccines are cheap and are easy to administer. It has been shown by many workers that even large doses of pneumococcus vaccine can be given in cases of pneumonia without risk of a negative phase, and Wynn has for many years been using stock vaccines as a routine treatment of pneumonia. Barach (1931) has shown that three days after the administration of pneumococcal vaccine to patients suffering from pneumonia specific antibodies can be demonstrated in their serum. Maclean, Rogers, and Fleming (1939) have demonstrated that mice which had received a single dose of pneumococcal vaccine and did not show a high degree of immunity recovered when treated with M & B 693, whereas the unvaccinated mice infected with the same dose of pneumococci and receiving the same treatment with M & B 693 all died.

These observations, taken together, make a good case for the use of pneumococcal vaccines in pneumonia in man in conjunction with M & B 693. If possible the pneumococcus should be typed and a vaccine of the specific type administered, but if typing is not possible then a stock polyvalent vaccine can be administered at once; and of course the sooner the vaccine is given the better the result is likely to be.

Failures and Successes in Vaccine Therapy

One sometimes hears that in a particular case or condition vaccine therapy has been tried and has failed. It is well to remember that there is vaccine therapy *and* vaccine therapy, and this may be illustrated by the following cases.

The first case was that of an American doctor practising as a specialist in diseases of the chest in one of the Western States. He had worked in our laboratories at St. Mary's for long periods before and during the war, and when he returned home he contracted severe influenza during the 1918-19 epidemic. After recovery he suffered from typical spasmodic asthma. He tried the ordinary remedies and climatic treatment; then he had his tonsils removed in New York, and there he was treated with a vaccine made from bacteria isolated from his sputum—all without benefit. Here, then, was a case in which vaccine therapy had been tried and failed. Fortunately he thought he would come to London to see whether his old colleagues at St. Mary's could help him. Immediately on arrival at Waterloo Station he had a severe asthmatic attack, so it could not be said that the London climate suited him. Examination of his sputum showed organisms, but nothing that seemed likely to account for his condition. The faeces were then examined, and an almost pure culture of a haemolytic enterococcus was found. He was treated with a vaccine of this organism in doses beginning with one-third of a million and increasing eventually to 1,000 millions. Apart from an attack soon after treatment was started he had no more asthma, and he is still free some seventeen years afterwards.

When he was convinced that he was recovering he sent the news to a fellow practitioner in the Western States who suffered from asthma with a similar history. She travelled some 6,000 miles to have a vaccine made from the haemolytic enterococci in her stool, for she also had a great preponderance of this organism. On the boat on the way over she found another asthmatic with a similar history. He, too, had an intestine full of enterococci, and a vaccine was successful in his case also.

These three cases happening together, all due to an enterococcal infection of the gut—a condition that is usually neglected—could not but make a lasting impression; but the moral of the tale is that in a particular case vaccine therapy was tried and had failed, and yet when it was tried again in another way it was eminently successful. This case could, I am sure, be paralleled by hundreds of others.

In conclusion I must thank my colleagues, and especially Drs. Maclean and Young, for permission to make use of work in which they took a considerable part.

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DERMATITIS FROM SULPHONAMIDE COMPOUNDS

BY

DAVID ERSKINE, M.D., D.P.H.

Dermatologist to the Dreadnought Hospital; Medical Officer in the Venereal Diseases and Dermatological Departments, Guy's Hospital

The extensive use of the sulphonamide group of drugs has resulted in a certain incidence of toxicity. The various manifestations of this toxicity have been reported in the literature from time to time, but comparatively little attention has so far been drawn to the skin eruptions that may be encountered during the administration of the drugs. These eruptions often raise problems of differential diagnosis, and their variations in type and degree and in their response to treatment are not without interest. A brief review is here attempted of some thirty-six cases of sulphonamide dermatitis seen chiefly at Guy's Hospital during a fairly extensive administration of these drugs in the venereal diseases and dermatological departments over the last three years. The cases are surveyed from a clinical aspect, and certain information which is now considered necessary has frequently not been recorded, as it was only during prolonged observation that various characteristics of the eruptions became more clearly appreciated. Nevertheless, it has been felt that the information available may be of some value in correlating the toxicity of the drugs.

Newman and Sharlit (1937) reported four cases of light sensitization following sulphonamide administration; the eruptions occurred on the exposed areas, between the second and fifth days; they were macular in type, with raised papules and oedema. The eruptions faded during five to six days of protection from light, and could be reproduced on giving further sulphonamide without exposure to light. These cases also exhibited patch sensitivity. Menville and Archinard (1937) reported similar cases occurring after large doses of prontosil—one case escaping eruption after exposure to sunlight on the ninth