

Original Articles.

THE PRESENT STATUS OF VACCINE THERAPY.*

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It will be clearly impossible to give, within the limits of a single paper, a complete survey of the very extensive literature on the treatment by vaccines. What I shall attempt to do is to indicate to you in what degree this form of therapy has fulfilled the very far-reaching claims made for it by Wright and his school.

Before entering into a discussion of the merits of vaccines, it will be well to consider briefly the principles on which the treatment rests. The term "vaccination," originally confined to the inoculation of the virus of cowpox, was extended by Pasteur to include the use of any living virus to produce immunity towards that virus. Wright has still further broadened the conception, so that, as defined by him, a vaccine is "any chemical substance which, when introduced into the organism, causes there an elaboration of protective substances." The term is certainly incorrect from the etymological point of view, but it has become too firmly rooted in the literature to be eradicated.

Immunity against a bacterial disease is *naturally* acquired, for a longer or shorter time, whenever the subject undergoes the disease in question. Thus a person recovering from typhoid fever is immune against that form of infection, usually for life. This immunity is due to certain substances which are formed in response to the stimulating effect of bacterial products, and are unfavorable to the multiplication of bacteria within the organism.

Immunity can be induced artificially by inoculation with non-fatal doses of the corresponding bacterium. Such a process is known as *active* immunization. The serum of such animals contains various substances unfavorable to the infecting organism and is called, for that reason, an anti-serum. The attempt to influence infectious processes by the inoculation of an anti-serum is called *passive* immunization. There is a wide difference between the use of the various anti-sera and the injection of bacterial vaccines; the former are chiefly employed for their direct action on the bacteria or their toxins, the latter to stimulate the formation of protective bodies.

These latter substances, or antibodies as they are often called, are found in the blood serum and act in various ways; the bacteriolysins destroy the bacteria, the antitoxins neutralize the bacterial poisons, the agglutinins bring about a clumping of the organisms, and, last but not least, the opsonins act on the bacteria in such a way that they can be taken in by the polynuclear leucocytes, a process known as phagocytosis. The opsonins require a somewhat more detailed consideration because their measurement has been declared by Wright to be an essential part of the vaccine treatment. Most bacteria undergo

only a slight amount of phagocytosis in the absence of serum. In normal serum there is a certain amount of opsonin, for if it is added to a mixture of washed leucocytes and bacteria, more phagocytosis will take place. There has been considerable dispute about the nature of this opsonin of normal serum, as to whether it is one substance which acts on many kinds of bacteria, or a number of substances which are specific, i. e., which act each on a single micro-organism and no others. According to this latter view there would be in normal serum a specific opsonin for the tubercle bacillus, another for the staphylococcus, and so on. The latest work on the subject seems to demonstrate the specificity of the normal opsonins. By active immunization the opsonin for the corresponding organism can be greatly increased. The opsonic content of a serum can be measured by an ingenious method introduced by Wright. A mixture is made in definite proportions of the given serum, of washed leucocytes and of the bacterium to be tested. The mixture is incubated for a certain time, smears are then made and stained, and the average number of bacteria taken in by a single leucocyte is determined. A similar process is gone through with, using normal serum, and the average number of bacteria per leucocyte undergoing phagocytosis is again estimated. The quotient obtained by dividing the figure obtained for the given serum by that of the normal serum constitutes the opsonic index.

Wright showed that after the inoculation of a given bacterium there occur certain definite changes in the opsonic index for that organism. First, there is a very brief rise, followed by a decided fall, called the negative phase, and lasting usually a day or two. Next comes a second rise to a point decidedly above normal, and this positive phase or high tide of immunity may be maintained for a considerable period, usually from several days to a week. Similar fluctuations have been shown for most of the other protective substances. After a while the index falls to normal again, but may be again raised by a second inoculation. In a number of chronic localized bacterial processes Wright found that the opsonic index was considerably below normal, and that the inoculation of the causative bacterium caused a rise in the index. By repeated inoculations, properly interspaced, he was able to maintain the index at a high point, and under these circumstances a cure took place. It was these observations which led him to recommend the use of bacterial vaccines to combat various infectious processes.

Wright claimed, and still claims, that the dosage and the time for repeating inoculations ought to be determined by means of the opsonic index. He showed that too large doses cause an unduly prolonged and severe negative phase, and that a repetition of the inoculation during this period causes a still further depression of the opsonic index, accompanied by a change for the worse in the disease process. The injection of too small amounts of vaccine, on the other hand,

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fails to stimulate the production of protective substances.

There can be no doubt of the fact that unduly large doses are harmful and that for each bacterium, and probably for each individual case, there is an optimum dose that will give better results than either larger or smaller amounts. Leaving aside, however, the question of the accuracy of opsonic methods, the technic is far too difficult and time-consuming ever to come into general use, and now that the maximum and minimum limits of dosage have been approximately determined, quite as good results are obtained by those using the clinical symptoms as a guide as by those who follow the opsonic index. For this reason the rest of this paper will deal with the results obtained by the use of vaccines, without regard to the opsonic index.

Prophylaxis.—The question of the prophylactic inoculation against infectious diseases might, strictly speaking, be held somewhat foreign to the theme assigned to me, but the two rest on the same scientific principles and a review of the results which have been obtained will be instructive on account of the growing importance assigned to the prevention of disease.

The fact that animals can be immunized against bacterial diseases by the inoculation of pure cultures of the corresponding organism, or "vaccination," was first discovered by Pasteur and applied by him in 1880 to the prevention of chicken cholera, and later to that of other animal pests. It was not till long afterwards, however, that this principle was applied to human epidemics, the first to employ it on a large scale being Haffkine. This patient investigator, a pupil of the illustrious Pasteur, having found it possible to immunize animals against cholera by the inoculation of living cultures, in 1894 began the immunization of human beings in India.¹ In all, over 100,000 persons were vaccinated. The incidence in the inoculated was reduced to one tenth that of the non-inoculated, but the disease once contracted did not run a milder course in the inoculated than in the controls. The most striking results were noticed in a village of 200 inhabitants, of whom 116 were inoculated. Among these latter there were no cases, as against 9 cases with 7 deaths among the non-inoculated. Immunity was obtained at the end of four days and persisted about fourteen months. Similar results have been obtained by Strong² in the Philippine Islands.

The success of this measure led Haffkine³ to the use of prophylactic injections against the bubonic plague, although his animal experiments with the bacillus of plague had not been encouraging. He employed old bouillon cultures killed by heat, containing both the bodies of the bacteria and the soluble products. These inoculations proved equally efficacious, although in a somewhat different way, for not only the incidence of plague was decreased, but also the mortality in the inoculated who became infected. The best results were obtained where the inoculations were done on a small scale; e. g., at the prison of

Byculla, among 177 non-inoculated, there were 12 cases and 6 deaths; in 147 inoculated, only 2 cases and no deaths. In the years 1902-3, in the Punjab, the inoculations were carried on on an enormous scale, in round numbers 187,000 being injected, with 640,000 controls. The incidence of the disease was 1.8% among the inoculated, 7.7% among the non-inoculated, while the mortality in those contracting plague was less than half as great among the inoculated. The total mortality from plague was thus ten times greater among the non-inoculated.

The rapid production of immunity in the case of the anti-plague vaccinations was very striking, a marked protective influence being apparent within twenty-four hours after injection. The immunity lasts for a number of years.

In the case of typhoid fever⁴ excellent results have been obtained by Wright and by the Germans. Immune substances appear in about a week after the injection and have been demonstrated in the blood four years afterwards. In 20% a negative phase was observed which might last as long as three weeks. The best results were obtained by using two injections about eleven days apart. Under Wright's direction 100,000 British soldiers bound for the tropics were inoculated. The morbidity was greatly reduced, and in those of the inoculated who contracted typhoid subsequently, the disease ran a shorter and milder course, with fewer complications and lower mortality. There is considerable variation in the figures given, partly owing to the fact that often no distinction is made between those who had received one inoculation and those with two. Perhaps the most striking results were seen in Egypt and Cyprus for the year 1900. Among 1,972 non-inoculated there were 68 cases and 10 deaths, while among 1,417 inoculated there was but 1 case, with 1 death. Moreover, this fatal case had been inoculated shortly before and was, therefore, very possibly in the negative phase, in which there is hypersusceptibility. There have been some other cases which have come down with typhoid soon after inoculation and these have run a severe and often fatal course, so that it is eminently advisable that the inoculations should be performed in a locality where there is no typhoid. Leishman⁵ improved the process of preparing the vaccine by reducing the temperature to which the bacteria are heated from 62° C. to 53° C. With this new vaccine still better results were achieved, the incidence per 1,000 in those exposed to infection falling to 3.7 in the inoculated, as against 32.8 in the controls. The Germans have had a similar experience with anti-typhoid inoculations, though less extensive, and Italian observers have reported favorable results from its use in villages where typhoid was endemic.

Vaccination against typhoid seems destined to play an important part in times of war and in the case of persons going to the tropics. It might well be used in this country in localities where typhoid is very frequent, and in the case of those especially liable to infection, particularly nurses

and ward-tenders in hospitals, who have been shown to be about sixteen times more likely than other people to contract this disease.

In the case of bacillary dysentery, that other scourge of armies in times of war, Shiga⁶ reports no effect on the incidence of the disease from prophylactic inoculation, but a great decrease in the mortality among the inoculated. Further progress may be expected in this direction.

There seems to be a possibility of some future development along these lines with other diseases which occur in epidemic form, and exposure to which may be foreseen. Thus it would be a distinct advantage if one could immunize against influenza. Unfortunately, however, so many different organisms have been found in epidemics diagnosed clinically as "grippe" that it would be of little use to immunize against Pfeiffer's influenza bacillus alone. Again, it might be possible to immunize against the pneumococcus and thus do away with that bugbear of the surgeon, post-operative pneumonia.

Several men⁷ have recommended the use of vaccines before operation with the idea of preventing secondary infections. They give injections of staphylococcus aureus and streptococcus, throwing in a dose of bacillus coli if the operation is on the alimentary tract. It is too early to say whether such procedures are worth while or not. Some interesting experiments might be performed, however, such as immunizing against the pus-producing cocci before opening cold abscesses, which in the ordinary course of events are almost certain to become secondarily infected.

When we come to consider the value of vaccines in the treatment of infections already established, the statistical method, so valuable in the case of prophylactic inoculations, leaves us more or less in the lurch. Many of the writers report only selected cases, or, where the end results are given, the number of cases treated is too small, and there are no controls. And even supposing that statistics were obtainable concerning large series of cases, it is often impossible to find reliable figures concerning the results under other forms of treatment.

Under these circumstances one has to fall back largely upon general impressions, the value of which varies, of course, immensely with the experience and reliability of the observer. Still, where opinions concerning a given treatment are nearly unanimous, and especially where large numbers of cases which have obstinately resisted other forms of treatment yield fairly promptly to the use of vaccines, it is fair to suppose that the relation is one of cause and effect. For, although it would necessarily often happen that such an occurrence was purely a coincidence, it could not be expected that such a thing should come to pass consistently.

In discussing the results obtained by the use of vaccines, it will be well to consider separately the localized infections and the general infections. Under each of these headings it will be convenient to take up the diseased conditions according to the bacteria involved.

Localized infections.—It is in the strictly localized infections without toxemia that, on theoretical grounds, we should look for the best results from vaccines, and these expectations in practice are not disappointed. The walling-off of the local process, with the blocking of lymph spaces, prevents not only the passing into the general circulation of toxic materials which might stimulate the formation of antibodies, but also the access of the opsonins contained in the blood serum to the focus. The exudate, which is, therefore, largely in a state of stagnation, becomes very poor in opsonins, owing to the absorption of these substances by the bacteria; phagocytosis is at a standstill and the bacteria are free to multiply. Add to this, in the case of abscesses, the tryptic substances set free by the disintegrating leucocytes, with their deleterious action on the tissues, and we have a combination of conditions unfavorable to cure. Recovery is hastened by the immunizator in two ways: First, by evacuating the exudate, either by tapping in the case of effusions into the serous cavities, or by incision and drainage; and, second, by raising the amount of protective substances in the blood by means of the injection of the appropriate vaccine. In poorly vascularized lesions it is necessary to determine a greater blood supply to the part by the use of heat, counter-irritants or similar measures. Thus, in the case of lupus, in the ulcerative type, a cure may be obtained by injections of vaccines alone, while in the dry, scaly variety it is necessary to induce local hyperemia to enable the opsonins to get into contact with the diseased tissues. Hence a combination of the use of x-rays and tuberculin may be successful where either measure alone fails.

The greatest triumphs of the vaccine therapy have been attained in infections with the staphylococcus. In furunculosis there is prompt relief to pain, suppuration takes place more quickly and there is early healing with very little scar. A "medical incision" to let out the pus will accelerate matters, but the extensive surgical measures formerly employed have become unnecessary. Moreover, recurrence of the boils, the worst feature of the disease, is usually prevented, or if not, the new lesions are more insignificant and promptly yield to one or two inoculations; of course a case will occasionally be met with which is refractory, and a few others may require a prolonged course of injections before immunity is finally attained. In infantile generalized furunculosis, a dangerous and often fatal disease, the mortality has been considerably reduced by the use of vaccines. The duration of freedom from attacks is still a matter of uncertainty and will depend largely on the circumstances of the individual case. Often, no doubt, it will be very lasting, for here, as elsewhere, it may be sufficient to break a single link in the chain of disease. In the case of carbuncles, fully as good results are obtained, and carbuncles of the lip, hitherto so dangerous to life, may be expected to yield to vaccines if taken before metastasis has occurred.

The results in acne are less brilliant, for while many, perhaps the majority, of patients are markedly benefited, complete cures are rather the exception than the rule; the treatment must often be prolonged over a period of months, and relapses are prone to occur. Still, in many instances, an improvement not attainable in any other way is seen. The cases most likely to derive benefit from vaccines are those with a tendency to form pustules; the indurated type of acne may show much improvement after a long course of injections, while the oily, seborrheic form is not likely to be improved. Probably the reason for this lies in the fact that the staphylococci are only secondary invaders, the real causative organism being apparently the acne bacillus. Quite recently Fleming⁸ reported greatly improved results from the use of acne bacillus vaccines, either alone or supplemented by the staphylococcus according to circumstances. A large majority of his patients was greatly improved, and in "a fair proportion" complete cure was seen.

Numerous other localized infections due to the staphylococcus have yielded very satisfactory results. With regard to "septic hands," Hartwell, Streeter and Green,⁹ in a rather large series of cases, did not feel that the vaccines had more to do with the favorable outcome than the surgical measures employed, except in indolent cases which had come to a standstill. Most other observers believe in the efficiency of vaccines in this condition, though the number of cases treated by each was quite small. It is certainly very difficult where operative measures are used coincidently with vaccines to tell how much is due to the one and how much to the other, and further investigation along these lines, with comparison of a large series of vaccine-treated cases with controls treated by surgery alone, is very desirable.

Data with regard to the results from streptococcus vaccine are somewhat scanty. Still it would appear that benefit is the rule, though not so striking or certain as in staphylococcus infections. In erysipelas little effect is seen; perhaps the disease is somewhat shortened. It is possible that some of the unsatisfactory results may have been due to the method of preparing the vaccine, for Weaver and Tunnell¹⁰ found a vaccine made from streptococci killed by heat quite without value in the complications of scarlet fever, while vaccines prepared by killing the bacteria by prolonged exposure to galactose gave very good results, though their series was much too small to be conclusive. And Leary¹¹ states that he has obtained of late much more success in streptococcus infections by using vaccines which have been killed by a much shorter period of heating than Wright prescribes. It is also apparently of great importance in streptococcal infections to use "autogenous" or "homologous" vaccines, i. e., those prepared from cultures obtained from the patient, and not "heterologous" or "stock" vaccines which are made from cultures obtained in other ways.

Experience with the pneumococcus has been chiefly confined to the treatment of sinuses following empyema. Here, although some failures are recorded, it is the opinion of reliable observers, among whom Hale White may be mentioned, that the sinuses heal more rapidly than they are wont to do under other treatment. It is very desirable that vaccines should be administered soon after operation in order that secondary infection may be avoided. The use of vaccines in pneumonia will be discussed later.

Of the localizations of the gonococcus, that in the joints seems most amenable to vaccine treatment, and it is not too much to say that vaccines offer better prospects of cure than any other treatment. A careful reading of the reports of Hartwell,¹² of Irons¹³ and of Cole and Meakins,¹⁴ comprising in all 97 cases, cannot fail to impress any one familiar with the tedious course of this form of arthritis as ordinarily treated. The best results are attained in subacute and chronic cases, in which, with few exceptions, the swollen joints return to their normal contour, frequently very quickly, the process is checked and the products of inflammation are absorbed. Naturally, fibrous ankylosis remains unaffected. Patients who have been disabled for months and even years, and have not benefited by other treatment, have become free from pain and have recovered satisfactory joint function. Hartwell treated five patients with "poker spines," four of whom had suffered for a year or more; all were relieved from pain and recovered a considerable degree of motion.

In acute cases the results, though favorable, are less striking. Hartwell observed that the first few injections did not seem to produce immunity, for they did not always prevent fresh joints from becoming inflamed.

As might be expected from what is known of gonorrheal infections, immunity is of short duration, 12% of Hartwell's series having a relapse within a year or so. It is encouraging to note, however, that in all but one of the cases the recurrence of arthritis was due to a fresh infection from without, to a fresh urethritis. Otherwise the cures seem to have been permanent. In one case of Cole's a patient dying of pneumonia four weeks after the last of three injections showed gonococci in pure culture in the affected joint, although a symptomatic cure had been attained. This is probably, however, an exceptional occurrence, and in any case merely shows that bacteria may remain in an inactive state without causing symptoms; it does not militate against the value of vaccine therapy.

In acute urethritis, vaccines have not proved useful, and in the chronic forms their value is, to say the least, doubtful. Some have thought them beneficial in posterior urethritis and prostatitis, while others have failed to see any effect. In epididymitis some favorable results have been noted. In gonorrheal ophthalmia the method has not been employed extensively.

In gonorrheal vulvovaginitis of children, a disease which, by reason of its obstinacy and the

danger of hospital and asylum epidemics, is especially important, encouraging results have been recorded. All observers except Park¹⁵ have found that the purulent discharge was rapidly diminished, though many of the cases had been treated locally for weeks with antiseptics without benefit. Butler and Long¹⁶ claimed a complete cure, both symptomatic and bacteriological, in all their 12 cases, but they were not followed after leaving the hospital, so that the possibility of relapses was not excluded. Hamilton and Cook,¹⁷ who made a very careful study, found that although the discharge was usually stopped, it was frequently impossible to secure negative smears, so that only 18 out of 30 patients could be discharged from the hospital free from gonococci; this, to be sure, was considerably better than the results in controls receiving local treatment, of whom only 8 out of 30 could be discharged without gonococci. They found that the results were much better if old strains of gonococci grown for a long time on artificial media were used. The chronic cases did better than the acute. In any case, vaccines have proved superior in this condition to local treatment, to which several grave objections may be made.

In the few cases of epidemic cerebrospinal meningitis treated with meningococcus vaccines the results were not striking, so that the serum treatment is greatly to be preferred in this disease.

Infections with the colon bacillus have been found, on the whole, amenable to vaccines. In cystitis and pyelitis due to this organism, even if of long duration, a symptomatic cure is often obtainable, although the bacteriuria usually persists. However, it should be borne in mind that in pyelitis it is the rule to have bacteria persist in the urine after apparent cure; Lenhartz,¹⁸ in a large series of women with colon pyelitis, found the bacilli in the urine at the time of discharge from the hospital in the majority. In acute pyelitis treated with vaccines a sudden fall of the temperature has been observed, but it should be remembered that this frequently occurs independently of any treatment. Many chronic cases of cystitis of an obstinate type have shown very marked improvement, though it is often necessary to continue the injections over a long time. Hale White¹⁹ has seen a cure in several cases of ulcerative colitis of long standing, and vaccines have been used with benefit in cholangitis, fecal fistulae, pelvic abscesses (after drainage) and in septic endometritis.

A very large amount of work has been done on the use of vaccines in tuberculosis of all sorts, and, on the whole, with gratifying results. The outcome seems to depend partly upon the vascularity of the lesion, partly on the extent and duration of the disease, and whether secondary infection has taken place or not. Tuberculosis of the iris, for instance, where there is a small focus easily detected and richly supplied with blood vessels, can be completely cured in almost every instance, as von Hippel²⁰ has shown. Again, lupus of the ulcerative type, especially

where it affects the mucous membranes, yields very good results, although prolonged treatment is necessary. The dry, scaly form of lupus, which is poorly vascularized, is apt not to do well with tuberculin, though some cases are cured by a combination with x-ray treatment or the Finsen light.

With regard to tuberculous lymph nodes, most observers agree that tuberculin is an invaluable remedy. If administered before caseation has occurred, a cure is the rule, though sometimes a few small glands remain. Caseated masses are absorbed extremely slowly and may require operative removal; abscesses must, of course, be emptied, but it may be sufficient to aspirate them instead of resorting to broad incision. Where sinuses are already present, the prospect is not so favorable and it may be necessary, owing to secondary infection, to use mixed vaccines. In short, the use of tuberculin will render many operations unnecessary and will be found of benefit before and after surgical measures and in inoperable cases, such as tuberculosis of the mediastinal and mesenteric lymph nodes.

Tuberculosis of the bones and joints may be taken together, as in almost all the cases reported as of the joints the primary lesion is in the bone. The tuberculous polyarthritis without bone involvement has not been extensively treated with tuberculin.

The bulk of the evidence here is very much in favor of tuberculin. Perhaps the most convincing work is that of Smith,²¹ of the Inoculation Department of St. Mary's Hospital, London, since his cases have been followed a long time and the end result is more or less definitely known. His cases were all ambulatory and did not have the advantages of sanatorium or hygienic-dietetic treatment. The usual surgical measures, such as immobilization and opening of abscesses, were employed when indicated. The joints involved were chiefly the knee, hip, ankle and wrist; there were no cases of Pott's disease. Out of the total number, 12 may be excluded because they were still under treatment at the time of writing. This leaves 20 cases, of which 17 were apparently cured, 10 of them with complete restoration of joint function, the remainder with some deformity. The other 3 cases were all greatly improved. The duration of treatment was from seven months to three years. Collier,²² another English surgeon, observed that in 150 cases of "surgical tuberculosis" treated with tuberculin, the general course was smoother and abscesses did not develop during the administration of tuberculin except where caseation or sequestrum formation had taken place previously. Painter²³ reported unfavorable results, only 2 out of 11 patients being markedly improved. It should be noted, however, that his cases were all either advanced or severe, and, consequently, on account of lowered resistance, unlikely to respond favorably to tuberculin, and also that the duration of treatment, about one year, was too short to admit of final judgment. However, one of his cases, with great emaciation and complicated

with amyloid disease, showed a very remarkable gain in every way.

A gratifying improvement in the symptoms may be expected in tuberculosis of the kidneys and bladder, with diminution of pain and frequency of micturition and gain in weight; the use of tuberculin should be persisted in, for occasionally a marked gain is apparent only after a year of treatment. Cures are the exception, being noted by Carmalt-Jones²⁴ in only 16% of 25 cases. For this reason, where it can be demonstrated that the disease is confined to one kidney, nephrectomy probably still offers the best prospects. Tuberculin remains a valuable resource for the numerous inoperable cases and after operation when it has been impossible to remove all the diseased tissue. The chances are apparently somewhat better in tuberculosis of the testicle, for the combined figures of Western²⁵ and Carmalt-Jones show 9 cures out of 22 cases, and only 3 not benefited.

In tuberculous peritonitis something like one half of the patients have improved greatly during a course of tuberculin, but the figures are too small for conclusive deductions. A great deal depends on the type of inflammation present, the power of resistance of the patient and on the question whether or not the lungs are involved. Intestinal tuberculosis of the ulcerative form offers little prospect of cure because it is usually secondary to phthisis. In one case of tuberculous tumor of the cecum²⁶ an apparent cure with disappearance of the mass was reported.

When one comes to consider the tuberculin treatment of tuberculosis of the lungs, it is very difficult to come to a conclusion, for the classification into stages is not always based on the same rules, controls are often lacking, or the cases are not followed long enough. The value of the statistics is further impaired by selection of the patients who are to have tuberculin, most authorities choosing only those patients who are afebrile and in good general condition. The following are perhaps the strongest arguments in favor of tuberculin: (1) The fact that many patients who have come to a standstill and failed to gain under the best hygienic-dietetic treatment respond promptly when tuberculin is given.²⁷ (2) The excellent results obtained by some with tuberculin in ambulatory patients who were not under the influence of other forms of treatment. (3) The opinion of men of the widest experience, such as Trudeau and Turban, that properly selected cases do better with tuberculin than without it. (4) The recent work of Engel,²⁸ from Schlossmann's clinic, on infantile tuberculosis. It is a matter of common knowledge that infants acquiring tuberculosis during the first months of life do not live to see the second year. To this rule there are few exceptions. And further, it has been shown that infants dying of tuberculosis do not at autopsy show any signs of attempt at repair around the tuberculous focus. Now Engel used tuberculin on 8 infants with tuberculosis, with ages varying from three to eight months, and all of these survived the first year in spite of the

fact that in 4 the lungs were involved. Moreover, one of these coming to autopsy later showed marked evidences of repair in the affected lung, with fibrous and granulation tissue about the tuberculous areas. Another showed calcification of a tuberculous bronchial gland.

The question of how tuberculin is best administered cannot be entered into fully here. Suffice it to say that there are two schools, the one using extremely small doses, which are only slightly increased during the course of the treatment; the other, also beginning with small amounts, but gradually working up to comparatively large ones, with the intention of producing immunity to tuberculin. The former method is that advocated by Wright and his followers; the latter is that chiefly employed by the Germans, and in this country by Trudeau and his disciples. It is impossible as yet to say which of these two radically different methods is the better, or which of the many forms of tuberculin is to be preferred. All are agreed, however, on the power of tuberculin to do harm if injudiciously used. In the case of phthisis, most authorities emphasize the advisability of avoiding even slight constitutional reactions so far as possible. In the more sharply localized forms of tuberculosis, such as that of the lymph nodes and bones, there is less susceptibility to tuberculin and less danger from the production of reactions, and in this form, some, like Engel, prefer to give a dose that will cause a decided reaction, repeating that dose until reaction no longer takes place, and then passing on to a higher one.

There remains to be considered a miscellaneous assortment of infections in which some favorable results have been obtained, but not enough to be conclusive. Freeman,²⁹ in a large series of children with whooping-cough, used a vaccine made from the probable causative organism, Bordet's bacillus, and found 31% greatly improved, as against 22% in controls treated with other measures. In bacillary dysentery in Indian jails Gillitt³⁰ observed great benefit from the use of a vaccine prepared from Shiga's bacillus, as recommended by Forster³¹; in 261 cases the mortality was reduced from 5% to .8%, the stay in hospital was shortened and the morbidity much diminished, probably owing to the prevention of chronic dysentery. Good results from vaccines in pyorrhea alveolaris have been reported by Carmalt-Jones³² and by Beebe.³³

Where secondary infections are present, particularly in the case of sinuses, most observers have obtained better results from the use of "mixed vaccines," i. e., from separate injections of vaccines prepared from both the primary and the secondary invaders.

Leaving the strictly localized infections, we come to some others in which there is, to be sure, a local process, but in which bacteria are practically always to be found in the blood stream at some stage of the disease. Of these, pneumonia, by reason of its frequency and high mortality, is the most important. Already a considerable amount of work has been done on the vaccine treatment of

pneumonia, by Wolf³⁴ and Leary¹¹ in this country; Harris,³⁵ and Willeox and Morgan³⁶ in England; and Böllke³⁷ in Germany. Excluding the cases of Harris, which were too few to be of value, and the cases in children, which notoriously give a better prognosis, 122 patients have been treated, with 15 deaths, a mortality of 12%. This includes several cases receiving vaccines very late in the disease and dying soon after. Besides the low mortality, there was a prompt relief of the toxic symptoms, and, in Wolf's series, an unusually early crisis; out of his 11 cases that recovered, in 10 the crisis took place within thirty-six hours after the inoculation, and in 5 it came on the third day of the disease. The other writers have not found any decided shortening of the febrile period. Chronic pneumonia with fever and unresolved pneumonia also have been treated with vaccines, with favorable results.

The best results are obtained by giving a stock vaccine immediately on admission, followed as soon as possible by an autogenous vaccine. The latter may be obtained from the sputum, but Willeox and Morgan believe it is better to use fluid obtained by puncture of the lung with an hypodermic needle. In this way the causative organism is obtained, usually in pure culture, and enough growth to prepare a vaccine can be got in twelve hours.

It is, of course, as the writers themselves emphasize, not permissible to draw conclusions from such a small number of cases in a disease with so variable a course as pneumonia. So much depends upon the condition and age of the patient and the virulence of the bacteria that a very large series of cases will be necessary before the true worth of vaccines in pneumonia can be gauged. In the meantime the results obtained certainly demand further work in this direction.

The value of vaccines in typhoid fever remains problematical. Richardson³⁸ believes that the use of bacterial products decidedly diminishes the incidence of relapse, though otherwise it has little influence on the course of the disease. Vaccines made from killed bacteria have been used so seldom that no conclusions can be drawn.

Generalized infections.—The last group of infections which we have to consider comprises the various forms of septicemia. Here the results are decidedly disappointing. It is true that occasional cures under the use of vaccines are reported, but that has been the case with all of the numerous forms of treatment which have been proposed from time to time. It will be remembered that similar recoveries were reported by the advocates of the intravenous injections of various antiseptics. Such events will happen occasionally in septicemia with any treatment or no treatment at all. With the great improvement of bacterial technic, it has become more and more easy to detect bacteria in the blood, with the consequence that cases are now diagnosed as septicemia which were not so classified in former days. This means that the prognosis of blood infections is considerably better than it used to be.

When we look over the various reports, we find only a small proportion of recoveries under vaccine treatment, so small that it may be fairly doubted if the inoculations had anything to do with the favorable outcome. This is especially true for malignant endocarditis. The only apparent exception is met with in puerperal sepsis. Here it seems very likely that vaccines do good. In most cases, however, the organism was cultivated from the uterus and not from the blood, so that there is a fair possibility that the condition was not one of septicemia, but of local inflammation with toxemia. The remaining cases with positive blood cultures are not sufficiently numerous to be convincing. Hartwell, Streeter and Green⁹ treated 18 cases of severe puerperal infection with vaccines and reported 18 recoveries. Blood cultures were taken in only 4, out of which 2 were positive. Such results are encouraging and call for further work, with more blood cultures and with control cases treated without vaccines.

There remain to be considered a few points connected with the employment of vaccines in general. And first, as to the question between stock and autogenous vaccines. This is a matter of great importance, for the stock vaccines are within the reach of the general practitioner, while the preparation of autogenous vaccines requires the services of a person familiar with bacteriological technic. Most authorities are agreed that in the case of the staphylococcus good results may be usually attained with stock vaccines. The same probably holds good for the gonococcus, though some report better results from the use of the patient's own bacteria. In infections with the streptococcus and the bacillus coli there is little doubt that autogenous vaccines are greatly to be preferred. Of each of these organisms there are a number of varieties differing quite widely in virulence and other characteristics, and it has been observed frequently that infections did not yield to stock vaccines, but improved promptly when bacteria cultivated from the patient himself were inoculated. Similar observations have been made with regard to the pneumococcus. In the case of the tubercle bacillus it has been up to the present impracticable to employ autogenous vaccines on account of the technical difficulties involved.

The very important question of dosage must be decided from the clinical symptoms and the circumstances of the individual case. The use of vaccines may harm the patient if the doses are unduly large, or fail to be of benefit if they are too small. In general a marked change for the worse in the symptoms occurring within a day or two after injection indicates that the dose should be reduced, while temporary improvement soon followed by relapse calls for a larger dose. Feeble, debilitated patients will naturally be more susceptible than the robust, and should, therefore, receive smaller initial doses. In children, as a rule, the dose should be smaller than in adults, though in respect to tuberculin they are often very tolerant, provided the lungs are not in-

volved. The period between doses also depends somewhat on the aspects of the individual case, and no absolute rules can be given. Usually, in chronic processes, the intervals are fairly long, from four days to two weeks, while in the acute infections smaller doses are given at shorter intervals. The following doses, compiled from figures given by various writers, will show the limits usually given, though some recommend even smaller doses than the minimum here given, and others exceed the maximum.

Staphylococcus,	100 to 1,000 millions.
Streptococcus,	5 " 200 "
Pneumococcus,	10 " 200 "
Gonococcus,	5 " 500 "
Colon bacillus,	10 " 200 "
Tuberculin T. R.,	1-10,000 to 1-500 mgm.

At the first injection a rather small dose is given, and this is increased usually to about four times the initial amount. For general infections the doses are smaller; of the streptococcus, 5 to 25; of the pneumococcus, 20 to 50; of the gonococcus, 5 to 100; and of the colon bacillus, 10 to 50 millions.

And now a word as to the limitations of the use of vaccines. They will not and could not be expected to cure all cases, for they depend for their effect on a responsive power on the part of the patient. If this is lacking, no benefit can result. Moreover, the vaccine, if it is to be of use, must contain the organism which is causing the disease process. The practice of injecting dead bacteria of all sorts, and frequently a mixture of various bacteria, in all kinds of conditions, with the hope that by some lucky chance the right organism may be hit upon, cannot be too strongly deprecated, for it is calculated to cast discredit on vaccine methods.

To sum up the present situation, in certain localized infections, particularly those due to the staphylococcus and tubercle bacillus, vaccine therapy has clearly proved its worth and stands on firm ground. In the general infections it has not so far shown results which are distinctly better than those obtained with other forms of treatment. There can be no doubt that there is going to be improvement in the methods of preparing vaccines and in the principles governing their administration. The vaccine therapy is still young and we may expect much progress in the future. The field of immunity is very fertile, and it is being assiduously cultivated.

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LOCAL ANESTHESIA (NEUMANN) IN EAR SURGERY.*

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THE writer had intended this for an original article, but as in the entire literature there were only four papers on the subject, three of them by the discoverer and one abridged translation by Ballin, of New York, which does not entirely cover the above title, he found it almost impossible not to take the words out of Neumann's mouth. With apologies to the latter for a quasi-translation, and with your forbearance, he will proceed.

At this time, when public interest in spinal anesthesia has been somewhat stimulated by the arrival in this country of Dr. Jonnesco and by the newspaper accounts of his work, and while the possibility of the method has been demonstrated, if its advisability is still *sub judice*, the writer thinks it may not be amiss to recall to you gentlemen the fact that in our own specialty we have a method of conscious anesthesia upon which the seal of approval has been set by the world's highest otological tribunal.

To the younger men who may not know, and to the older who may have forgotten, the following quotation from the proceedings at a former session of the International Otological Congress may be of interest: "The Lenvai prize [capital, 3,000 francs] was founded by Baron de Lenvai in the year 1880, the four years' interest of this sum to be awarded to the author of the most marked progress in the practical treatment of affections of hearing since the last congress, or to the inventor of a new apparatus easily portable and considerably improving the hearing power of deaf persons."

This, the Nobel prize of otology, was awarded to Docent Heinrich Neumann, of Vienna, by the Lenvai Prize jury of the International Otological Congress sitting at Buda-Pesth during the last summer.

The award was for his work in local anesthesia in ear surgery. This Jury having rendered its

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