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SOME CAUSES OF FAILURE IN VACCINE THERAPY*

BY

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Vaccine therapy is estimated by various observers^{1 2} to give approximately 80 per cent. satisfactory results. My own experience in over 1,000 cases indicates similar findings. In examining the cases of failure in vaccine treatment the causes can be grouped under the following headings.

UNSATISFACTORY ANTIGENS AND PERSISTENCE OF INFECTIVE FOCI

A successful vaccine depends upon the isolation of the infective organisms in the patient concerned, and a common cause of failure is the employment of unsatisfactory specimens, which may prevent the isolation of the essential pathogenic organisms and therefore render impossible the production of a suitable antigen. In cases of chronic infection particularly, specimens should be examined from all possible sources of infection in the patient. It is not sufficient to presume that the source of infection in such cases is necessarily confined to the condition of which the patient particularly complains. Therefore it is not enough to assume that all or any of the organisms so isolated are pathogenic to the patient, and it is essential that, as far as possible, the antigen employed shall include, at least in the greater proportion, the organisms which can be shown to be pathogenic. The only practical method so far available for obtaining such evidence is the employment of the pathogen-selective culture method introduced by Solis-Cohen in 1927³ and described, as used

by myself, in other publications.⁴ There is still no universal standardization of vaccine dosage, and this variability is frequently a cause of confusion which is difficult to avoid, as the susceptibility of individuals to vaccine dosage may be as real as in the case of a therapeutic drug.

Persistence of infective foci is another frequent cause of failure in vaccine treatment. There are many conditions where a closed focus is present, such as may be found in cases of accessory sinuses, gall-bladder, perirenal, or prostatic infection. If these are allowed to remain closed, vaccine treatment may not only be a failure, but may be definitely harmful, and therefore contraindicated. It is essential that a path of exit for discharge of pathological material from any such focus must be ensured, otherwise a focal reaction may result and develop into a generalized spread of infection. Apart from closed foci, the pathogen-selective method frequently demonstrates the presence of an active infection in areas such as those detailed above, and these findings will call for local treatment, without which vaccine therapy can at best be of only temporary value or may be entirely unsuccessful on account of the persistent reinfection.

IMPROPER SELECTION OF THE PATIENT

Every case of infection is not necessarily suitable for vaccine therapy. There are several conditions which may contraindicate or render such treatment of no avail, and therefore it is essential that some knowledge of the clinical condition present be obtained before prescribing a vaccine.

Prophylaxis

Preventive treatment by vaccine against the risk of infection from catarrhal, intestinal, or septic infections in persons of normal health is usually successful and uneventful. Failure, however, occasionally occurs, and the presence of an unsuspected focus of infection is usually the reason. This may have rendered the patient sensitive to the usual and comparatively large dose of prophylactic vaccine, and such findings may require that subsequent immunization should be carried out with small doses of the appropriate autogenous vaccine, while at the same time the infected foci, if found, must be efficiently dealt with by operative or local treatment.

Therapeutic Treatment

In acute cases of infection failure of vaccine therapy is frequently caused by the indicated vaccine not being administered early enough to ensure any chance of success. In cases of pneumococcal, staphylococcal, streptococcal, or gonococcal infection, large doses, given in the earliest stages, will usually either abort the infection or rapidly raise the patient's specific resistance so that the condition is brought to a satisfactory termination more speedily. There is comparatively little risk of reaction in acute cases, as the patient is not sensitized to the infection, as is apt to be the case in subacute and chronic conditions. In acute purulent conditions, if adequate drainage is not present, vaccine therapy should be withheld until such is established. Indeed, disturbing or even disastrous results may follow the administration of vaccines in cases of antral, ethmoidal, and mastoid infections, or abscesses, empyemata, etc., when inefficient drainage exists.

In subacute infections vaccine therapy may fail, not by its being unduly postponed, but through the patient's inability to respond owing to temporary exhaustion of the normal antibody. This indicates the need for reinforcing the general tissue response before vaccine therapy can be effective.

In chronic infections, such as catarrhs of long standing, asthma of bacterial origin, infective arthritis, and gastrointestinal and cutaneous infections, the need for a general

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blood and biochemical examination is frequently of even greater importance, and through the neglect of this precaution some haemopoietic, metabolic, or endocrine defect may well be overlooked, the correction of which is essential either to the recovery of the case or to its ability to respond to specific immunization. For example, the finding of a leucocytosis may indicate the presence of an unsuspected focus of infection, requiring special surgical treatment. The presence of a leucopenia may suggest the inability of the patient, exhausted by a prolonged infection, to respond to active immunization. A marked eosinophilia may suggest that the patient is hypersensitive, and, as is frequently found in the asthmatic and allergic conditions, requires special attention. Lymphocytosis may indicate the presence of an unsuspected leukaemia, while an agranulocytosis will contraindicate any attempt at vaccine therapy until a normal leucocyte content of the blood has been redeveloped.

Secondary anaemia, of a more or less severe degree, which exists in cases of chronic infection more frequently than is realized, may, according to its type, demand arsenic, iron, or liver treatment, etc., before satisfactory response to vaccine therapy can be obtained. The finding of an increased non-protein nitrogen and uric acid content of the blood may disclose an unexpected nephritis, while in other cases a glucose tolerance test may show a defective pancreatic or hepatic metabolism, requiring suitable dietary regulations or endocrine reinforcement. Observations upon the calcium content of the blood are of value in chronic catarrhal and other infections, particularly of young persons, and, when present, the general response of the patient to vaccine treatment may be enhanced by endocrine treatment and by suitably increasing the vitamin content of the diet. These, and other blood examinations should form a routine part of the pathological examination associated with the essential bacteriological investigation of a large proportion of cases of chronic infection before a course of vaccine treatment is decided upon. Less would be heard of the failure of vaccine therapy in such conditions were it more frequently recognized that when there are underlying pathological lesions or metabolic derangements vaccine treatment of the infective condition cannot do more than maintain an improved antibacterial defence, although in doing so it will probably prevent further damage if adequately used along with whatever other general therapeutic measures are indicated.

DEFECTIVE SELECTION OF TYPE OF VACCINE

As mentioned above, infective conditions of acute, subacute, or chronic nature may be present in patients in which very variable states of physiological efficiency exist, and if vaccine therapy is to be scientifically prescribed, it would be possible to differentiate these conditions and determine the most appropriate treatment for each. There is often need of careful consideration in choosing the right type of vaccine for an individual case if failure is to be avoided.

Several varieties of vaccine are available which allow of a considerable range, and while none of them has a special application to any particular disease or infection, each has a fairly definite place in the treatment of infective conditions generally. Any of these may be used as stock or autogenous preparations. The former are usually employed for prophylactic treatment, but also for general therapeutic purposes, and are essentially valuable for the immediate treatment of acute cases, for which there is not time to prepare an autogenous vaccine, and for the initiation of treatment in subacute cases while an autogenous vaccine is being prepared. Autogenous vaccines are more frequently essential in the treatment of subacute and chronic infections, and failure of vaccine

treatment in such conditions may be prevented by replacing a stock vaccine by an autogenous preparation.

1. *Ordinary vaccines*, which are simply killed bacterial suspensions, are the most useful for prophylaxis and also, whenever possible in suitably graduated doses, for general therapeutic purposes. They produce a better and more lasting immunizing effect than the other types of vaccine to be mentioned later, but demand a response on the part of the patient which may not be possible in a debilitated case. Further, in chronic infections, a sensitiveness may develop which makes the patient exceptionally reactive to the most minute doses. In such cases, therefore, it is necessary to commence with one of the preparations described below, which will stimulate immunity without making undue demands upon the patient's exhausted economy.

2. *Sensitized Vaccines*.—These are ordinary vaccines which have been treated with homologous antibacterial serums, so that the antigenic bacteria are combined with antibody, and the antigen is ready for immediate phagocytosis without further elaboration on the part of the patient's tissues. These are of special service in acute infections, where the question of time and rapid immunizing effect is of the greatest importance. They may be given in large doses, repeated at twenty-four-hour intervals, and, if employed at the earliest stage of infection, are particularly successful.

3. *Detoxicated vaccines* are ordinary bacterial emulsions, so treated by chemical reagents that the bacteria no longer exist as such, the vaccine containing a suspension of the stroma of the bacteria with their endotoxins removed. These are of undoubted value, and are available for similar cases to those for which sensitized vaccines are applicable. They have the advantage of not requiring specific anti-bacterial serums in their preparation, but the disadvantage of being not so devoid of reactive effects upon a sensitive patient. They have a valuable place in the commencement of vaccine therapy of chronic cases of the less sensitive type. The dosage interval is usually shorter than is the case with ordinary vaccines, and makes possible a rapid initiation of specific immunization—to be followed later with an ordinary autogenous vaccine.

4. *Reinforced Vaccines*.—As mentioned above, many failures result, not from any fault in the vaccine, but from the patient's lowered vitality preventing the tissues from responding to the specific stimulus of an autogenous vaccine. In these conditions some leucocytic stimulation is required before such response is adequate. It is frequently obtained by using a 5 per cent. solution of sodium nucleinate as the diluent in the vaccine preparation. This can be used with any of the three types of vaccine mentioned. Such reinforcement is by no means new, but if more often used it would avoid failure in the type of case indicated.

5. *Oral Vaccines*.—The four types of vaccines already mentioned are usually employed by hypodermic injection. It has, however, been shown by many workers that the oral administration of vaccine, both stock and autogenous, will produce immunity responses. In cases of young children and hypersensitive adults, to whom the procedure of a hypodermic injection is so great a horror as to preclude therapy by such means, and in whom failure is a foregone conclusion, merely because treatment cannot be carried on sufficiently long or regularly to produce any lasting result, the possibility of raising a specific immunity by oral administration has a special advantage. Either ordinary or detoxicated vaccines may be given orally. The doses are usually larger than would be employed if injected. The intervals between doses may be less. In sensitive patients reactions may occur as definitely as

with an injected vaccine, and curative response has been completely satisfactory in many cases. The oral method has this advantage, that, owing to the simplicity of administration, treatment will be continued for a sufficient length of time to obtain a successful and lasting result.

FAULTY DOSAGE AND DOSE INTERVAL

This is probably a frequent cause of failure in vaccine therapy. Apart from routine prophylactic treatment it is irrational to fix a dosage standard for vaccine administration, for not only do patients vary widely in their individual susceptibility to bacterial stimulation, but the infection from which they suffer may vary from a local to a generalized one, and each such variation may require some graduation of dose to meet the individual requirements.

In the usual series of prophylactic vaccine doses a standardization has to be adopted. Instances may, however, be encountered in which a normal person is unduly reactive to, and disturbed by, doses quite suitable to the majority of cases, and in such a case the doses must be reduced. The result of immunization will be just as effective as that in patients who receive considerably larger amounts of the same vaccine. On the other hand, there are others for whom the usual prophylactic doses may prove insufficient to obtain the desired immunizing response, and for these doses considerably larger than those usually prescribed should be given if failure is to be avoided. As regards repetition of prophylactic doses, a longer interval than usual should be arranged. Too rapid repetition is more likely to prove unsatisfactory than is the use of an interval longer than the usual one.

Acute Infections.—In the treatment of these cases, where there is a good leucocytic response, and the patient has not become sensitized, as in a chronic infection, success of vaccine therapy depends upon the early administration of a sufficiently large dose. The adoption of this procedure in pneumococcal, streptococcal, staphylococcal, and gonococcal infections will result in the abortion of a threatened attack in the large majority of cases, while failure follows all too often the tardy and timid attitude, which only calls for the help of vaccine treatment when the patient is toxic and overwhelmed by a massive infection—a time when the opportunity of success from such a method of treatment has passed. Although ordinary vaccines are frequently used in acute cases, the more rational and safest treatment is to employ those specific vaccine preparations which will make least demand upon the patient's immunizing responses, and as far as possible present the antigen ready for defensive stimulation. For this purpose sensitized or detoxicated vaccines are preferable, and may be used in comparatively large doses at a twenty-four-hour interval. An attempt is thereby made to rush forward a specific active immunity to the infection present before the patient's tissue responses are exhausted, and the result of this mode of vaccine treatment is frequently successful.

Subacute Conditions.—The infection has been present here for some time, and there is not the same urgency for rapid or large doses. The initial leucocytic reaction has often been followed by a leucopenia of lymphocytic type, and in such cases, although good response is frequently obtained with small doses of the appropriate ordinary vaccine (autogenous or stock) a more satisfactory result may be obtained from the use of either sensitized or detoxicated vaccine, which allows of a more rapid repetition of dose and the quicker initiation of a defensive immunity, besides being less likely to give rise to reactionary flares that may dishearten both patient and doctor, and attribute failure to the vaccine employed. As the immunizing response to these vaccines is not so lasting, and relapses of infection may occur, they should,

as soon as sufficient improvement is obtained, be followed up by a carefully graded series of doses of ordinary vaccine at longer intervals, with the object of establishing a more lasting bacterial resistance.

Chronic Infections.—The greatest difficulty experienced here is in adjusting the appropriate vaccine dose to an individual case. Irrational dosage may in certain cases completely negative any chance of success from such treatment. As many have emphasized, each dose of vaccine in these cases must be considered as a test dose, and although for convenience a vaccine may be supplied in a series of graded doses, these must always be considered as liable to alteration by the practitioner responsible for the administration. The patient's satisfactory response or unsatisfactory reaction to a dose of vaccine is the best criterion of its being correct or otherwise. As a rule it is best, in cases of chronic infection, to commence with small doses repeated at moderate intervals of three to five days, and carefully increased until some slight sign of reaction is detected. The dosage interval should then be lengthened and the subsequent dose reduced to one-half or less of the previous one, very slight increments being made to the amount being given so as to keep below the reactive dose. Any dose of vaccine, however small, which produces improvement in the condition under treatment, is sufficiently large for that case, and should be increased only when such improvement ceases. Any sign of overdosage should be followed by a temporary lengthening of interval and reduction of the next and subsequent doses.

In the chronic case the initial course of vaccine treatment is frequently the most important, but often the most troublesome, and the necessary manipulations of dosage may demand much patience and thought. This type of case is apt to be sluggish in response, but once the initial process has been satisfactorily started, more normal and satisfactory responses will follow subsequent doses, and it may ultimately need larger doses before a satisfactory conclusion is reached.

Hypersensitive Type of Case.—This is apt to be found among those suffering from long-standing infections—often when a latent focus of infection exists. These cases may be so intolerant of even the smallest dose of vaccine as to contraindicate such treatment. Under such conditions a detoxicated preparation may be successful in desensitizing the patient, or the removal of an active focus of infection may result in a loss of the sensitiveness. These hypersensitive cases are often found to have an eosinophilia, and its presence should suggest the possibility of the patient being sensitive, and indicate the need for special precautions in commencing vaccine treatment. Certain cases are sensitive to their own particular infective organism, and as they may be more disturbed by autogenous vaccines than by a stock preparation of similar composition the use of the latter may be more effective. In cases of marked sensitiveness, oral administration may be successful when hypodermic administration has proved impossible.

Insensitive Type of Case.—Instances occur, especially in the chronic and subacute group of infective conditions, where the patient's economy is unable to respond to a vaccine stimulus. The infective process has lowered the general tissue vitality, and this is shown in such cases by the presence of a more or less marked leucopenia, a relative deficiency in the polymorph leucocyte content of the blood, and the presence of a preponderance of lymphocytes. Under such conditions it is necessary either to employ all possible means to obtain a regeneration of the blood-forming centres before commencing vaccine treatment, or to combine such treatment with small and very carefully graduated doses of the appropriate vaccine.

In the more severe type of non-responsive case, an even more elaborate form of vaccine treatment may be required as a preliminary measure—namely, the employment of a donor to provide an autogenous immune serum. A whole-blood immune transfusion may be used as an alternative in specially debilitated cases with good immediate, though temporary, results, and may be followed up by the sensitized vaccine similarly obtained.

The other and commoner group of non-reactive and non-responsive cases does not show these grave signs of debility, but is apparently impervious to any effect whatever of ordinary full doses of vaccine. Such a condition is often found in cases with marked furunculosis and other conditions of local infection, less frequently in chronic catarrhal and rheumatic conditions. The usual vaccine doses are inadequate, and will be written down as a failure unless doses of much greater amount than usual are employed. For instance, in certain cases of furunculosis which have been abandoned as failures, completely satisfactory results have been obtained when the dosage has been increased to three or four times the usual maximum amount.

INSUFFICIENT DURATION OF TREATMENT

This is a further cause of failure, and applies especially to the chronic type of infections. It is irrational to expect a few small doses of vaccine, however carefully they are prepared and arranged for, to arrest an infective process that has been present in the system for months or years, and much less to reduce or replace pathological processes which have been established. Good results are usually obtained by persistent, careful treatment. But vaccine therapy is not a simple and easy matter. It frequently demands much patience and thought, and gives scope for considerable nicety in the successful management of a difficult case. Without such care, failures are more often due to the lack of proper administration than to any fault in the vaccine or therapy itself.

Although many may do well after a single course of ten to twelve inoculations, most cases of chronic infection, such as the rheumatic group, will require many more, and it is quite usual to have to continue a systematic treatment with vaccine for at least a year. Nor should it be considered extravagant to suggest that in the severe cases treatment may have to be carried on, perhaps with intervals, for two or even three years before ultimate success is obtained, when it is considered how extensive the tissue damage may be, how long the infection has been present, and how debilitated the patient's general condition has become. If vaccine treatment in cases of rheumatic infection, for instance, was commenced earlier and persisted with efficiently, a large percentage of the permanent disabilities from this cause would be prevented.

The first aim of vaccine therapy is to arrest the infective process by raising an efficient bacterial resistance. When this has been accomplished, further treatment must still be directed to the maintenance of an active immunity and to the recovery, so far as is possible, of pathological tissues. These later courses of vaccine will usually allow of a considerable increase of interval between doses, which are themselves only increased in amount when further improvement is absent. In some cases the natural power of maintaining an adequate resistance to a particular infection appears to be deficient, and in such the best method of maintaining their freedom from reinfection is by the persistent continuation of vaccine treatment at, perhaps, monthly intervals. Numerous sufferers from chronic respiratory, intestinal, and rheumatic infection have been changed from a life of invalidism to comparative normal activity by the employment of this method of continuous vaccine treatment, which, if omitted for too long an interval, results in the gradual reappearance of some well-recognized symptoms of relapse.

IRRATIONAL EXPECTATIONS FROM RESULTS

This is the last cause of failure to be mentioned. Too much in certain cases is expected of a mode of treatment, the action of which must necessarily have definite limitations. Vaccine therapy is not in any sense a "cure-all," and even if there are conditions in which it may be more or less successfully employed as a non-specific agent in protein shock therapy its essential sphere is that of a specific immunizing agent against specific infections.

If a presumed infective condition proves, on investigation, to be one of metabolic derangement, and the infector is only one of secondary although perhaps contributory importance, vaccine treatment of this must not be blamed if failure to correct the primary non-infective condition results. In most chronic infections it is at times more important to treat the associated and resultant derangements of tissue metabolism than to concentrate solely upon the infection itself, and, unless vaccine treatment is combined with other remedial measures, it cannot be expected to produce the result or improvement which is anticipated clinically. Vaccine treatment is an invaluable therapeutic measure, and all too frequently advantage is not taken of its help in the scope of clinical practice. It is either not employed early enough to be of real service, or too much is expected of its exhibition under conditions which preclude its success.

There are, therefore, several causes of failure in vaccine treatment, some of which may be avoided by a proper appreciation of the underlying difficulties which are apt to exist, others which depend upon the presence of pathological conditions beyond the scope of clinical control. Nevertheless, when all details are considered, failures occur in not more than 20 per cent. of cases, and, as pointed out above, may with proper care be definitely less.

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THE MODERN TREATMENT OF GASTRO-ENTEROPTOSIS

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Inefficacy in the treatment of gastro-enteroptosis is due to our erroneous conception of the unity of this morbid condition. Gastro-enteroptosis is not one disease. There are four distinct forms of it, and we could, in fact, from the nosographical point of view, speak of four different diseases. These are (a) the constitutional gastro-enteroptosis, or Stiller's syndrome; (b) the neurotic gastro-enteroptosis, or Adler's syndrome; (c) the organic gastro-enteroptosis, or Glenard's syndrome; and (d) the gastro-enteroptosis complicated by perivisceritis. For a perfect individualization of our therapeutic handling—the only safe way to success—we must consider this division, which is based, not on a static, but on a dynamic clinical observation of gastro-enteroptosis and also on the observation of the action of various therapeutical agents.

STILLER'S SYNDROME

The term "Stiller's syndrome" is applied to this form of gastro-enteroptosis because it was Stiller (of Budapest) who first pointed out the relation of gastro-enteroptosis to a type of constitution—that is, to a particular psychophysical construction of the individual.