

BACTERIAL VACCINE THERAPY*

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"If at the present time ten years of public notoriety have passed over any doctrine professing to be of importance in medical science, and if it has not succeeded in raising up a powerful body of able, learned, and ingenious advocates for its claims, the fault must be in the doctrine and not in the medical profession." This old criterion of Holmes is applicable to bacterial vaccine therapy this year, for though Fraenkel's work dates back a quarter of a century and Wright's fifteen years, in this country it was not until about ten years ago that any great degree of notoriety attached to the subject. The profession generally was about to grant vaccine therapy, at least autogenous vaccines, a more or less definite place when the new mass of data regarding nonspecific reactions began to appear and to cause grave doubts as to what were formerly regarded as fundamental principles.

A clear differentiation must be made between vaccine therapy and prophylaxis. The value of typhoid vaccine in prophylaxis is unquestioned, but the immunity thus obtained, if doses small enough to spare a sick patient from the danger of a reaction are given, may not be rapid enough to be of use in therapeutics. The impression has become more and more dominant that in order to have any definite assurance of improvement from vaccine injection, there must be a reaction. These reactions occur in nonspecific injection therapy. Whether all the improvement in specific bacterial therapy depends on the nonspecific reaction is still questionable. The tendency toward recurrence forms one of the objections to accepting improvement after vaccine therapy as being specific.

Regret over the extension of the meaning of the word vaccine beyond the true jennerian sense is now useless. Pasteur himself applied the term to his attenuated anthrax injections, and it has been broadened by some to include every substance injected for the purpose of producing an active immunity. A stricter use, and one which I believe should be generally followed, includes under vaccines only suspensions of the bodies of micro-organisms, living or dead. The products of bacterial growth are thus not vaccines, neither are they toxins, though poisonous or toxic, unless they have the property of stimulating the production of demonstrable antitoxins.

As between stock and autogenous vaccines in therapeutics, there is no question that the reports favor the latter. The vote is so strong that the evidence on first thought would be overwhelming for specificity. In fact, one of the great objections to vaccine therapy has been the apparently extremely narrow specificity of some of the reactions, no other vaccine than that made from the patient's own strain proving beneficial; and we are advised that sometimes even strains isolated early in the course of a treatment become useless and a fresh culture from the infected focus must be made for a second and again for a third vaccine. Autogenous vaccines are practically always fresher than stock vaccines, and there is ground for believing that toxicity or the reaction-producing quality decreases on storage. The commercial stock vaccines of the large biologic manufacturing laboratories, on

the other hand, are safer than the usual autogenous vaccine. The vaccines made by laboratories holding federal license, while impossible of accurate control as to potency, are generally more carefully tested as to sterility and content of preservative, and are less likely than other vaccines to contain an excess of toxic protein. If the number of these preparations on the market were an index of their efficacy, one would say that they must be of some value.

NEED FOR CONTROL OBSERVATIONS

The literature abounds with observations on this form of therapy, but the vaccine was administered for the most part without controls. It is obvious that the tendency is to report favorable results, while the series of unsuccessful cases are less likely to be published. Largely on uncontrolled, but remarkably uniform, experience, we have come to think that staphylococcus vaccines are of benefit when proper surgical relief is also given. Why should we demand more scientific checks on observations in the wider field? Because it is high time that bacterial vaccines should either be found definitely useful under clearly outlined conditions or be discarded; in other words, practice has jumped far ahead of knowledge, and knowledge should recover its place. It is hoped that military hospitals in the various countries at war will enable studies to be made on a sufficiently large and complete scale to justify permanent conclusions. The uncertainties due to enthusiasm for any rather new treatment are obvious, but in the case of vaccine therapy our vision is particularly clouded. The seemingly scientific basis for the treatment tends to impress both doctor and patient, and the injection, the reaction and recovery therefrom can hardly help having some psychic effect. Vaccine therapy was formerly considered to be practically devoid of danger, but since benefit is now thought to be proportionate to toxic reaction, and particularly with the intravenous administration, accurate knowledge is essential to replace the present hit-or-miss plan.

My plea, then, is not for utter abandonment of therapeutic inoculation, but for its better control, and for the collation of such reliable data as will more clearly guide our future use of the method. In a laboratory experiment, unless a reaction is quantitatively well established when all the elements are known, there should always be as large a number of control or check tests using the known elements as there are of tests with the unknown element which is under trial. So with the therapeutic test of such substances as bacterial vaccines, since we cannot accurately forecast what will happen in the untreated cases, there should in each series be as large a number of these (or of cases treated nonspecifically) as of vaccine-treated cases, at the same time, under the same conditions, and with the same impartial observation, in order to secure the greatest accuracy from a given number of tests. It would be invidious to indicate examples, but a great part of the unqualifiedly favorable communications on vaccine therapy, reporting uniform benefit without severe reaction, bear internal evidence of lack of careful control, and as a rule the more favorable, the greater is this evidence.

On the other hand, we have some very carefully controlled reports. Last year Captain Whittington¹ of the Royal Army Medical Corps reported 230 cases of

1. Whittington, T. H.: A Report on the Use of Stock Vaccine in Infection by the *Bacillus Typhosus*, *Lancet*, London, 1916, **190**, 759-766.

* From the Hygienic Laboratory.

typhoid fever, selected to conform to rigid standards of diagnosis and classified as to relative severity, and divided them into two lots, so that each vaccine-treated case was accurately checked with a nonvaccine-treated case in the same state of prophylactic vaccination, of the same severity, occurring in the same season, climate and locality, of the same sex, of about the same age and previous health, and receiving the same general treatment as to nursing, dieting, etc. Captain Whittington had the advice of Sir William Leishman on the earlier cases, so that there should be little to criticize as to dosage and time between doses. Such a series, though small, is far more valuable than thousands of cases collated from different observers without proper controls, with the chance favorable results in many instances acting as a spur to publication. Whittington's result are recorded in the accompanying table.

COMPARATIVE RESULTS FROM THE USE OF VACCINES IN TWO HUNDRED AND THIRTY TYPHOID FEVER CASES

	Mortality Per Cent.	Average Days Fever	Relapsed Cases Per Cent.	Cases with Complications or Sequelae Per Cent.
Vaccine-treated cases.	25	29.2	10.4	49.5
Controls	21	26.1	7.8	46

A comparison of these results shows that the controls did a little better than the vaccine-treated cases. Moreover, from the promptness with which some of the hemorrhages followed a vaccine injection, there was a decided suspicion that the vaccine might have induced this complication.

Whittington started with a bias in favor of the vaccine, which his earlier cases tended to confirm. This is one reason for lack of sufficient controls in most published series. Inspired by hope, the workers become so enthusiastic that the majority of the patients are given the "benefit" of the vaccine. To a laboratory worker it would seem that, with our present knowledge, no patient is unjustly treated in having this so-called specific treatment withheld.

The recent intravenous treatment of typhoid fever and some other conditions with various bodies, specific and nonspecific, gives striking results in a proportion of cases; but the dangers in the general use of this method, admitted by practically all who use it, restrict its field at present to the same carefully controlled circumstances as those previously outlined. These dangers are very apparent in intravenous treatment of animals with bacterial suspensions.

One other small but well controlled series was recently reported by a group of workers² under Dr. Park, of the Bureau of Laboratories of the New York City Health Department. These authors also, even up to the time the results were tabulated, believed that the vaccine (pertussis in this case) was of specific benefit. Outpatient material was used, open to the usual objection of uncertain home conditions and questionable information on the part of the parents. Of the more than 1,000 cases, 75 per cent. were rejected because they were not in the proper period of the disease for good comparison, because the diagnosis was somewhat uncertain, because the address was changed, because of unreliability, or for some similar reason. The parents were carefully cross-examined to rule out false reports, and visits were continued at the homes to complete the records. Alternate patients were chosen for

the pertussis vaccine, the others receiving either influenza vaccine, milk solution diluted to resemble vaccine, or merely terpin hydrate by mouth. "In recording the remarks on the charts, the investigators were not biased by a knowledge of the vaccine employed, as they did not know until the study was finished which was which. The secret was safeguarded by the maker of the vaccine." Yet when the data were assembled, no matter what the grouping, whether according to intensity of onset, stage of disease, duration of disease, or intensity of paroxysms, the result was the same. The pertussis vaccine showed no superiority over the non-specific treatments.

The experience of such clinicians as Dr. Billings, who has had the most expert technical assistance and advice, with parallel serologic studies, is more important than the mere numerical summary of the overburdened and much vaunted favorable literature on specific therapy. After years of trial, especially in chronic disorders which should offer the most favorable field, Dr. Billings³ says that a personal and general hygienic management will accomplish quite as much without as with vaccines; and that vaccines without proper attention to a hygienic management are more likely to be harmful than helpful. It has been justly said that autogenous vaccination involves a hunt for latent foci of infection, and that this attention to the patient, with consequent local treatment of such foci as are found, is of itself of great benefit. Properly prepared and tested autogenous vaccines, however, are not within the reach of the great majority of patients. The bulk of vaccine therapy, if it is to become generally available, must be on the stock basis. Autogenous vaccines are often as ludicrously abused as stock vaccines. The differentiation of organisms is largely morphologic; the most easily grown are those found. The securing of a bacterium from the bodily discharges or mucous surfaces, even with a positive serum reaction, cannot be accepted as demonstrating a causative relationship to the disease, or any part of it, unless the bacterium is well known to be a pathogen. As for deeper cultures, those who work with laboratory animals know that normal tissues are by no means found constantly sterile.

The case in general is not proved, and doubt is increasing. Many keen observers believe that specific bacterial therapy is a failure. In some diseases claimed to be within the field of vaccines, such as pertussis, asthma, or bronchitis, a smallpox vaccination, a minor operation, or an intercurrent infection has been observed to precede partial or complete recovery. Why not a hypodermic injection, especially if followed by a systemic reaction? Moreover, there is a difference between changing the course of a disease, and changing it beneficially with any degree of certainty.

Negative results by one set of workers should not discredit the whole method of treatment. Slight but important modification by other workers may give more favorable results; but we should have the details, and above all, proper controls.

Hygienic Laboratory.

3. Billings, Frank: Discussion on Vaccine Therapy, *Tr. Cong. Am. Phys. and Surg.*, 1916, **10**, 135-138.

2. Von Sholly, Anna I.; Blum, Julius, and Smith, Luella: Therapeutic Value of Pertussis Vaccine in Whooping Cough, *THE JOURNAL A. M. A.*, May 19, 1917, pp. 1451-1456.

Science.—To the natural philosopher, to whom the whole extent of nature belongs, all the individual branches of science constitute the links of an endless chain, from which not one can be detached without destroying the harmony of the whole.—Schoedler.