III

THE VACCINE TREATMENT OF GONORRHOEA

Based upon an Address delivered before the Medical Society for the Study of Venereal Diseases on January 23rd, 1925, by ARNOLD RENSHAW, M.D., B.S. (Lond.), D.P.H. (Man. and Cantab.).

In discussing the efficacy of vaccines in the treatment of gonorrhoea and its complications the following scheme will be adopted:

(i) Specific vaccine therapy of gonococcal infections.
   (a) General observations.
   (b) Observations in special cases.

(ii) Diagnosis of gonococcal infections.
     (a) Direct.
     (b) Complement fixation test.
     (c) Suggested methods.

(3) Difficulties in regard to the preparation of gonococcal vaccines.
     (a) Personal obtaining of specimen.
     (b) Difficult to get from complications arising in gonorrhoea.

(4) Non-specific vaccine therapy.

(5) Summary.

I. SPECIFIC VACCINE THERAPY OF GONOCOCCAL INFECTIONS.

(a) It is difficult to precisely ascertain the effect that gonococcal vaccines have in the course of acute gonorrhoea.

I have obtained the opinions of my surgical friends and colleagues on this point, and the general opinion appears to be that no very striking difference is caused by the use of gonococcal vaccines in the early stages.

Dr. Gordon Whitehead, of the Ancoats Hospital V.D. Clinic, does not consider their use of great value in the early stage. It would be necessary, however, to take a large number of cases occurring about the same time and
THE VACCINE TREATMENT OF GONORRHŒA

divide them into two sections—the first to receive only the usual treatment, and the second, vaccine treatment in addition.

Such an experiment has, I believe, been commenced at the Salford Royal Hospital under the direction of Mr. J. B. Macalpine; and, although the series is not completed, I believe he holds the opinion that the duration of attendance is slightly shortened with vaccines. Another surgical colleague, however, with considerable experience of gonorrhœa, expresses himself in regard to treatment of these cases by saying that “the cure of gonorrhœa is an act of God. The cases which one expects to do well do badly, and the cases which one expects to do badly do well.” In all these cases, however, I would say that no vaccine can be of any benefit if the use of strong metallic antiseptics is continued. These antiseptics, by forming insoluble albuminates, often cause plugging of the mouths of numerous mucous glands and consequent sealing in of the infection for long periods of time.

The use of the more harmless antiseptic dyes, such as auramine or the solution known as glauramine, is to be advised, since the staining effect is such that the antiseptic action is more prolonged in consequence of the gradual re-solution of stain which has dyed the mucous membrane.

(b) One of the great difficulties in evaluating the effects of vaccines in any pyogenic process is that usually the inflammatory area is hidden from sight and any precise observation as to the condition at any one moment is difficult to state in definite terms. This difficulty is, however, not so great in one particular site, e.g., the eye, and the condition at any one time can be expressed mathematically in terms of visual acuity in addition to direct observations on the various parts of the eye affected.

This organ has always appeared to me to be of great value in determining the immunity response to vaccine and serum therapy, and I have accordingly collected several references to the effects of vaccines in gonorrhœal conditions of the eye. It is an organ in which local treatment by antiseptics enters less into the evaluation of treatment by vaccines than is the case in the genito-urinary tract. My own observations in gonorrhœal
BRITISH JOURNAL OF VENEREAL DISEASES

diseases of the eye are confined to gonorrhœal iritis or irido-cyclitis. In this infection—induced, maybe, years after the primary infection has been subdued—treatment by stock vaccines is usually necessary, since it is almost impossible in these late cases to culture the gonococcus. My general opinion of these ophthalmic cases is that a few injections will arrest the acute condition, but permanent improvement is slow, and relapses are liable to occur even after a prolonged course of vaccine, occurring usually some months after vaccine treatment has been stopped. Again, however, vaccines will usually assist in checking the severity of symptoms during this relapse, and patients willingly attend for further inoculations.

In one case associated with chronic arthritis and disseminated sclerosis thirty-five inoculations of detoxicated gonococcal vaccine had kept the eye quiet, but there was no great visual improvement, and there were still K.P.

In another case, after fifteen inoculations the right eye showed a fair number of fine greyish-brown K.P., and the left showed very abundant K.P., a slight amount of ciliary injection and exudate into pupillary area, the vision in this eye being slightly better than on admission.

In another case, after eighteen inoculations the eyes, although not yet quiet, were holding their own very well.

B. H. St. Clair Roberts ¹ states that the use of stock gonococcal vaccines has given good results in gonorrhœal invasion of the uveal tract; there is usually a marked improvement after three or four injections given at intervals of fourteen days and in large doses—250 million. He had not used gonococcal vaccines in ophthalmia neonatorum, since with early and efficient local treatment one seldom saw the cornea involved.

Dr. Gibbon Fitzgibbon, Master of the Rotunda Hospital, Dublin,² states that during the twenty years from 1898–1919 there were ninety-two cases of ophthalmia neonatorum occurring amongst 38,106 infants born which left the hospital alive, e.g., 0·24 per cent.

During the whole of this time Crède's prophylactic measure was used. For one year only did argyrol supersede a ¹ per cent. silver nitrate solution, and this was

96
THE VACCINE TREATMENT OF GONORRHOEA

replaced by the silver nitrate solution, since the argyrol was not regarded as so efficient. Usually two-thirds of the ophthalmia neonatorum cases are gonococcal in origin, so that, in view of the large amount of gonorrhoea at one time present in Dublin, it can be stated that apparently only sixty cases of gonorrhoeal ophthalmia occurring in over 38,000 infants represented a real achievement in preventive medicine.

Of these gonococcal cases a number received vaccine treatment. Dr. Fitzgibbon concludes that: "Vaccine therapy is of considerable benefit in all gonorrhoeal infections . . ."; but he points out that an efficient vaccine must be used, that it must be recently prepared, and that it does not matter whether it is autogenous or not. With such a vaccine the dose for an infant should be one quarter to half a million, and for an adult three to five million, as a maximum initial dose, and the vaccine may be given every three or four days.

Mr. M. S. Mayou: "Vaccines given in large doses seem to have no effect on ophthalmia neonatorum, although perhaps, if continued over a long period, they may produce some improvement in some chronic lesions, such as arthritis." He considers that the disease clears up as the result of a local immunity to the gonococcus rather than as a general immunity, and that it is associated with the breaking up of plasma cells which emigrate to the place.

As evidence of the development of local immunity he quotes the fact that in one case an acute recurrence was noted in one eye after an interval of sixteen days, whilst only a slight discharge was present in the other, yet the gonococcus was present in both; and, again, that frequently a very severe attack may be present in one eye, whilst there is only a slight discharge in the other, the gonococcus being found in both.

Mayou has used both ordinary and detoxicated vaccines extensively, and also serum, but he did not think that they have any influence in shortening the ordinary period of the disease. In a few cases in which a slight discharge persists in spite of local treatment he thinks that vaccine treatment may have helped to clear it up.

Von Hippel (Gottingen) is inclined to doubt the value of specific treatment by arthigon and vaccines, and considers that the reaction may be harmful.
2. Before Vaccine Treatment is Initiated, Accurate Diagnosis of the Nature of Infection is Necessary

(a) The diagnosis of gonococcal infection in the early acute stage is usually a simple matter.

Direct microscopical examination of the stained slide is usually quite sufficient to indicate whether the infection is solely a gonococcal one or whether it is a mixed infection of staphylococci or diphtheroids or other organisms associated with the gonococcus. In the latter case, to obtain optimum results from vaccine treatment of gonorrhoea, an autogenous vaccine of the other associated organisms ought also to be used.

(b) The diagnosis of gonococcal infection in the later stages, and particularly in complications such as arthritis, iridocyclitis, etc., is very much more difficult.

The complement fixation test has been suggested as a means of ascertaining whether in these cases the gonococcus is the causative antigen.

The experimental work with this test has, however, proved decidedly disappointing, and it is not in very great favour with most pathologists. The reasons for this are sufficiently obvious; in the first place, the gonococcus produces a very poor anti-body response. Moreover, the number of different types of gonococci is probably fairly considerable. It is thus impossible to obtain specific antigen by the use of any one strain of gonococcus. Thus Torrey is stated to have described at least ten separate strains of gonococci, and, in addition, there are a large number of various types which show no serological relationship to one another as far as specific agglutination is concerned. It would obviously, therefore, be an absurdity to expect to get complement fixation in which only one-tenth of the antigen used was specific, and, on the other hand, it would cause very great difficulty in performing tests on a large number of cases if at least ten antigens had to be used; gonococcal complement fixation, therefore, is not a practical possibility.

(c) On the other hand, it is barely possible that another method might be used, namely, the method of ascertaining any alteration in electrical conductivity of the serum when the antigen is added. This can be fairly quickly done, but requires very sensitive instruments,
THE VACCINE TREATMENT OF GONORRHOEA

and so far has not yet been applied to serological methods.

3. DIFFICULTIES IN REGARD TO PREPARATION OF GONOCOCCAL VACCINES

(a) Personal obtaining of the Specimen

Gonococcal pus cannot be allowed to remain at less than body temperature for more than a few moments, otherwise the gonococci die. Hence it is necessary that the patient should be in close attendance upon a laboratory when a gonococcal vaccine has to be prepared from an autogenous strain.

It is also difficult to obtain gonococci from gonococcal complications such as arthritis, irido-cyclitis, and in many of these cases it is quite out of the question obtaining a gonococcal autogenous vaccine at all.

4. NON-SPECIFIC VACCINE THERAPY

It is a fairly general opinion that vaccines of other organisms, such as diphtheroid vaccines, streptococci, staphylococci, often are of very great use in chronic gleet; and it is possible that the chronic infection is maintained by these organisms. On the other hand, it is possible that a vaccine which is not specific may produce substances which may have an effect upon eliminating residual gonococci.

Allisson, of Geneva, in the Revue General d'Ophthalmologie for March, 1922, discusses the possibility of heterobacterio-therapy in gonococcal conjunctivitis in adults.

Dorrier had previously stated his belief that every antitoxic serum, in addition to its specific action, possessed the property of giving the body a general repressiv mechanism which could attenuate the symptoms produced by other bacteria.

Von Szily and Sternberg, in 1917, published results showing the effects obtained in twelve cases of adult gonorrhœal conjunctivitis by the use of typhoid vaccine, and in 1918 published the results in forty cases. Shortly after injection, hyperæmia of the affected eye was present, and subsequently pain and oedema became less, and the gonococci disappeared in ten to forty-eight hours. Of the twenty with corneal lesions, fourteen were cured with
scarring of the cornea which was more or less extensive. In the remaining six perforation occurred. They stated that local therapeutic measures were unnecessary. Allisson has obtained good results in two out of three cases tried in this way with typhoid vaccine. The vaccine used is prepared according to Von Szily and Sternberg as follows:

Five agar tubes having a surface of about 5 sq. cm. are inoculated each with 2 mg. of freshly-prepared typhoid bacilli. After twenty-four hours the resulting cultures are diluted into 200 c.c. of saline solution. This is shaken for half an hour, and then carbolic acid is added up to one half.

Delorme (of Bordeaux) has recorded eight cases of gonorrhoeal ophthalmia treated by Nicolle and Blaizot’s vaccine—a syncoccus + gonococcus. After a maximum of five injections, five of the eight cases, in spite of early corneal involvement, were completely cured. In one case, after four injections a relapse occurred three days later, but four more injections resulted in final cure.

In one case, a youth of seventeen, only slight improvement was noticed.

One failure occurred in a debilitated woman of seventy-four, who refused food.

This vaccine was described by Nicolle and Blaizot. They ascertained that another organism, which they named the “syncoccus,” was frequently associated with the gonococcus. It was Gram positive, grew in the absence of serum, and produced an orange pigment. This coccus forms nine-tenths of their vaccine, which is prepared as follows:

Separate cultures are put up on to a special medium of—

(a) A gonococcus which has been trained to grow on relatively small amounts of serum.

(b) The syncoccus.

The medium consists of—

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<th>Ingredient</th>
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<tbody>
<tr>
<td>Meat broth</td>
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<tr>
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<tr>
<td>Agar</td>
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To which is added, when tubed, 0.5 c.c. serum to each 5 c.c. medium.
THE VACCINE TREATMENT OF GONORRHŒA

The syncoccus tube does not require serum to be added. A twenty-four hours' culture is made into an emulsion with 2.7 per cent. sodium fluoride solution, washed, and centrifuged.

The vaccine is made up with nine parts syncoccus culture, one part gonococcus culture.

Sauvineau 8 in 1919 employed the Nicolle and Blaizot vaccine in one severe case of gonococcal conjunctivitis associated with articular troubles of a severe type. At the commencement of treatment the conjunctivitis was hanging fire, the cornea was affected, and the joints were threatened with ankylosis.

An immediate response was achieved, and the whole infection was subdued with a restoration to normal of the articulations.

My colleagues, Dr. Gordon Whitehead and Dr. Wilson, at the Ancoats Hospital Clinic, are both of the opinion that autogenous vaccines of other organisms have proved useful in gonorrhœal cases where coincident infection of the urethra or cervix has been present. Thus, in these cases, staphylococci, streptococci, or diphtheroid vaccines may be tried, and probably cause an effect not only upon these organisms, but also produce a non-specific or protein “shock” effect which increases the resistance generally and assists in promoting a leucocytosis, which has a beneficial effect in reducing the gonococcal infection.

I should like to ask in this connection what is the President’s experience in Haffkin’s plague prophylactic serum? I have been informed that in India some of the troops used to believe that injection of this used to clear up a chronic gleet.

5. Summary

From the consideration of the above questions it is obvious that the vaccine treatment of gonorrhœa cannot be regarded as a permanent asset to clinical treatment.

Vaccines in other conditions are often of benefit; thus in tuberculous bone conditions or tuberculous gland conditions tuberculin is often of very great benefit. Similarly, streptococcal vaccines, pneumococcal vaccines, may be of use in chronic conditions, such as chronic bronchitis. When we consider gonococcal vaccines, however, their value is very much less. The Gram-negative diplococci, as a class, do not immunise well. By analogy we may con-
sider the meningococcus. Enormous doses of meningococci and prolonged treatment are required to produce anti-meningococcal serum.

During the war I had the opportunity of conducting the bacteriological work on over 150 cases of cerebro-spinal meningitis, and it was well recognised that in these cases simple drainage often gave us as good results as the use of serum.

Gonococcal vaccines are variable in their action, and they do not produce anything like the strikingly dramatic results which are obtained by the use of salvarsan in syphilis, or emetine in dysentery, or of the more recently isolated substances, such as Bayer "205" and Fourneau "309," in regard to effects upon trypanosomes.

At the moment, however, it is one of the main stand-bys which we have for the treatment of gonococcal complications, and although it is recognised distinctly that very much good may not accrue from their use, yet in some cases, if any complication does occur, it is only just and fair to give the patients the benefit of the doubt and to see whether any possible benefit can be derived from the use of gonococcal vaccines. They must not be regarded as the last word in the treatment of this disease by any means; they are purely auxiliary, and they are agents whose use is probably not very great in gonorrhœa.

Too much attention has been focussed upon opsonins, etc., namely, on the molecules surrounding the gonococcus, and not enough on those molecules which will "bang their way through the bacterial envelope." In other words, chemo-therapeutics must be developed. Too much attention has been paid to a study of gonorrhœa and too little to a study of the gonococcus. The chemistry of this organism must receive adequate attention.

Vaccine therapy of gonococcal infections must ultimately give way to something better, more vigorous, more decisive in action, and the diagnosis of gonococcal complications must be neater, more precise, and more generally applicable. Until that time comes it behoves bacteriologists not to blind themselves to the deficiencies of the methods now available, but to look ahead to more precise methods and to more adequate means, and to assist the clinician by studying other means of dealing with this organism.

The sooner one admits this position and the earlier one
THE VACCINE TREATMENT OF GONORRHOEA

becomes completely and entirely dissatisfied with the existing state of affairs, the sooner will efforts be launched along newer lines of attack.

REFERENCES

(5) A. S. COBBLEDICK. Lancet, March 2nd, 1918.
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