of bismuth was 0.2 gram daily. He asked whether the blue line on the gums, a common concomitant of bismuth therapy, contraindicated the continuance of the treatment.

Dr. MARY MACNICOL (Edinburgh) said that she had been using bismuth now for three years as an adjuvant of arsenic, and thought it more valuable than mercury. In those cases which, although reacting well clinically to arsenical treatment, persisted in giving a positive Wassermann reaction, bismuth had often succeeded in reducing the reaction. She quoted two cases in illustration of this, and referred to its utility in old tertiary cases of gummata. She had found the drug very useful in cases of intolerance to arsenic; and had not met any case intolerant to bismuth, and only one in which there was stomatitis. In congenital cases she had also been able to obtain negative Wassermann reactions. Lately, however, she had found arsenic and mercury better than arsenic and bismuth in very bad congenital syphilis, but bismuth had the great advantage of being painless. She also found it convenient to give arsenic by the mouth during a course of bismuth; it still acted as a tonic and obviated the continual hypodermic injection which many women disliked.

Dr. E. T. BURKE (Manchester) placed bismuth just second to arsenobenzol as an antisyphilitic, but much higher than mercury; he said it must be realized that bismuth was a reinforcement and not a substitute for arsenobenzol. He was in favour of bismuth being given alternately with arsenobenzol—not concurrently. He thought that the experiments of Lehoff-Wyld to show that the therapeutic action of arsenobenzol was enhanced by the presence of another metal in the blood were very unconvincing. Personally he believed that when two highly treponemicidal drugs were used simultaneously either the tissues of the patient would refuse to react properly or the treponema would become resistant. He thought that the practice of concurrent administration was the cause of many persistent positive Wassermann reactions. He was now able to convert many of these into negative reactions by means of potassium iodide followed by metallic bismuth. Arsenic and bismuth might have an actual neutralizing effect on one another. Cases treated with bistovol—a bismuth and arsenic combination—gave extremely disappointing serological results. If, as Kolle held, bismuth merely kept syphilis latent, the concurrent administration of the two elements might be very harmful. Bismuth was particularly useful in syphilitic lesions of the circulatory mechanism; in cases of coronary and aortic disease it was safest to rely on it, possibly to the exclusion of arsenobenzol. In the newly-born syphilitic child carrying an enormous burden of treponemata he also began always with bismuth. One of its greatest uses was in interstitial keratitis; he only administered arsenic after the eye condition had cleared up. He thought that the best method of administering the drug was in the metallic form suspended in glucose and injected intramuscularly; the intravenous injection of any bismuth salt was dangerous.

Dr. W. R. SNODGRASS (Glasgow) considered that metallic bismuth in isotonic glucose solution was the most satisfactory preparation. Up to the present the quantity of a standard bismuth preparation necessary to effect and maintain a clinical and serological cure had not been established.

Colonel L. W. HARRISON (London) drew attention to the work of Collard and Evans, who formed a depot of bismuth in a rabbit's ear and then attempted to inoculate it with syphilis. So long as the depot was there no chancre was produced, but as soon as the depot was excised the chancre appeared, showing that the bismuth had only kept the syphilis latent. As regards the effect on the Wassermann reaction he thought there was but little difference between the effect of bismuth in combination with arsenic or mercury in combination with arsenic. He had found bismuth particularly useful in myocarditis, sometimes in conjunction with very small doses of sulfarsenol. The toxic effects of bismuth had not proved very severe, but he had

had occasional complaints of rheumatic aches and pains and also of colitis, and he had known dermatitis to be produced.

Dr. STOPFORD TAYLOR (Liverpool) described a severe case of toxic reaction due to bismuth. The patient had suffered from abdominal pain, sickness, diarrhoea, a measly rash, and gingivitis. He also recommended sulfarsenol in very small doses for cardiac cases.

Mr. LEES, in reply, agreed that bismuth alone should not be used in early cases. He did not regard the appearance of the blue line on the gums as a contraindication to the continuance of bismuth, but merely as an indication for dental attention. The principal contraindication to further treatment was loss of weight. Bismuth was exceedingly well tolerated as a rule; unlike mercury it never produced nodules. It was painless, and very useful in cases of parturient women before starting arsenical treatment. It was also particularly useful in cases which were clinically syphilis but serologically negative. He considered that the inunction and oral administration of bismuth were far inferior to injection. He did not agree that the joint and simultaneous administration of arsenic and bismuth and of arsenic and mercury reduced the bodily resistance of patients, though theoretically it might possibly be expected to do so. Myocardial cases, in his opinion, were the only ones in which bismuth should be used alone; in other cardio-vascular patients it should be combined with sulfarsenol. He found it difficult to explain the cases of dermatitis. Some of the cases of gross intolerance he thought might be due to a slight embolism, a small quantity of the metal finding its way into a vein during injection.

THE EMPLOYMENT OF "POLAR-BODY" DEVELOPING STRAINS OF THE GONOCOCCUS IN TREAT- MENT OF GONOCOCCAL INFECTION.*

BY

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AND

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For the last two years, at the Royal Herbert Hospital, Woolwich, we have been endeavouring to elaborate a line of treatment of gonorrhoea in the male by intensive immunizing methods. Preliminary reports of this work have already appeared in the *British Journal of Venereal Diseases* for January, 1927, and in the *R.A.M.C. Journal* for last March. For the present report we cannot claim any degree of finality; our researches are continuing and our methods constantly changing.

The treatment of gonorrhoea at Woolwich aims at: (1) Raising the immunity of the mucosa through which the organism enters the body. (2) Raising the resistance of the particular glands and organs susceptible to attack by the gonococcus. (3) Raising the antibacterial properties of the blood and tissue fluids in order to minimize the risk of systemic spread of the infection. (4) Bringing the patient under certain precise biochemical and colloidal-chemical conditions which have been found to give optimum results as regards defence against the invading organism, and placing the infecting organism under conditions in which it is least able to withstand the defence mechanism of the body. (5) Providing a means of determining whether any local foci of the disease remain or whether the patient is completely freed from the infecting organism—in short, to provide a "test of cure."

These objectives have been sought in the following ways: (1) Thorough drainage of the whole urethra by mild irrigating fluids. (2) The maintenance of the patient's urine reaction at a pH of 7.2 to 7.4. (3) The intraurethral instillation of a product of gonococcus metabolism which may be referred to as "exotoxin." (4) The parenteral

* A paper read in opening a discussion on this subject in the Section of Venereal Diseases at the Annual Meeting of the British Medical Association at Edinburgh.

administration of this "exotoxin." (5) The instillation into the urethra of another gonococcus product which we call "endotoxin."

Drainage.

The procedure advocated is the posterior irrigation method. The most efficient drainage is obtained by educating patients to irrigate in this way. The irrigating fluid is potassium permanganate (1 in 20,000 strength) which is the least irritating to the urethral mucous membrane. No bactericidal or astringent action is desired. All that we expect from irrigation of the urethra is drainage and cleanliness, and, as a consequence, probably a more intimate and prolonged contact of the intraurethral vaccine preparation with the affected mucous membrane. The results obtained without irrigating methods were poor, and we were compelled to fall back on routine irrigations.

It is not easy to carry out perfect irrigating methods in the acute stages of the disease, but the time and trouble spent in educating patients to irrigate efficiently are well repaid by results, and as our vaccine methods become more efficient, we find that it is only when patients cannot be induced to irrigate efficiently that results are disappointing.

The Hydrogen-ion Concentration of the Urine.

The body's optimum response to the attack of the gonococcus occurs when the hydrogen-ion concentration of the urine is within the limits of pH 7.2 to 7.4. Within these limits phagocytosis is at its maximum and the gonococcus is least favourably placed to withstand the attack of the body cells and fluids. Below this reaction on the acid side conditions favour the gonococcus; phagocytosis is at a minimum, and the invading organism, surrounded by a tough capsule of sclero-protein, is in its most resistant form.

With an alkaline reaction there is a tendency to autolysis of the gonococcus with liberation of toxic "endotoxin," which has an irritating and provocative effect on the body. In practice we endeavour to bring the patient into this optimum state by administration of comparatively enormous doses of disodium monohydrogen phosphate by the mouth. Our dosage amounts to 240 grains four times a day. Even in such large doses it is extremely difficult to maintain the desired reaction, especially at the stage of the disease when the diet tends to be more generous. The reaction is determined roughly by daily urine titrations; thus, to 1 c.cm. of urine add a drop of phenol red solution—a pink colour indicates a pH of 7.2 to 7.4 approximately.

Other alkalis have been tried, but for one reason or another have been abandoned; for example, sodium bicarbonate raises the CO₂ content in the tissues, and CO₂ is a gonococcus growth stimulant. We thought there might be an appreciable danger of overalkalinization with lysis of the gonococcus in the urethra and consequent elaboration of toxic endotoxin, but we believe now, on clinical grounds at least, that the danger is exaggerated and that a very alkaline reaction, which is almost invariably temporary, is of little consequence.

Gonococcal Exotoxin.

By special cultural methods it was found by Major Dimond that, when gonococci are grown on a medium rich in animal nucleo-protein, approximately one-third of the isolated strains develop polar bodies (Babès's bodies), which can be demonstrated histologically by staining methods identical with those employed in the demonstration of the polar bodies in *Bacillus diphtheriae*. The polar bodies are composed of alpha-nucleo-protein and beta-nucleo-histone. They are only loosely attached to the bodies of the gonococci, and can be separated easily from these by washing off the culture with 2 per cent. saline solution and fractionally centrifugalizing the emulsion, or by means of gravity; the polar bodies are then found in the supernatant fluid. Since the 2 per cent. saline solution dissolves the beta-nucleo-histone, the solid elements in the supernatant fluid are the alpha-nucleo-protein fraction of the polar bodies. Clinical experiments have shown that both the alpha-nucleo-protein and beta-nucleo-histone are antigenic (the beta-nucleo-histone more so than the alpha-nucleo-protein) and relatively non-toxic.

Human serum we have found to be the best vehicle for the separation of the polar bodies from the gonococci, as by this means the polar bodies are retained intact, and clinically the best results have been obtained by using the serum washes. However, serum has at least two serious disadvantages: an adequate supply is difficult to maintain, and the question of keeping the emulsion sterile for universal use has not yet been satisfactorily accomplished, although experiments are in progress to test the value of the addition of weak antiseptics, both as regards maintaining sterility and as regards the effect, if any, on the antigenicity of the emulsion. Substitutes for serum, such as Ringer's solution, have been found useless for the purpose.

The employment of 2 per cent. saline solution is not altogether a perfect method for the separation of the polar bodies. The beta-nucleo-histone is in solution and the alpha-nucleo-protein in suspension, but on separating the supernatant fluid from the bodies of the gonococci much of the alpha-nucleo-protein is lost, as it is unwise to pipette too close to the bodies of the gonococci lest large numbers of them be included in the product. It has been found clinically that there is a definite provocative effect if gonococci are included. So that the use of 2 per cent. saline by itself results in much loss of what we consider to be the true gonococcus antigen—namely, the polar bodies or their product.

Recently it has been found that if the pH of the 2 per cent. saline during the process of gravitation be kept at 7.2 the alpha-nucleo-protein fraction is kept in suspension much longer, and at the end of twenty-four hours the deposit of this fraction on the bodies of the gonococci is very appreciably diminished, the supernatant fluid in consequence being richer in antigenic substances. This same observation as regards reaction applies to the serum washes of polar bodies—they remain very appreciably longer in suspension.

For intraurethral use the 2 per cent. saline or serum washes are standardized so that the nucleo-protein of 500,000 million organisms is contained in 15 c.cm. Larger doses than this can be given without any signs of provocation and with even better results, but as polar-body producing growths on nucleic acid media are never luxuriant, there is a limit to the number of culture tubes which can be dealt with in the conditions under which we work. To this 15 c.cm. of 2 per cent. saline—representing, say, the product of 500,000 million gonococci—is added 5 per cent. sodium taurocholate and the reaction brought to a pH of 7.2.

Most samples of sodium taurocholate are acid and cause great irritation; the only preparation of sodium taurocholate which we have found to comply with our requirements is that produced by Fairchild. To this mixture of taurocholate and polar body emulsion we add umbilical cord mucin 1 per cent. up to 100 c.cm. The dose is 20 c.cm. intraurethrally, representing the product of 100,000 million gonococci. Formerly we had hoped that commercial mucin might be used as a substitute for the umbilical cord mucin, but, unfortunately, all the subsequent samples we obtained were adulterated, and did not represent true mucin, and the results were irritative.

For intradermal, subcutaneous, and intramuscular administration we use the same serum or 2 per cent. salt emulsion of polar bodies or their products, but standardized to represent 1,000 million per c.cm.

Instillation of Endotoxin.

For the preparation of endotoxin we have used strains which do not throw out the polar bodies employed in the exotoxin preparations. These strains comprise roughly 66 per cent of those isolated. They are grown for ten days on a special alkaline autolysate of ox heart. The culture is washed off and, after being repeatedly frozen and thawed, yields a product of albumoses in a blue opalescent solution. It is made up to a strength representing the product of 250 million gonococci in 1 c.cm., the diluent being chemically prepared colloidal silver. The effect of an intraurethral injection of this preparation in a quiescent gonococcus carrier is to produce a temporary activity with the appearance of gonococci in the urethral discharge.

This product, which we believe to contain the true toxic elements of the gonococcus, is the original gonococcus product which has been employed for over four years as a "test of cure" both at Woolwich and at other military hospitals; to Major A. T. Frost, R.A.M.C., is due the credit of conceiving the possibilities of an efficient "test of cure," and of encouraging by his advice the manufacture of this product.

The provocative effect may be observed as early as twelve hours, or may be delayed several days, sometimes a week, and to cover all cases we keep the patient under observation for seven days after an endotoxin instillation before we pronounce him free from active signs. We have comparatively recently put up this "endotoxin" preparation in weaker strength—for example, 1 c.cm., to represent 50 million of the organism—and employed it as an intraurethral instillation much earlier in the course of the disease as a mild provocative in certain cases. This introduction of the provocative products of the gonococcus at an early stage was at the suggestion of Colonel Harrison, the idea being mildly to provoke infected urethral foci, which appeared on clinical grounds to be developing into indolent and probably latent foci.

To summarize our methods:

1. We bring the patient's urine and tissues to what we conceive to be the optimum pH reaction.
2. We attempt local immunization by the intraurethral instillation of exotoxin (gonococcal) in mucin.
3. An effort is made to raise the general immunity response by the parenteral administration of gonococcal exotoxin vaccine.
4. Endotoxin is injected into the urethra as a "test of cure," and in certain cases to stimulate a reaction in the course of treatment.

The Clinical Application.

As regards general treatment, all our patients in the army are treated in hospital, and for the first fourteen days are confined to bed on a low diet. At the end of that period they are allowed "up" and given fish diet, and graduated exercises are permitted; these latter are not special exercises, but comprise the ordinary hospital fatigues, which vary from quite light duties to comparatively heavy work.

Urethral smears are taken and examined microscopically daily, and a rough daily estimation of urine pH value is made. Immediately the case is diagnosed routine local treatment is commenced; this consists of an irrigation, followed by an intraurethral exotoxin instillation, which the patient retains in the bladder and urethra for as long as possible—three hours or more. At the same time he receives an intradermal injection of exotoxin vaccine into the skin of the shaft of the penis, and an intramuscular injection of the same vaccine at any convenient site.

As regards the intraurethral instillation, this is repeated as soon as the urine pH becomes optimum, and subsequently whenever urethral smears show the presence of gonococci throughout the course of the disease. This instillation causes no irritation or provocative effect, and in practice it can be repeated whenever an antigenic or ameliorative action is desired. As regards the intradermal injection, this route and site are chosen with the object of stimulating the local reticulo-endothelial system, in which immune bodies are manufactured. The administration at this site causes a slight local reaction and a definite temporary tenderness of the lymph glands of the groin. The intramuscular injection causes only the slightest local reaction.

The two initial doses by the intradermal and intramuscular routes are 0.2 c.cm.=200 million respectively. In the average case they are repeated at ten-day intervals, the intradermal dose remaining the same, but the intramuscular doses are gradually increased. Every case is treated on its own merits as regards intervals and dosage; many cases can be given larger doses at shorter intervals.

When, on clinical grounds, the course of events justifies the consideration of cure, the patient receives an intraurethral injection of endotoxin, the dose being 1 c.cm.=250 million. This is to provoke into activity any latent active foci. If following this provocative injection the case

relapses, treatment with exotoxin intraurethrally is repeated. Should there be no recrudescence after seven days' observation the patient leaves the hospital; there have been very few subsequent relapses.

For a long time we had observed that although there might be an immediate recrudescence of the disease following an endotoxin injection as a "test of cure," the subsequent course of events was good. When this "flare up" of the disease had settled down the case went on to recovery, and subsequent endotoxin injections failed to provoke a relapse. This induced us to try the effect of endotoxin locally in its original strength at an earlier stage of the disease; but the results were not good; there was severe provocation in the average case, and there followed what appeared to be a prolonged "negative phase."

Latterly we have reduced the strength of endotoxin for special use in treatment to 1 c.cm.=50 million, and to distinguish it from the original product used as the "test of cure" we have called it "treatment endotoxin." Thus, by reducing the dose, we can employ it much earlier in the course of the disease as a mild provocative. For example, quite a fair proportion of cases are apparently cured clinically after one or two initial instillations of exotoxin. These cases often progress until the third week without any active signs, when they relapse with a "gleet" showing gonococci occasionally. They may go on in this state indefinitely, the origin of the trouble being a few local submucous foci which have become indolent and resistant. The instillation of the "treatment endotoxin" at an earlier stage would appear to be of use as a mild provocative of such indolent foci, and this specific stimulation gives the necessary filip to complete their cure.

Although we believe that endotoxin contains the true toxic derivatives of gonococcal metabolism, there is no doubt that clinical experiences point to the fact that it also possesses antigenic properties when administered in correct dosage and at the right time in the course of the disease. Major A. T. Frost, R.A.M.C., observed this clinical fact in the early days when Major Diamond first produced endotoxin, but we have been inclined to forget it in our enthusiasm to produce a non-toxic exotoxin.

Deductions and Results of Treatment.

Except in a general way we do not venture, at this stage, to claim that in employing these methods for the treatment of gonorrhoea we have elaborated a perfect line of treatment, or even that we have very appreciably decreased the duration of the disease. We feel that in attacking gonorrhoea by these special polar-body-producing vaccines we have accidentally tackled the most difficult disease in which to apply these methods. The gonococcus is notoriously a toxic organism, and the anatomy of gonorrhoea is exceptionally difficult.

Another unfortunate fact was the elaboration of endotoxin—our "test of cure"—before the production of the non-toxic exotoxin. By applying endotoxin as our "test of cure" our standard of cure is exceedingly high—in the opinion of many, too high. Certainly patients are kept in hospital when to all intents and purposes they are clinically cured, for they are incapable of being provoked to relapse by any other method than by endotoxin. If we had not employed endotoxin we might have produced some excellent statistics as to days under treatment. However, we are conscious that there has been a general all-round improvement clinically: complications are comparatively rare, and the relapse incidence is lower than it has ever been. The most striking feature is the great diminution of the urethral discharge with corresponding decrease in the number of gonococci in the films after an intraurethral instillation of exotoxin. In an early acute case, with all essentials at an optimum, such as the pH reaction and efficient irrigation, the sequel of events is dramatic. Naturally such happy results are not frequent, but they occur sufficiently often to convince even the sceptic that their occurrence is no mere coincidence.

All of us who have followed this research from the beginning feel that we have not yet perfected our methods of application and that we are not getting the optimum of results which we are so confident are to be obtained. As regards the exotoxic vaccine used parenterally, its anti-

genic value is high, it is non-toxic, and has given very good results in many severe cases of local and metastatic complications.

Polar Body Production in Organisms other than the Gonococcus.

Although perhaps outside the question under review the following general remarks may be of interest by way of confirmation.

Polar bodies, which we have been able to obtain in 33 per cent. of all gonococcus strains—provided the necessary elements for their formation are present in the culture medium and the physical conditions required for their development are maintained—have also been found to develop in a certain percentage of strains of every organism investigated up to the present. For example, this development has been observed in strains of *B. tuberculosis* (bovine), staphylococci, streptococci, pneumococci, Friedländer's bacillus, *B. coli*, *B. catarrhalis*, *B. crassus*, *B. influenzae* (Pfeiffer), *B. septus*, Hoffmann's bacillus, *B. xerosis*, etc.

In the case of the above, with the solitary exception of *B. coli*, a very large percentage of the strains show this development. In the case of the true *B. diphtheriae*, this organism, as is well known, develops polar bodies on Loeffler's medium, and when subcultured upon nucleo-protein media shows a remarkably increased production of polar bodies.

Of interest is the culture of true Klebs-Loeffler bacilli upon Dorset's egg medium; the primary culture invariably shows a certain number of elements containing polar bodies, apparently due to the carrying over to the medium of nucleo-proteins derived from the leucocytes and cells of the membrane. In the second, third, and fourth subcultures, however, no polar bodies are developed. However, if such a non-polar body culture of Klebs-Loeffler bacilli from the third or fourth Dorset medium subculture be transferred to a nucleo-protein media an immediate and enormous development of polar bodies can be observed as early as the seventh to eighth hour of culture.

As in the case of the gonococcus, if vaccines have been cultured upon media providing for detoxication during the period of subculture, and if means are taken during the process of manufacture of the vaccine to prevent further development of toxin, it is noteworthy that there is a complete absence of negative phase following the administration of such vaccine, as compared with the marked negative phase resulting from vaccines prepared from non-polar-body-producing strains. For example, polar body strains of *M. catarrhalis* sterilized by means of 0.5 per cent. phenol cause an immediate positive phase and amelioration of symptoms in *M. catarrhalis* infections. On the other hand, if such vaccines are heated at 60° C., though a favourable antigenic action is ultimately obtained, there is a definite negative phase, apparently due to the liberation of some toxin by the action of heat. The same effects are seen following the employment of gonococcus vaccines both locally and parenterally.

In tuberculosis *B. tuberculosis* will probably be of value when cultured and detoxicated with the development of polar bodies. A bovine strain of tubercle bacilli with abundant polar body production, brought about marked clinical improvement in a case of pulmonary haemorrhage, and with no evidence of negative phase.

Observation of the serum ferments in the mononuclear digestion of a polymorph leucocyte shows the following invariable time reactions. The cytoplasm of the cell is first digested, leaving the nuclear lobes free in the cytoplasm of the mononuclear, the nuclear reticulum disappears and the lobes are stained a uniform blue. Subsequently the nuclear lobes gradually become smaller and smaller until completely dissolved by the cytases of the reticulo-endothelial cell vacuole.

Precisely similar is the course of events in the case of the polymorphonuclear leucocyte laden with polar-body-containing gonococci, here the cytoplasm of the polymorph cell and that of the gonococcus first disappears, leaving the nuclear lobes and polar body granules free in the mononuclear cytoplasm. Subsequently these disappear at a much later period.

It is possible that in the above phenomena we have an explanation of the positive and negative phases resulting from vaccine administration—the negative phase being due to the liberating of endotoxin from the early digestion of the cytoplasm of the organism, whereas the positive phase may occur later as a result of the liberation of the antigenic complexes present in the polar body fraction of the organism.

If this explanation is a true one, the negative phase as a result of vaccine administration does not appear to be necessary to the development of the ameliorative positive phase—this being confirmed by the fact that it is possible with properly detoxicated polar-body-producing strains of all organisms to bring about immediate positive phases with clinical improvement.

This has been our experience after eighteen months' employment of this toxin-free gonococcus vaccine, provided every precaution is taken against the elaboration of endotoxin during manufacture. In a certain number of cases when, for experimental reasons, various modifications in the technique of culture and preparation have resulted in the causation of a negative phase, this has invariably been found to be the result of the presence of endotoxin caused by faulty methods of manufacture.

DISCUSSION.

Colonel HARRISON said he had always thought that these variations in potency were due to differences in the strains of gonococci employed to make the vaccine, and he had also hoped that perhaps by means of special cultural methods the antigenic properties of the vaccine might be enhanced. He had had some of the new vaccine satisfactorily prepared and tested at St. Thomas's Hospital. So far as could be ascertained from investigation of only a few cases by Dr. Oliver, utilizing the complement fixation test they had established that the polar body vaccine was of definite value in raising the production of antigen. Clinically they had had one brilliant result—an absolute cure in three days after one injection, notwithstanding the most vigorous efforts to excite a relapse. Other cases had cleared up more quickly than usual but had then relapsed. He asked, Why should the vaccine-producing body be called exotoxin when it was not toxic?

The PRESIDENT believed that the authors had opened up a subject which might eventually yield important results in the treatment of gonococcal infections, and also produce an explanation of the discrepancies known to all who had used vaccines for gonorrhoea and other infections. There was a large field for reliable vaccine therapy in the treatment of female gonorrhoea.

Major LAMBKIN, in reply, said that the term "endotoxin" was scientifically correct, as the substance was the product of the disintegration of the gonococcus. The term exotoxin was more debatable, since it was doubtful whether the substance was a true toxin, but it was difficult to find a more appropriate and descriptive name.

WORLD EPIDEMICS AND THEIR RELATIONSHIP AS CAUSE AND EFFECT TO SOCIAL CONDITIONS.*

BY

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ONE who speaks with authority has told us that—

"There are nine-and-forty ways of constructing Tribal lays,
And every single one of them is right."

Much the same might be said with regard to history, only the number of methods would require to be indefinitely extended, since almost every historian has his own views of the manner in which it should be written, and there is scarcely a philosopher, from Aristotle onwards, who has not tried to show the professed historian how his work should be done. The reader of history, therefore, comes under a spell of infinite variety. In one volume he will

* A paper communicated to the Section of the History of Medicine at the Annual Meeting of the British Medical Association, Edinburgh, July, 1927.