

**Vaccine therapy, its administration, value and limitations / a discussion
opened by Sir Almroth E. Wright.**

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**VACCINE THERAPY:
ITS ADMINISTRATION, VALUE
AND LIMITATIONS**



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Vaccine Therapy: its Administration, Value, and Limitations

A DISCUSSION

OPENED BY

SIR ALMROTH E. WRIGHT, M.D., F.R.S.



[From the *Proceedings of the Royal Society of Medicine*, 1910, Vol. III]

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PREFACE

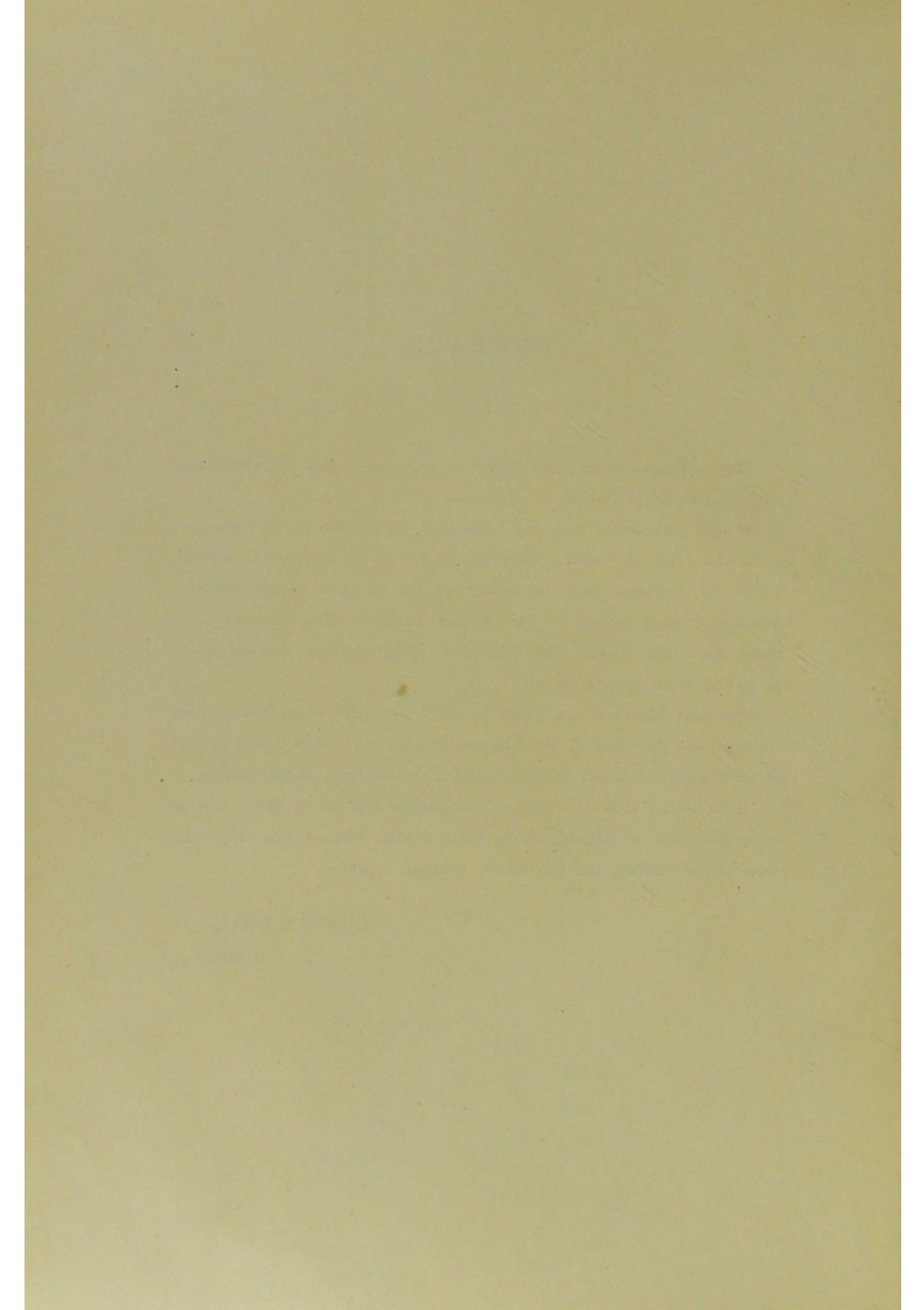
THIS volume contains the Report of the second General Discussion held by the Royal Society of Medicine.

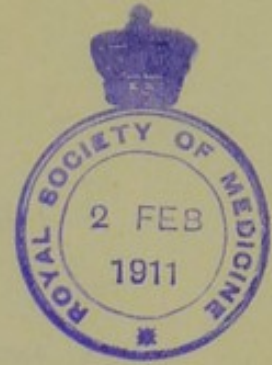
It was considered that the time had come when a full statement as to the value of Vaccine Therapy, as far as is known at present, would be welcome, and, on behalf of the Council of the Society, invitations were issued by Dr. Arthur Latham (Hon. Secretary) to those who had, during the past few years, devoted themselves to to special work in this branch.

The first Meeting took place on May 23, 1910, when the opening Address was delivered by Sir Almroth Wright. The Discussion proved of such general interest that it occupied six meetings of the Society.

It is hoped that the present publication will be of great service to practitioners in general, giving them a clear idea of the scope and aims of the method and the results hitherto achieved.

JOHN NACHBAR,
EDITOR.





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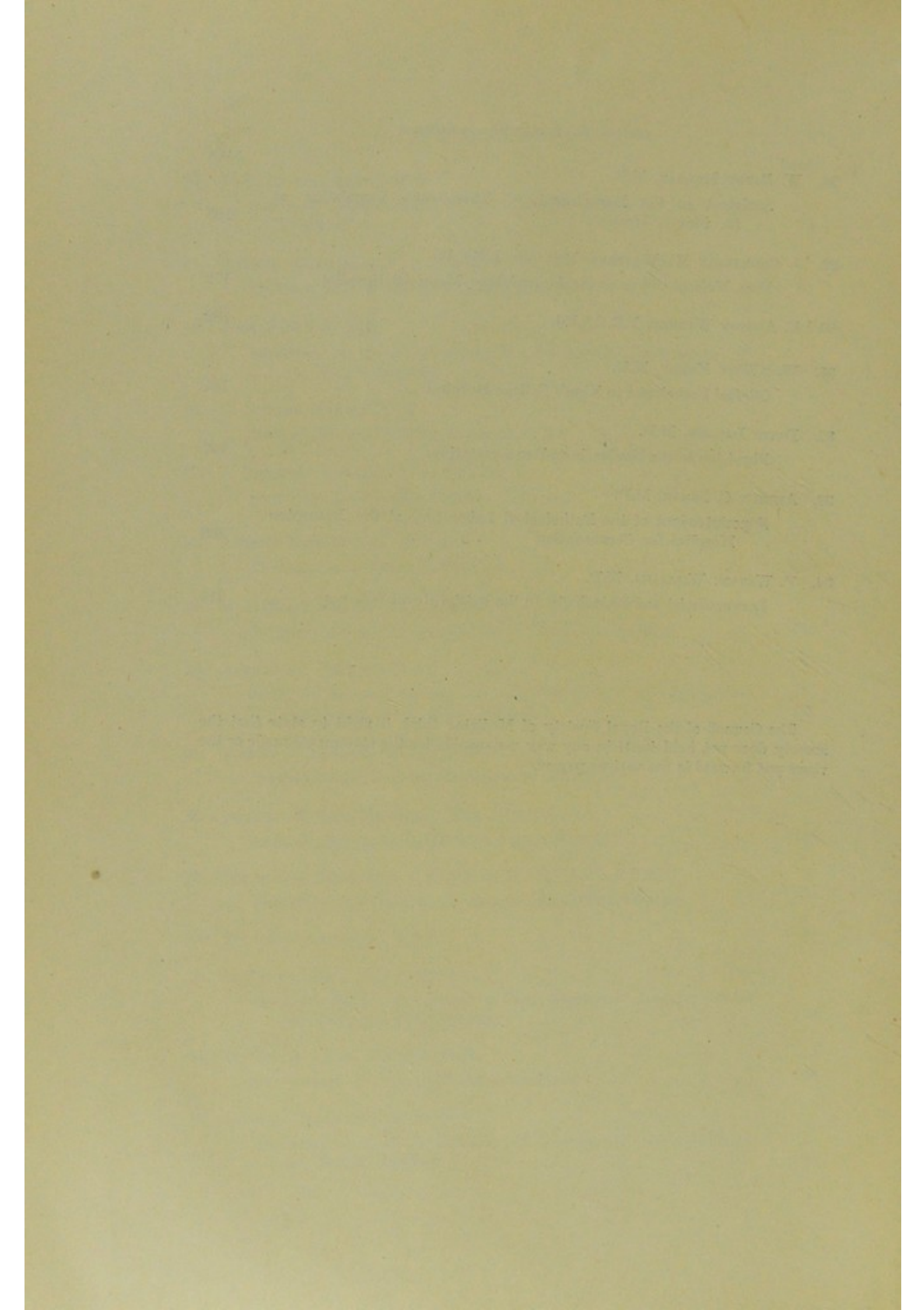
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The Council of the Royal Society of Medicine think it right to state that the Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.





Royal Society of Medicine

May 23, 1910.

Sir WILLIAM S. CHURCH, K.C.B., President, in the Chair.

Vaccine Therapy : its Administration, Value, and Limitations.

An Address Introductory to a Discussion on the Subject.

By Sir ALMROTH E. WRIGHT, M.D., F.R.S.

6 I DO not conceal from myself that in opening this debate I am undertaking a task of quite exceptional difficulty. I have to set out to you such new points in connexion with vaccine therapy as may seem to me to deserve attention. I have to attempt to take the measure of the achievements of this new therapeutic method. I have to discuss its limitations. And, above all, I desire to suggest to you in connexion with all these subject-matters certain canons of criticism.

Before I embark upon these tasks I may perhaps with advantage consider for a moment the rationale of vaccine therapy. The fundamental principle of vaccine therapy, as I conceive of it, is to exploit in the interest of the infected tissues the unexercised immunizing capacities of the uninfected tissues. Let me illustrate my meaning. I will take the case of a localized infection. We have here a condition in which the invading microbes are holding their own or getting the upper hand, and our object must be to turn the tables upon them. For this purpose we inoculate into some other part of the body microbes which are similar to those which the patient has to combat. Such inoculation is not, however, as the unthoughtful immediately assumed, a mere replica of the original infection. There are two points of difference. *First*, the

microbes in the vaccine have been devitalized, so that their multiplication is impossible; *secondly*, the dose of vaccine is so regulated that the organism of the patient must inevitably win at the site of inoculation. Now a victory such as this is won by the elaboration of antibacterial substances, and these are generated in such a case on a scale which is more than adequate to bring about a destruction of the bacterial elements which have been incorporated. The surplus of specific antibacterial substances which have thus been elaborated will now find its way by the channel of the blood to the focus of infection. There it will bring aid to the defensive forces of the organism which before were ineffectually combating the invading microbes. The victory which the uninfected tissues have won over the microbes of the vaccine will in this way lead up to a victory of the infected tissues over the microbes they have to combat.

A therapeutic method which proceeds on this new-found principle must, of course, make new demands. It will be well to realize what they are.

The medical man who has recourse to vaccine therapy ought to have a familiar acquaintance with the microbes which affect the human body. He ought to appreciate the fact that vaccines owe their efficacy to the reaction they set up in the tissues, and not to any action exerted directly by the vaccine upon the invading microbe. He ought to have mastered the general principles of immunization. He ought to know in connexion with each vaccine the *minimum effective dose*—i.e., the dose which gives the minimum immunizing reaction without any intervening negative phase—and the *medium*, or average, dose—i.e., the dose that gives, after a negative phase, a more powerful immunizing reaction. He ought to know the general conditions which affect the sensibility of the organism. He ought to understand how to adjust the dose to the requirements of the individual patient. And he ought to have a knowledge of the conditions which obtain in the focus of infection, and of the methods of circumventing the difficulties which are introduced by these conditions.

If vaccine therapy demands all this of the medical man, it is clear that the discussion of vaccine therapy must inevitably lead on to the opening up of the question as to whether the medical practitioner must of necessity be a bacteriologist.

If, in the course of this discussion, it becomes clear that vaccine therapy is more effective than any other method of treating bacterial disease, and if it is conceded that it holds out in very many cases the

only real prospect of advantage to the patient, such concession will in reality be tantamount to a declaration that applied bacteriology is the essential and indispensable part of medicine, and that the practice of medicine must be reorganized upon that basis.

If, on the contrary, the conclusion is arrived at that vaccine therapy has, as compared with other methods, only a limited utility and a limited application, this will be tantamount to a declaration that the reorganization of medicine on the basis of bacteriology may still a little longer be postponed. Such reorganization, of course, becomes inevitable as soon as an effective application of bacteriology has been made.

Inasmuch as these are, if I understand the matter aright, the real issues which lie behind this debate, I think it will not be unprofitable if, before dealing specifically with vaccine therapy, I pass in rapid review the recent history of medicine and of its relations to bacteriology.

As one looks back on the history of medicine, and recognizes that the successive applications of bacteriology stand out as great landmarks, one often wonders that medicine was not long ago swept along irresistibly into the channel of bacteriology. One wonders, for instance, in connexion with the advent of antiseptic surgery why this triumphantly successful application of bacteriology was not immediately followed up by a serious attempt on the part of our profession to study and turn to account this new science. Perhaps it was that the science of bacteriology was then quite in its infancy, and perhaps that the thoughts of our profession were here too engrossed in experimentation with different antiseptics. But the dominant factor in the situation was, I feel sure, the fact that antiseptic procedures could be successfully carried out without any knowledge of bacteriology. Seeing that the action of antiseptics is exerted upon all microbes without distinction of kind, the study of bacteriology appeared to the surgeon to be merely a work of supererogation.

When, following in his wake, the physician embarked upon the treatment of bacterial diseases by antiseptics, his thought followed upon the same road. He saw in antiseptics therapeutic agents which would be effective indiscriminately against all microbes, and seeing this, he, like the surgeon, held himself absolved from any study of bacteriology.

In the meanwhile the science was advancing with giant strides. One by one the pathogenetic microbes with which we are now acquainted were discovered and their rôle in connexion with the production of disease was elucidated. At the same time methods for identifying and making cultivations of each of these species of microbes were gradually

elaborated. Then followed the discovery of agglutination, and with this the recognition of the possibility of diagnosing the nature of a bacterial infection by testing the properties of the blood fluids. After this came the discovery of the "deflection of complement test" and the discovery of the opsonic power of the blood, and with this another and much greater extension of the method of serum diagnosis. Finally came the recognition of the possibility of inducing auto-inoculation for diagnostic uses, and with this the serum tests which previously gave assistance only when spontaneous auto-inoculations were taking place became applicable also in connexion with strictly localized infections.

But the clinician has not yet been prevailed upon to reconsider his position. He still—in face of these discoveries—claims to be absolved from a study of bacteriology; and he is still bemused with the idea that the final appeal must always be to himself and to his methods of physical diagnosis.

Let me, in connexion with this fixed idea, invite you to consider the following points:—

(1) There was undoubtedly a time when the verdict of the pure clinician on a question of a diagnosis was incontestable. That was when the disease could be recognized and identified only by its clinical symptoms. Diphtheria then meant a condition where a particular kind of false membrane appeared on the throat; typhoid fever, a fever where the temperature ran a particular course; and phthisis, a disease in which certain noises could be heard down a stethoscope. With the discovery of the specific causes of these diseases came a quietus to all this. Diphtheria now means an invasion of the throat by diphtheria bacilli; typhoid fever an invasion of the blood by the typhoid bacillus; and phthisis an invasion of the lungs by the tubercle bacillus. It is not, at this hour of the day, arguable that the verdict of a bacteriologist stands in need of confirmation from a clinician. In blunt language, "the boot is on the other foot."

Let me pass to a further point:—

(2) While it must be conceded that clinical methods do furnish in many cases a bacteriological diagnosis, this is reached only by a process of inference, and the chain of inference is in this case made up of a series of open links. I should not have thought it necessary to emphasize this so obvious fact were it not that I was recently assured by a reputable clinician that it had never crossed his thought that dullness over the apex of the lung did not supply proof of tubercular infection.

And there is yet one further important point:—

(3) A diagnosis of the nature of a bacterial infection which is based upon the physical signs comes short not only in the respect that it can never be wholly trustworthy, but also in the respect that it must almost always be belated. For physical signs such as can be appreciated by clinical methods can, in the nature of things, be elicited only after comparatively gross physical damage has been done. I need not insist that bacteriological methods have from this point of view a great superiority. Pathogenetic microbes may, as you know, often be found in the secretions or the blood long before a diagnosis can be arrived at by clinical methods; and when methods of direct bacterial diagnosis give negative results, we can nearly always by inferential methods—by the opsonic index, or the agglutination test, or the deflection-of-complement test—arrive at the nature of the infection long before its clinical features have become distinctive.

While all this was, and is, uncongenial to the pure clinician, he did not fail to appreciate that there could be no question of ignoring bacteriological discoveries which were of fundamental importance for medicine. He was therefore face to face with the problem as to how to make provision for the carrying out of the necessary bacteriological tests and examinations. The proper way of confronting the situation would, of course, have been to look the future fairly and squarely in the face, and to enact that in the future no one should qualify as a medical man without some elementary knowledge of bacteriology, and that no one should proceed to any of the higher qualifications without a thorough training in this science.

If that course had been taken even a few years ago—and it has not yet been taken—the younger rank and file of the profession and the younger generation of clinical teachers would now be abreast of any work which might fall to them in connexion with vaccine therapy.

There was, however, one way of escape out of the situation. This was to delegate all bacteriological work in hospitals to a special bacteriological department, and in private practice to such public or private laboratories as might be disposed to undertake it. For a time—as in the case where the Merovingian Kings delegated all their functions to the Mayors of the Palace—everything smiled upon this arrangement. In particular the next great advance in bacterial therapeutics—I refer, of course, to the serum treatment of diphtheria—seemed to fit very harmoniously into this scheme. The medical man who had divested himself of all bacteriological work found here, to his joy, that it would be practicable for him to get his diagnosis from one bacteriological laboratory and his remedy from

another, and that there would still remain for himself a dignified rôle as a middleman between the patient and the bacteriologist. Moreover, this rôle would, it was anticipated, continually grow in importance as serum therapy found new application in connexion with one acute disease after another. The medical man even dreamed dreams of polyvalent sera that would make everything in the nature of minute bacteriological diagnosis superfluous.

Upon this basis the march of bacteriological discovery seemed to promise advantage to the medical profession—advantage in the form of greater therapeutic success—and there would not be as counter-weight any added burden of unaccustomed labour.

The advent of vaccine therapy has disturbed this carefully thought-out scheme, for it has brought home to us that bacteriological work is called for in connexion with nearly every case. And that is a fact which gives, as you will see, quite a new complexion to the proposal that the medical man should depute to others everything that relates to bacteriology. In point of fact we are here brought up against a very fundamental question—the question as to when, and under what circumstances and to what extent, the skilled work of a profession may legitimately be delegated. We may here confine ourselves to the case of the delegation of skilled work in connexion with our own profession.

It will prevent a confusion of issues if we at the outset discriminate between the case where a consultation is held over a patient and the case where a specimen is sent to a laboratory for report. In the former case the consultant is brought face to face with the patient and with the problem which is to be resolved. He is asked to undertake any examination which may seem to him required for the elucidation of the case, and to discuss the whole problem with the practitioner; and the consultant and practitioner can then, as fellow experts, consider exactly where and to what extent "*functional errors*"—concerning which I shall presently have something to say—may be affecting their several findings, and exactly how far these findings may be accepted as assured. And, finally, when, by such collaboration, a decision has been arrived at, the responsibility for any action taken rests upon the shoulders of both.

In the case where a specimen is sent to a bacteriological laboratory for report, we have utterly different conditions. The bacteriologist is not brought face to face with the problem. Instead of being afforded an opportunity of obtaining his own specimen in the way that he judges best, or even an opportunity of suggesting the proper way of approach-

ing the bacteriological investigation, he is tied down to the examination of such specimens as may be submitted to him. Again, the bacteriologist is generally very imperfectly informed with respect to the nature of the problem which is to be resolved. Moreover, when the written bacteriological report comes to hand the practitioner, who has not himself been a laboratory worker, will be quite unable to exercise any expert criticism upon it or to see where fallacies may come in. He will, in the ordinary case, assume that laboratory methods are not subject to fallacy and "functional error," and that the "Yes" of the laboratory means definitely "Yes," that the "No" of the laboratory means definitely "No," and that in the case of a laboratory result which is expressed in terms of figures, those figures must be an absolute mirror of reality. And even if it should so happen that the practitioner to whom the bacteriological report is sent has expert knowledge of laboratory work, he will, in default of personal knowledge of, and opportunity for questioning, the bacteriological worker, be quite unable to evaluate the "functional error," and to assign in accordance with this its proper value to the report.

Having discriminated the case of the consultation which is, as we have seen, really the case of collaboration in skilled work from the case where a specimen is referred to a laboratory for report, we have now to try to arrive at a considered decision upon the morality of that kind of delegation. Three different cases of delegation must be distinguished.

The *first* is the case of a man who, being himself skilled in the whole of the work which he undertakes, has part of it carried out by an assistant, satisfying himself that it has been done in the proper manner and accepting the responsibility for this. It is the case of the delegation of duties by the honorary physician or surgeon to the resident staff of the hospital, by the director of a laboratory to his staff, and by the practitioner to the nurse.

The *second* is the case of a man who, when invited to undertake work which lies outside the range of his competence, hands over that work and the attaching responsibility to another who has the special kind of skill which is required. This is the ordinary case of a practitioner sending on a case to a specialist.

The *third* is the case of the man whose studies have not covered the whole of his professional work and who arranges to delegate to others that portion of the work which he has omitted to learn, while retaining for himself the responsibility for the whole, along with the higher scale of rewards which goes with that responsibility. You will, I think,

recognize that this is the case of the medical man who, finding that bacteriological work is required for diagnosis and treatment, makes shift, without learning any bacteriology, to depute that work to others while retaining for himself the control of the case.

I have no doubt that you will adjudge the *first* of these forms of delegation to be both legitimate and necessary to the carrying out of work on any large scale; that you will commend the *second* while recognizing that it can only exceptionally be resorted to; and I believe that you will see that the *third* case is not very clearly distinguishable from the case of a layman who should undertake to treat a case on condition of his being permitted to consult by correspondence competent medical authority whenever he might see occasion for doing so.

When I suggest that these cases are comparable, I do so because I want to put this issue before you. If we, as a profession, deprecate treatment by the unqualified on the ground of the dangers which may attach to the treatment of grave cases by the ignorant, can we then refrain from condemning, as perilous to the patient, the treatment of grave bacterial infections by those who are ignorant of bacteriology? And if we as a profession condemn consultation by correspondence on the ground that a trustworthy opinion cannot be based upon medical data which are furnished by an ignorant patient, how then shall we refrain from condemning the system by which a medical man who is ignorant of bacteriology selects the bacteriological data upon which a diagnosis is to be based?

I confess that I myself can find only one answer to that question. But let me assume that the question as to whether this kind of delegation is legitimate is still doubtful. There is then still another way by which we may arrive at a decision. Every tree is known by its fruits. We may therefore inquire into the practical working of the system. I would point out here—for we must judge everywhere by one and the same standard—that if we deprecate the treatment of cases by the unqualified on the ground that such treatment may sometimes be perilous to the patient, and if we condemn consultation by correspondence on the ground that this system would often work badly, we must, on the same basis, condemn the system by which the bacteriologically uninstructed delegate bacteriological work to the laboratories if this system is occasionally perilous to the patient and if it often works to his disadvantage.

I suppose that no one who has any experience of the practical working of this system of delegation has any doubt on this point. Every worker in such a laboratory could tell a tale of opportunities

of diagnosis missed, of misdirected searches, and of quite incredible solecisms committed by distinguished clinicians whose qualifications date back to pre-bacteriological days. It is probable that every worker in a clinical laboratory has frequently been sent blood in a capillary tube with a request that it should be examined microscopically with a view to the detection of pathogenetic microbes. Or he has been sent a specimen of desiccated blood in a capsule with a request to examine for the malaria parasite. Or he has been asked to report on the opsonic index of a charred specimen of blood—the opsonic index being, in the view of the sender, a function which does not stand in need of any further qualification, and a function which is indestructible by heat. Or he has been asked to find the malaria bacillus in a specimen of urine, or has been sent a twenty-four-hour specimen of urine from a case of septicæmia to make a vaccine for the treatment of the case. Or he has exhibited a preparation showing phagocytosis and has been asked by a high clinical authority to say which is the microbe and which is the phagocyte. In fact every bacteriological worker has been asked to place his services at the disposal of medical men who are in everything that appertains to bacteriology more uninstructed than the educated layman.

One ought perhaps here, you think, to accept as a counterpoise to the bad results which accrue from this system of delegation the good results which accrue from it in connexion with the diagnosis of diphtheria from swabs sent to the laboratory, and in connexion with the treatment of this disease by diphtheria antitoxin. I do not for one moment wish to overlook either these or the many other advantages which may have accrued from the establishment of laboratories for clinical bacteriology; but if I take these into consideration, I am, by the same compulsion, obliged to take into consideration also that treatment by the unqualified and consultation by correspondence may also do good. And I put it to you that if we, as a profession, are under an obligation to call attention to the shortcomings of unqualified practice and consultation by correspondence, are we not under the same obligation to exercise censure upon ourselves when we have recourse to a system of delegation which involves us in similar shortcomings?

But let me deal with the suggestion that our present system of delegating bacteriological work, as exemplified in the case of the diagnosis and treatment of diphtheria, is an ideal system. I am very far, indeed, from taking this view of the matter. I regard our present system of dealing with the diagnosis and treatment of diphtheria as essentially defective. It is defective, first, in the respect that it takes

into account only one bacteriological factor—the diphtheria bacillus—and one of its pathological effects—the intoxication by diphtheria toxin. It is defective, secondly, in the respect—and this defect attaches to nearly all our therapeutic efforts—that, instead of adapting itself to the particular requirements of the individual case, our present treatment of diphtheria aims only at securing a high average of successes. I hold it to be a great defect in our methods of diagnosis of diphtheria, that attention is concentrated on the presence or absence of the diphtheria bacillus. We simply close our eyes to the fact that there may be associated with the diphtheria bacillus other pathogenetic microbes, such as streptococcus, whose presence may perhaps involve almost as much danger to life as the diphtheria bacillus itself. This neglect of the associated infections is only a natural outcome of the delegation of bacteriological work to bacteriologists who are out of touch with the case, and of the faulty appreciation of bacteriological data by medical men who are uninstructed in bacteriology.

Nor even if we leave entirely out of sight the question of therapeutics of the associated infections, and confine ourselves to the question of the therapeutics of the diphtheritic infection, would it be possible to applaud the policy of delegating the manufacture of the serum to a bacteriologist who is not in personal charge of diphtheria cases. For the laboratory bacteriologist almost by necessity sets himself, in the manufacture of serum, an ideal which is merely a laboratory ideal. He aims at the production of a serum which will conform to accepted laboratory tests, and, in seeking to achieve the greatest possible antitoxic potency, he leaves out of sight the fact that a diphtheritic infection is something more than an intoxication by diphtheritic poison. In other words, he makes no provision to secure a serum which would promote the rapid casting off of the diphtheritic membrane and extermination of the diphtheria bacilli. So even in the case of diphtheria a policy of delegation, which absolves the clinician from all concern with bacteriology, and commits his work to the purely laboratory bacteriologist, would seem to be merely a policy of the second-best.

(I) LIMITATIONS OF VACCINE THERAPY.

And now I pass to deal with the subject which is set down for me. That subject is vaccine therapy: its administration, value, and limitations. Let me begin with the discussion of the limitations of the method. To the man who is not in sympathy with vaccine therapy

the discussion of its limitations must be pre-eminently welcome; and to those of us who desire to see vaccine therapy employed whenever it can do good, such discussion must be equally welcome. With a view to facilitating the consideration of this question, I have here set out, in the form of a tabular statement, certain salient points with reference to the limitations of vaccine therapy. I have, as you see, divided my table into two columns. In the first column I have set down a list of the objections which I have heard urged by pure clinicians. In the second column I have set forth the limitations which I myself, in common I hope with every bacteriological worker, would wish to insist upon (*see p. 12*).

When you have scanned the suggestions with regard to the limitations of vaccine therapy which are set out in Column I of the table on next page, you will, I think, recognize that we have in No. 1 the objection of the practitioner who shuts his eyes and ears to the facts until it becomes absolutely impossible any longer to do so. In Nos. 2, 3, 4, and 5, we have the usual objections of the general practitioner, consulting physician, operating surgeon and specialist who desire to stand upon the old paths, and to be let alone. Lastly we have in No. 6 the objection of the man who has no conception of the rôle which bacteria play in connexion with disease.

The contention that therapeutic inoculation has a useful application only in connexion with staphylococcus infections finds its exact parallel in the contention that prophylactic inoculation finds a useful application only in connexion with small-pox. We all now know that prophylactic inoculation has achieved brilliant results in man in connexion with typhoid and plague, and in animals in connexion with anthrax and many other diseases, and we infer from this that the principle of prophylactic inoculation is a principle of general application. In the same way we all know — all of us who care to know — that therapeutic inoculation is every day applied successfully in connexion with every kind of pathogenetic microbe. And we know also—and those of us who are actually at work on the question have realized this from the outset—that we have here a principle of general application.

We pass now to the contentions 2, 3, 4 and 5, to the contentions of those who urge that their particular spheres of practice cannot usefully be intruded upon by vaccine therapy: to the objection of the consulting physician that vaccine therapy has no useful application to any of the graver bacterial infections which he is called in to see; to the objection of the operating surgeon that vaccine therapy may never take the place

LIMITATIONS OF VACCINE THERAPY.

(I) *Limitations as contended for by the clinician who regards vaccine therapy as an uncomfortable innovation.*

(1) Vaccine therapy finds no useful application except in connexion with furunculosis.

(2) Vaccine therapy is of limited utility, because it can be applied only by those who have devoted study to bacteriology and immunization.

(3) Vaccine therapy finds no useful application in connexion with the graver infections, such as pneumonia, rheumatic fever, typhoid fever, phthisis, meningitis, and streptococcal endocarditis.

(4) The proper sphere of vaccine therapy is not to take the place of any surgical operation, but to supplement it.

(5) Vaccine therapy finds no useful application in connexion with the ordinary infections of those regions of the body which fall within the sphere of the particular speciality that may happen to come under discussion.

(6) Vaccine therapy is of limited utility because it is applicable only to disorders which are referable to bacterial infection.

(II) *Limitations as contended for by the bacteriological worker who looks forward to vaccine therapy being applied in conformity with scientific principle.*

(1) Vaccine therapy can be applied only where an exact and complete bacteriological diagnosis has been made, and where the diagnosis is kept up to date.

(2) Vaccine therapy can be applied only by those who have some acquaintance with bacteriology, some understanding of the rationale of vaccine therapy, and a knowledge of the dose of the particular vaccine which it is proposed to employ.

(3) A limit is placed to the efficacy of inoculations by the fact that there are definite limits to the responsive power of the patient.

(4) Successful results can be obtained only where an efficient lymph stream can be conducted through the foci of infection.

(5) In long-standing infections vaccine therapy can give definite results only after a long succession of inoculations, and there is no security against a relapse until the infection has been completely extinguished.

(6) In a not inconsiderable percentage of cases it is essential to success that the dose of vaccine shall be controlled by measurements of the opsonic index.

of operative procedures; and to the objection of each several specialist that useful application cannot be found for vaccine therapy within the particular speciality which he himself practises.

In reality there is no kind of necessity for combating these contentions. In so far as they are the outcome of hasty generalizations, and in so far as they are irrational and interested, they will crumble away of themselves; while in so far as they are based on reason and upon a real insight into facts of nature they will, of course, hold good.

For the present I will content myself with pointing out that already vaccine therapy promises to be brilliantly successful in pneumonia; that it holds out promise in typhoid fever and in many forms of rheumatism; that it supplies the only ray of hope we have in endocarditis; that it or a system of regulated auto-inoculation—such as Dr. Patterson has suggested and carried out at Frimley Sanatorium—is our only stand-by in phthisis; that it has already—pre-eminently in the case of tuberculous glands and many other forms of tuberculous infection—proved its superiority over operative procedures; and that it has given very favourable results in treatment of diseases of mouth, nose, ear, and genito-urinary system.

There remains to be considered objection No. 6—the objection that vaccine therapy is of limited utility because it is applicable only in disorders which are produced by microbial infection. While the world in general has progressed up to the point of accepting from the bacteriologist the fact that epidemic disease is due to microbial infection, the medical profession in general has not yet accepted it from the bacteriologist that we have in practically every disease a bacterial infection, or the result of a bacterial infection. It is still comparatively unfamiliar matter that jaundice, bronchitis, common colds, many cases of asthma, infantile paralysis, and almost all cases of cardiac disease are one and all referable to microbial infection.

And though it is made a reproach to the bacteriologist that he finds everywhere a bacterial infection, it is in reality the besetting sin of the bacteriologist to underrate, in common with every other man, the part played by microbes in disease; and he constantly has the mortification of finding that he has failed to appreciate the microbial factor in a disease, and has therefore misapprehended its nature. I would invite you to reflect in this connexion how few of us are prepared even to give a hearing to Metchnikoff when he urges that atheroma of the arteries may quite well be the result of an intoxication by bacterial products absorbed from the intestine, or to Mr. Arbuthnot Lane when

he urges—as I understand him to do—that where the breasts and ovaries of the middle-aged woman are not regularly flushed through with blood in the hyperæmia of the sexual orgasm, they tend to undergo cystic degeneration under the influence of toxins absorbed from the intestinal canal.

But perhaps I shall press home my point better if I tell you some of the awakenings that have only recently come to me, and if I show you how prone one is to be misled by tradition and nomenclature and to overlook everything that does not directly obtrude itself upon our senses. I may take these things in any order, just as they come to mind.

Formation of Scar Tissue.—It has been handed down to us as a dogma that where there has been very considerable loss of substance as the result of deep and extensive ulceration, or deep and extensive burns, the best result which one can look for is healing by scar tissue. I remember being wakened out of this belief by finding that very deep and extensive tuberculous ulcers may heal up under vaccine therapy with a complete *restitutio ad integrum*. In the first case, I remember, the ulcer was situated on the back of the hand. It was more than 2 in. in diameter and it went down to the bone, and the *restitutio ad integrum* was here so complete that, a year afterwards, it was practically impossible to tell the hand which had been ulcerated from its fellow; and the patient, who, as a furrier, had to undertake very delicate manipulations, found his hand as flexible as before. The second case was that of a patient who has now for two years been one of our laboratory men. In his case a tuberculous ulcer which measured not less than 10 in. by 4 in., and which extended from the ear to the point of the shoulder, and which was at one point so deep as to seem as if it must burst into the pharynx, has now for years been covered in with a soft white elastic skin which shows no sign of contraction and is not very different from normal skin. It would seem in view of these and other similar scar cases that it might perhaps be practicable to avoid the formation of scar tissue after burns by combating the supervening bacterial infections. We are trying to see what can be done on these lines.

X-ray Dermatitis.—It will perhaps seem to you that only a man who was riding a hobby to death could suggest that a bacterial factor entered into the pathology of X-ray dermatitis. I will confess that it had never occurred to me that this might be the case until I was asked to see an X-ray operator whose hands were in a terrible condition with cracks and ulcers. Cultures here disclosed the fact that we had to deal

with an extensive streptococcus infection, and the patient received great benefit from vaccine therapy, the intractable ulcers rapidly healing up as soon as the proper dose of his vaccine had been arrived at. I ask myself, in view of the burning quality of the pain in X-ray dermatitis, and of the course that the disease runs, whether a streptococcus may not often be an important factor in this complaint.

Inflammatory Trouble at the Roots of the Teeth and Toothache.—It probably has not occurred to the ordinary man to connect trouble at the root of the teeth and toothache with a bacterial infection. But no sooner does one make an effort to shake off the disease of not thinking, and to sit down to reflect upon the subject, than it becomes clear that trouble at the roots of the teeth must be due to microbes finding their way down. And a very simple bacteriological observation then suffices to show that we have in those cases where there is trouble at the roots of the teeth generally to deal with the ordinary streptococci of the mouth. We have, therefore, here a source of trouble which may quite well fall within the range of vaccine therapy; and as a matter of fact I have often seen such trouble quiet down under the influence of a vaccine. I would suggest here, as a point for investigation, whether the burning pain of actual toothache is not analogous to the burning pain of the streptococcus ulcer, and whether it may not be due to a quite similar infection.

Pruritus ani.—Pruritus ani is, again, one of those disorders which the ordinary man would not think of referring to a bacterial infection. At any rate, it had not occurred to me that it might be due to such an infection until a patient who was suffering from this condition was referred to me for the treatment of an associated furunculosis. I now find it difficult to understand how it is possible to look at pruritus ani from any other point of view than that of a bacterial infection. I have had under observation and treatment, in addition to the case just referred to, three very desperate cases of this affection. In each case I have found that a platinum loop applied to the seat of irritation brought away quite astonishing numbers of microbes, invariably staphylococcus and pseudo-diphtheria, and occasionally tetragenus; and in each of these cases life has been rendered comfortable, or, if not quite comfortable, at any rate quite endurable, by the use of appropriate vaccines.

Hay Fever.—Although the brilliant researches of Dunbar have put it beyond doubt that hay fever is to be traced to the toxic action of pollen, it would none the less seem possible that bacteria play a rôle

in connexion with it. On the one hand the consideration that the coryza which begins as hay fever may culminate in an asthma which may last for months after the season of pollen is over, and on the other hand the fact that cultures made from the mucous membrane of the nose in hay fever often furnish voluminous growths of staphylococcus, and *Bacillus septus* and other organisms, make it probable that the action of the pollen may pave the way for a microbial infection, and that this may seriously aggravate the disorder. If this is so, and if the exaggerated susceptibility to pollen which is the prime cause of the disease cannot be successfully overcome, bacterial vaccines may quite well prove useful in these cases.

Urinary Calculus.—It is now perfectly well understood that the formation of biliary calculi stands in connexion with a coli infection of the biliary ducts and gall-bladder, and it has been known for very many years that phosphatic calculi form in the urine as the result of changes produced by bacteria. It is only going one single step further to search for a bacterial cause in connexion with every case of urinary calculus, and to try to identify the bacterial cause if such should exist. I have not undertaken any systematic observations along these lines, but, again, in the course of our daily routine of work a certain number of facts which all point in one direction have thrust themselves on my attention.

Case I.—A medical man who had suffered for years from a bacteriuria, which furnished in every case a pure culture of staphylococcus, developed a renal calculus and was operated upon.

Case II.—The daughter of a medical man, who had undergone an operation for renal calculus which resulted in the removal of twenty-one oxalic-acid calculi from the pelves of the kidneys, was brought to me with a view to something being done to prevent a recurrence of her troubles. A series of cultures made from her urine furnished in each case a copious growth of staphylococcus.

Case III.—A patient whose urine had for years furnished on each occasion a pure culture of a coliform bacillus, and who had undergone vaccine treatment for this, developed symptoms of renal calculus. The operation revealed the presence of a stone, and cultures made from the pelvis of the kidney furnished copious cultures of staphylococcus. A similar operation for calculus, undertaken twelve months later on the other kidney, again furnished a culture of staphylococcus.

Case IV.—A patient who had been admitted to the Inoculation Wards at St. Mary's Hospital for the treatment of a deep and extensive ulceration caused by a combined syphilitic, streptococcal, and staphylo-

coccal infection, developed symptoms of renal colic. Radiographic examination showed the presence of a stone in the pelvis of the right kidney, and a similar calculus in the right ureter. An examination of his urine revealed the presence of staphylococci in fair numbers.

Indigestion, Vomiting, Flatulent Distension of the Stomach.—The fact that these are often prominent features in early phthisis is one of those facts which have been known so long that no one any longer asks for an explanation of them. I believe the answer to the problem may perhaps be found in the fact that pyorrhœa alveolaris is a frequent accompaniment of phthisis. I can hardly doubt, after what I have seen result from vaccine treatment in these cases, that the gastric disturbance must often be due to streptococci, swallowed with the food. I have, for instance, seen vomiting that had occurred regularly every day for six months disappear after the inoculation of a vaccine made from streptococci derived from the mouth. We must remember, in connexion with gastric disturbance which is associated with pyorrhœa, (1) that cooked food is for all practical purposes sterile food; (2) that the admixture of microbes which gives rise to fermentation can only come from the mouth or stomach; (3) that inasmuch as a more or less effectual process of sterilization takes place in the stomach, while the development of microbes goes on without such check in the mouth, the cause of the gastric fermentation is probably to be found in the microbes of the mouth which are swallowed with the food.

Epilepsy.—It would seem as if we had in epilepsy a condition which could not by any possibility stand in any ætiological connexion with any bacterial infection. But even here the judicious will find ground for hesitancy. He will reflect that in infancy almost any infection which is associated with the setting free of bacterial toxins in the organism will produce convulsions. It may therefore not unreasonably be surmised that a bacterial focus which stood in connexion with the nervous system might even in the adult produce a like result. And I believe that I have seen epilepsy in tuberculous patients improve under inoculation treatment.

Cancer.—In spite of the fact that a moment's consideration would bring it home to anyone who had come into intimate contact with cancer that the microbic infections make a large part of the misery of the disease, both for the patient and for those that come in contact with him, the rôle which microbic infections play in connexion with cancer is as yet almost unrecognized. In reality that rôle is far more important than appears at first sight. Owing, no doubt, to that defective resistance

which seems to be a feature of all neoplastic tissues, cancer, very early in its history, long before it has burrowed its way to the surface, becomes the seat of a staphylococcus infection—an infection by the so-called *Micrococcus neoformans* of Doyen. And there is reason to believe that much of the pain and swelling and inflammation in connexion with the tumour, and much, if not all, of the so-called cancerous cachexia, is due to this micro-organism. In view of this it is clear that, even though we cannot hope to strike at the root of the evil by anything in the nature of a vaccine treatment, cancer—and in particular inoperable cancer—comes within the range of vaccine therapy.

Diabetes.—It must over and over again have suggested itself that diseases which are due to the faulty functioning of some organ—diseases, for instance—such as Graves' disease and pancreatic diabetes—may ultimately be traced to bacterial infection. Countenance is given to this suggestion by such work as has recently been done in connexion with the vaccine therapy of diabetes. I may refer to a case of pancreatic diabetes which was treated by my colleague, Capt. S. R. Douglas, where the secretion of sugar and the symptoms of the patient were found to vary with the patient's resistance to a coliform bacillus which had been isolated from her fæces. I may refer also to the interesting facts which Dr. McWatters is bringing forward in this discussion in connexion with the treatment of glycosuria by staphylococcus vaccine. I think you will see that his facts suggest that glycosuria and carbuncle, which we have always supposed to be related as cause and effect, may perhaps in some cases be merely two different manifestations of a staphylococcus infection.

Enuria.—Finally, let me invite you to consider whether a bacterial infection may not in some cases turn out to be the cause of enuria. I can call to mind a case where enuria was apparently attributable to an unsuspected coli infection of the urine, and another case in which it was also associated with the same infection. Both cases yielded to treatment by vaccines.

I have perhaps said enough to rebut the contention that the range of vaccine therapy is restricted. In point of fact it not only covers almost the whole range of our present medicine, but also much that lies altogether outside its borders. For it beseems every doctor to remember with humility that there are an infinitude of chronic or recurrent ills affecting mankind which are never seriously brought to his notice, because no one believes that there is any understanding of them in the medical profession, or any possibility of a cure being found for them.

In this connexion I may just glance at another point which, perhaps more than any other, will bring home to you how extensive is the range which opens out before vaccine therapy. It is certain that we come into this world each with his individual susceptibility to microbic invasion. I am here thinking not of our susceptibility to those microbes which can pass from man to man in the form of epidemics—those microbes which alone come into the field of view of the hygienist. I am thinking rather of the fact that one man is by nature deficient in his resisting power to the staphylococcus, another to the pneumococcus, another to the bacillus of Friedländer, another to the influenza bacillus or to the acne bacillus, another again to some one of the different forms of streptococcus, or of the pseudo-diphtheria bacillus or of the coli bacillus, and another to the tubercle bacillus. And I would have you reflect, in connexion with these microbes, that, while their ravages may not be dramatic, they are collectively responsible for nine-tenths of human disease. And then I would have you reflect that while man makes efforts to guard himself against epidemic disease, and while he enlists the help of the State in this task, he accepts it as if it were an unalterable law of nature that he should be buffeted throughout his life by the particular microbe to which he individually is liable. Thus one man puts up with recurrent influenzal attacks, another man with a succession of sore throats, another man with continual recurrences of boils, another man with chronic bronchitis, another with perpetual trouble in the roots of his teeth, another with a continuous discharge from the ear, another with sycosis or acne, another with the coli infection of the urine, another with continual pruritus, another with tuberculous glands, another with phthisis, another with recurrent intestinal attacks, and so on through the whole gamut. Vaccine therapy will, I believe, help every man to keep under the particular microbe which besets him.

I now pass to consider Column II of my table; in other words, to consider the limitations of vaccine therapy, which must—if I see the matter aright—be contended for by every bacteriological worker who desires to see vaccine therapy applied in conformity with scientific principles.

I think that only the first and the last two of the contentions in Column II stand in need of anything in the way of amplification and defence. There is no one I conceive who would think of questioning that a complete and exact diagnosis is a necessary preliminary to a successful application of vaccine therapy. Nor will any one who has done work

on a case of mixed infection have any doubt as to the absolute necessity of keeping the diagnosis up to date. It must none the less be emphasized that as soon as ever a definite label has been placed upon a case, that label generally dismisses from view all further bacteriological possibilities.

The risk of accepting an incomplete for a complete diagnosis, and so imperilling the success of our treatment, is perhaps most conspicuous in connexion with syphilitic and tubercular infections. And yet in many cases the very clinical characters which serve as stigmata of tuberculous or syphilitic infection are characters which ought properly to go down to the account of other microbes; and when we go into the matter it becomes clear that it is the presence of these microbes in the lesion which puts the clinician on the trail and furnishes him with the logical justification for the diagnosis of syphilis or tubercle.

A typical instance is furnished by rupia. The characteristic rupial scab testifies to the presence of a bacterial agent which induces a copious transudation of lymph. The bacterial agent which has a pre-eminent power of doing this is the streptococcus. But in the case of a typical pure streptococcal infection the exudate is wont to be a perfectly clear lymph which sets into an amber-yellow scab which crumbles down into a powder like gum arabic. In rupia, however, the discharge is semi-purulent, and the heaped-up scab which suggests the idea of a streptococcus infection is very tough and opaque. It is, in fact, a scab that contains a large admixture of leucocytes. This suggests a superadded infection, and the commonest infective agent which leads to an emigration of leucocytes is the staphylococcus. The characters of the rupial scab thus furnish presumptive proof of the presence of streptococcus and staphylococcus—in reality both these are regularly to be found in rupia—and, little as the pure clinician appreciates the fact, it is this twofold infection which leads him to the diagnosis of syphilis. For we have apparently in the spirochæte a microbe which brings about a general lowering of the resistance of the body to microbic infection. I may say, in passing, that the inference that a multiple infection such as we have in rupia is *always* due to syphilis is not always correct.

It is, however, certain that there is no tuberculous or syphilitic ulceration of a mucous membrane, and no extensive tuberculous or syphilitic ulceration of the skin, which is not complicated by secondary infections. It follows that it is improper in any case of tuberculous ulceration of the larynx or tongue to depend entirely upon tuberculin and to overlook the associated infections. Similarly, it is important, in any connexion with

syphilitic ulceration, to keep in mind the possibility that chemotherapy may be ineffective if we do not turn our attention to the associated microbes. And in such cases it often does not suffice to combat only one variety of associated microbes. One comes across case after case where, owing to the fact that one of a batch of infecting microbes has been overlooked, a wound obstinately refuses to get well. I have, for instance, in mind a case of tuberculous ulceration of the chin which failed to make progress when treated with a combination of tubercle and staphylococcus vaccine, and which healed up rapidly when, after the discovery of a streptococcus in the wound, a combination of tubercle, staphylococcus, and streptococcus vaccine was employed. The subsequent history of this case is interesting also, as showing the necessity of keeping the diagnosis up to date. When some months after the patient had gone back to the country the ulceration broke out again, the same triple combination proved quite ineffective. The ulceration spread in an alarming manner, and the patient returned to hospital for treatment. It was then found that the *Bacillus proteus* had established itself in the wound, and that his blood gave a positive reaction with Wassermann's test. A proteus vaccine was now administered, and under the influence of this, in combination with a few doses of iodide of potassium, the wound healed up rapidly.

The fact that long-standing infections cannot be got under save by a long succession of inoculations is obvious to anyone who understands anything of the rationale of vaccine therapy. I, however, specially emphasize it here because I find that the most unreasonable expectations are afloat as to what may legitimately be expected from vaccine therapy. In view of these, I must try to make it clear what we can and what we cannot hope from the method, in a case of long-standing infection.

Perhaps the easiest way of bringing home some appreciation of the conditions is to compare the human body to a garden, the vaccine-therapist to the gardener, and the pathogenetic microbes to weeds which can be thinned out, but which, so long as any of them remain over, retain their power of multiplying and regaining lost ground.

This analogy makes it plain that the most that can be achieved in a long-standing infection by one dose of a vaccine is a temporary reduction in the number of the infecting microbes, and that it is not worth while, in such a case, to embark upon anything less than a systematic campaign. And it also makes it plain why it should be necessary to inoculate again and again for an unlimited time when a vaccine is employed for therapeutic purposes, and once or twice only where it is

employed for prophylaxis. Clearly where inoculation is resorted to for therapeutic purposes, the surplus of anti-bacterial substances, which is elaborated, is immediately expended in the destruction of microbes; where inoculation is resorted to for prophylaxis, such surplus is not used up, but is kept in reserve against future eventualities.

When a patient is informed of these facts, and when he is told that it will be necessary to inoculate again and again for an unlimited time, he will inevitably ask how long it will take to accomplish a *cure*.

It will be profitable, therefore, to clarify our ideas about this question of the achievement of a cure.

Bacterial infections fall in reality into two classes:—

(a) Into the first class would fall "surface infections" by microbes which are normally saprophytic on the affected surfaces. The pneumococcal or streptococcal infections, which are the commonest causes of bronchitis, are instances in point.

In this class of infection it is unreasonable to aim at a complete extinction of the infecting microbe. What we can here hope for in the way of a cure is to keep the number of microbes within bounds, and to minimize the chance of a recrudescence by keeping the patient's resisting power up to the mark.

(b) Into the second class would fall infections by microbes which are extraneous to the normal organism, which are always pathogenetic, and which can only be acquired by infection from the sick. Tuberculous infections are instances in point.

In this class of cases the extinction of the infection is quite a reasonable ideal. But if now, in connexion with this class of infections, the question is pressed as to how soon this can be achieved, the vaccine therapist is bound to reply that he can never say beforehand, and can never guarantee the attainment of this result. But, though he cannot prophesy, he can from time to time take stock of the patient's condition, and tell him whether or no he has made progress, and whether or no the infection has been extinguished.

In reality, we have in addition to the clinical condition—which, of course, cannot tell us whether an infection has been extinguished—not less than four different methods by which we may see how we have progressed. Let me explain what these are:—

(1) In the case where the patient's index is being regularly taken, let us say at the expiration of ten days after inoculation, we have an automatic check upon the progress of the case. For if we find that, instead of sinking rapidly away to below normal, as it did at the outset, the opsonic index now maintains itself at the level of the normal, or a

somewhat higher level, we may—if we have excluded the fallacy of auto-inoculation—confidently conclude that the patient is making good progress. For clearly as the pathogenetic microbes in the body diminish, there must be a proportionately slower expenditure of anti-bacterial substances. When we have satisfied ourselves that this is the case, and if also all the overt signs of infection have disappeared, we may proceed cautiously to apply the next test.

(2) Where we have reason to believe that the infection may have been extinguished, and want to make certain that this is really the case, we may tentatively give up the inoculations but continue to make measurements of the opsonic index. And if, under these circumstances, we still find the opsonic index remaining normal month after month, we may conclude that the drain upon the patient's anti-bacterial resources—it is probably that drain which accounts for the subnormal indices found in the early stages of tuberculous infection—has been arrested. This will signify the complete, or all but complete, extinction of the infection. A table showing the results obtained by this method of testing on a series of patients is subjoined (*see* p. 24). If we desire an even more searching test, we may take either the next or the one following.

(3) This test is based upon the consideration that if we send a lymph stream through a limb or any other region of the body which has been the seat of a bacterial invasion, that lymph stream will, as it returns to the blood, carry bacterial poisons back into the blood, with the result that a characteristic fluctuation will occur in the opsonic power of the blood. This test furnishes information which is specially valuable where the decision of the question as to whether the patient may use his limb depends upon the question of the extinction of the infection in a joint. For the purpose of this test, active hyperæmia is induced in the suspected focus of infection, a bandage is then applied to the vein in such a way as to obstruct the blood current, and when a transudation of lymph has in this manner been obtained, the lymph is driven back into the circulation by massage or active movements. In order that the test may yield conclusive results, it is advisable, in cases where there can be only very little remaining infection, to keep the limb at rest for a day or two before undertaking the test, in order to allow of an accumulation of bacterial toxins in the focus (Chart I, *see* p. 25).

(4) While the test which has just been described resolves the question as to whether there is still lurking infection in a suspected focus, consideration will show that it will not resolve the question as to whether there may not be elsewhere in the patient's body an unextinguished focus. If this question should not be held to be sufficiently resolved by

TABLE OF CASES IN WHICH THE INFECTION IS INFERRED TO BE EXTINCT FROM THE MAINTENANCE OF A NORMAL OPSONIC LEVEL, AND IN WHICH CONFIRMATION OF THIS INFERENCE HAS BEEN AFFORDED BY THE FACT THAT THE PATIENTS HAVE REMAINED QUITE FREE FROM ALL SIGNS OF INFECTION.

Case initials	Nature of tuberculous infection	Length of treatment up to complete disappearance of all evidence of infection	Measurements of opsonic index undertaken after cessation of treatment.										
			Months										
			1	2	3	4	5	6	7-8	9-12	13-16	17-20	21-24
A. H.	Extensive ulceration of skin and subcutaneous tissues	3 months	—	.86	—	—	—	1.06	—	.93	—	—	—
F. M.	Peritonitis ...	39 "	1.13	—	.95	.91	—	—	1.05	1.05	—	—	—
M. B.	Adenitis ...	6 "	1.11	—	.98	.94	.94	—	*.84 1.07	—	—	—	—
W. C. P.	Cystitis ...	5 "	1.17	—	—	.88	+.69 .96 .88	—	—	—	1.13	—	—
G. E. G.	Epididymitis ...	2 "	.96	—	—	—	—	—	1.02	—	—	—	—
W. M. P.	Tubercular mass in vitreous	23 "	—	—	—	—	—	1.01	—	.96	—	—	—
E. P.	Adenitis ...	11 "	1.13	—	1.30	1.06	—	1.15	—	—	.96	1.12	—
L.	Ulceration of hand	7 "	1.18	—	.94	—	1.00	—	—	.86	1.04	—	1.20
G.	Adenitis ...	14 "	—	.83	—	.94	—	1.12	—	—	—	—	—
R. M.	Arthritis of knee ...	25 "	1.17	—	.98	—	1.06	—	1.11	—	1.14	1.19	—
R. W.	Adenitis ...	9 "	.80	—	.97	—	.96	—	.87	—	1.05	—	—
W. S.	Arthritis of knee ...	34 "	1.00	.93	.92	—	—	—	1.04	—	—	—	—
G. L.	Adenitis ...	22 "	1.12	—	—	1.18	.93	—	.84	1.07	—	—	—
G. M.	Arthritis of knee ...	13 "	1.21 1.08	1.07	1.02	—	—	—	—	—	—	—	—
G. S.	Adenitis ...	21 "	.92	—	—	1.28	—	—	.90 1.24	1.37	1.11	1.04	—

* Patient suffering from a temporary indisposition. + There is a doubt as to the accuracy of this estimation, as the patient was in perfect health, and the blood, when tested three days later, gave an index of .96.

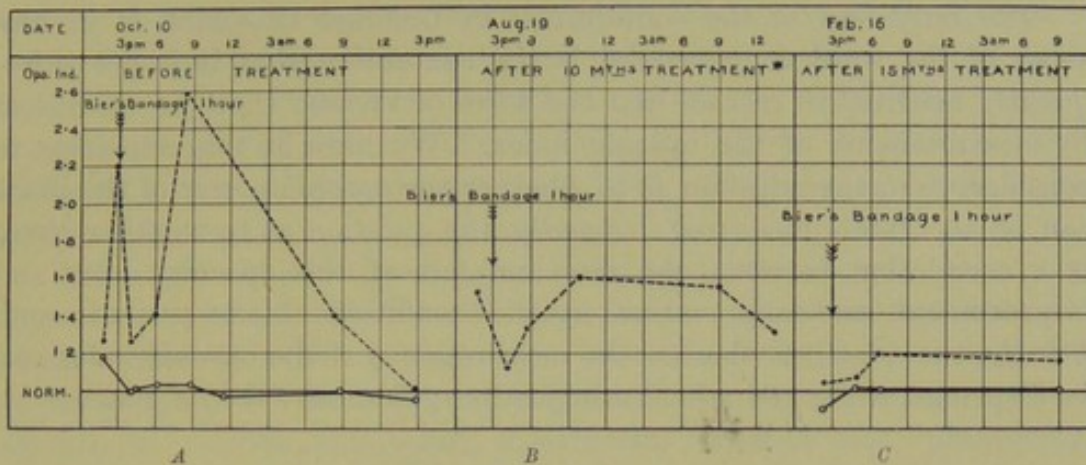


CHART I.

Chart showing results of auto-inoculation tests carried out in a case of gonococcal arthritis of wrist. ---- = Gono-opsonic index. — = Tuberculo-opsonic index. A, before treatment; B, after 10 months' treatment with gonococcic vaccine; C, after 16 months' vaccine treatment.

such a series of tests as is described under (2), it can be further put to the proof by testing the patient's blood before and after severe exercise. The routine procedure which we employ in such a case is to test four samples of the patient's blood—the first drawn off immediately before exercise, the second immediately after, the third six hours after, and the fourth twenty-four hours after. A pair of companion charts showing the results obtained by this method of testing is subjoined:—

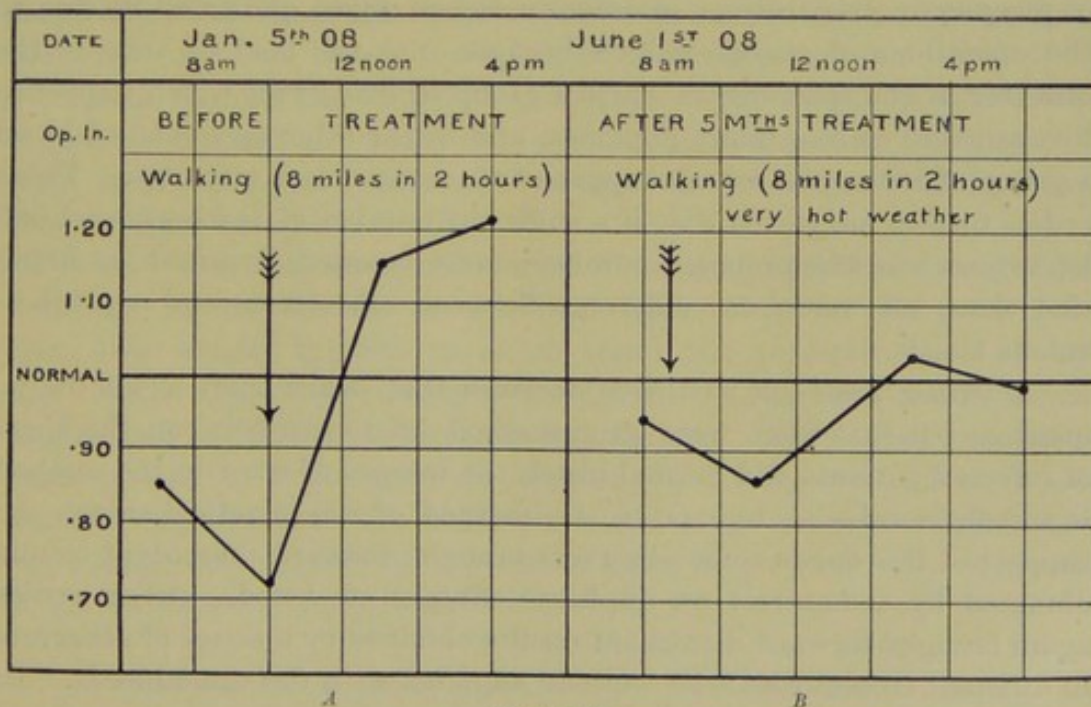


CHART II.

G. D. O. Phthisis. Auto-inoculation tests carried out: A, before treatment; B, after 5 months' treatment.

The only one of the contentions in Column II which is in any sense of the word controversial is the contention that it is not infrequently essential to success that the doses of vaccine shall be controlled by measurements of the opsonic index. We have in this connexion to consider, *first*, the question as to whether the opsonic power of the blood can be accurately measured; *secondly*, the question as to whether there is a correlation between the rise and fall of the opsonic index and improvement and aggravation in the condition of the patient; and, *thirdly*, the question whether the measurement of the opsonic index can be dispensed with, and whether any other guide can take its place.

(i) *Question as to whether the Opsonic Power of the Blood can be accurately Measured.*

I may point out, *in limine*, that the controversy which has taken place on the subject of the accuracy of the opsonic index is only what might have been expected, seeing that it is in connexion with the measurement of the opsonic index that the capacity of bacteriological workers for accurate quantitative work has for the first time been seriously put to the test.

I may very briefly refer here to three schools of criticism.

The *first*, represented by Pigg-Strangeways and his collaborators, asserted that differences such as emerge in connexion with the counting of phagocytic preparations of different bloods might quite well be due to the operations of chance, which brought into the field of view of the observer in one specimen of blood a group of leucocytes which happened by chance to contain more microbes, and in the other specimen of blood a group of leucocytes which happened to contain less microbes. These critics further suggested that if a sufficient number of leucocytes—1,000 leucocytes was the proposed number—were counted, it might be found that there was never any difference between tuberculous and non-tuberculous bloods.

A *second* school of criticism declared that, while there could be no question but that there were often marked differences between the blood of infected patients and normal blood, the margin of error in the method is so considerable as to deprive the method of any practical value. In support of this thesis some observers brought forward discordant results obtained by themselves on duplicate samples of blood. Other critics again brought forward discordant results obtained by a series of observers in different laboratories who were all supplied with the same bloods. In

connexion with the last-mentioned results, it is to be observed that in tests thus organized the results of inaccurate workers throw doubt upon the work of accurate workers. Moreover, as I have already elsewhere¹ pointed out, results obtained in different laboratories with different strains of microbes are not, and cannot be expected to be, comparable *inter se*.

A *third* school of criticism proclaimed that, inasmuch as the average ingest of a certain number of leucocytes is taken to represent the opsonic power of a blood, there here enters into the method a certain factor of chance—a factor whose magnitude can be calculated only by a statistician. Again, this school of criticism contends that, inasmuch as the phagocytic power of the individual leucocyte varies within certain limits, there here enters again into the method another factor of chance which also is a proper subject-matter for mathematical evaluation. On this basis the statistician puts forward a claim to determine the limit of error of the opsonic method.

In reality, however, in addition to the two factors which have come within his purview, there are many others which have an important influence on the result.

In the first place, the range of variation in the phagocytic power of the leucocytes, which is by the statistician assumed to be a constant, is a factor which is in reality profoundly modified by the treatment to which the leucocytes are subjected. While we have in some cases a comparatively small range of variation in cases where the leucocytes have been maltreated we have a much larger range of variation.

Again, though the statistician assumes that a record of bacteria counted in a series of leucocytes is as unambiguous and as little open to error as, let us say, a record of pips counted on a series of cards, this is very far from being so.

Microbes cannot be satisfactorily counted unless the leucocyte has first been spread out flat as a card. Again, the microbes must have been differentially stained so as to stand out perfectly clear against the background of the leucocyte. Again, the bacteria must not be fragmented or gathered together into groups. They must not be so numerous as to make accurate counting difficult. And there is also another requirement; the observer must bring to the task of counting exceptional concentration, and he must display no little judgment in the avoidance of pitfalls and fallacies.

¹ "Studies on Immunisation," p. 450, footnote 2. (Constable, London, 1909.)

It follows that the figures which represent the number of bacteria counted in the individual leucocyte are affected by the treatment to which these have been subjected *in vitro*, and these figures are also affected by the degree of skill and attention which has been brought to bear upon the preparation of the bacterial suspension, the spreading of the blood film, the fixing and staining of the preparation, and the counting.

Figures which are the resultant of all these factors, which are personal to the individual worker, cannot, I submit, possibly furnish a "*mathematical limit of error*" for a method. What they may, perhaps, furnish is a value for the "*mathematical limit of error*" in combination with what I may perhaps call the "*functional error*" of the particular observer, or groups of observers, whose work is under review.

Let me try to make clear to you—in so doing I shall only be elaborating what is familiar matter to us all—the importance of the "*functional error*" in connexion with our work.

The "*limit of error of a method*" is, if I understand the expression aright, a function which can attach only to quantitative methods in which we have an inherent factor of chance. It is a value which is unalterably fixed by mathematical laws, which can be arrived at only by a mathematician. It is a value which is exactly the same for every worker. No one can emancipate himself from it, or do anything to diminish it; and it is indissolubly attached to the *method*.

The "*functional error*" is an error which attaches only to methods which involve a certain amount of skilful functioning. It attaches to the *operator*. It has a different value for every operator. It may in the case of one and the same operator vary from hour to hour with his physiological efficiency. Its value can be diminished by practice and attention. It cannot be evaluated by a mathematician. It can be pretty accurately gauged by the operator himself.

The "*working error*" corresponds sometimes to "the limit of error of the method," sometimes to the "functional error of the operator," and sometimes to the sum of these values.

In the case of such an exercise as counting of the number of pips on a series of cards and taking the average of these, or in going through the same operations with a series of throws of the dice, nothing in the nature of skilful functioning is required. The "*functional error*" is therefore here negligible; and the "*working error*" may be identified with the "*limit of error of the method*."

In such a case as the auscultation and percussion of a chest the whole "working error" is the "functional error of the operator."

In the case of the measurement of the opsonic index "the working error" is the sum of "the limit of error of the method" and "the functional error of the operator." Of these, by far the most important factor is the "functional error."

I have satisfied myself, and all my fellow-workers have satisfied themselves, and I am glad to say a very large and increasing number of bacteriological workers all over the world have satisfied themselves, that when the "functional error" has been reduced, as it can be by practice and patience, to small dimensions, and when, in connexion with tubercle, the customary counts of 100 or more leucocytes are made, the "mathematical limit of error" of the opsonic index is such as need not seriously be taken into account.

(ii) *Questions as to whether the Rise and Fall of the Opsonic Power of the Blood is correlated with Improvement and Aggravation in the Condition of the Patient.*

I have elsewhere¹ discussed at some length the questions as to whether it is a practical ideal to make a *complete evaluation* of all the factors which make up the resisting power of the organism to bacterial invasion. I have pointed out there that inasmuch as it would be necessary for a complete evaluation of the antibacterial power of the organism to enumerate all the leucocytes, to measure their individual phagocytic activity—and, I may add, their power of digesting the ingested microbes—and to consider the question as to how far the leucocytes which are available could be brought into application; and, further, inasmuch as it would be necessary for a complete evaluation to evaluate all the known antibacterial elements which may affect the microbe from which the patient is suffering, and to make allowance for all the antibacterial elements which have not yet been discovered; and, lastly, inasmuch as there is no common denominator to which we can refer these different classes of defensive elements so as to add the one to the other or to set off the one against the other, it must for ever be impracticable to make a complete evaluation of the antibacterial forces of the body. And I have pointed out² that it is for these reasons

¹ "Studies on Immunisation," pp. 331-5.

² *Ibid.*, p. 334.

absolutely necessary—if we are to have any direct guide in our immunization proceedings—to content ourselves with a confessedly *partial evaluation* of the antibacterial powers of the blood. Again, I have pointed out that we can quite well turn to account a partial evaluation if the antibacterial element which has been selected for measurement is an element which can be accurately measured, which decreases and diminishes in the blood in response to inoculations of vaccine, and which increases and diminishes in correlation with the clinical condition of the patient.

The measurement of the opsonic power of the blood is *confessedly* and *in intention* a partial evaluation of the antibacterial defences of the body; it can be accurately measured, it is an element which decreases and diminishes in the blood in response to inoculations of vaccine; and the question for discussion is whether it increases and diminishes in correlation with the patient's clinical condition.

I have affirmed that there is such correlation. If anyone desires proof of this, he has only to watch the effect which is produced on the clinical condition and the opsonic power of a tuberculous patient by an excessive dose of tuberculin or an excessive auto-inoculation. Or if he wants to see that a rise in the opsonic index is correlated with an improvement in the patient's condition, he has only to take a tuberculous patient who has a chronically low index and watch the improvement that goes hand in hand with an improvement in the index. Or if he wants to watch the way in which the clinical condition varies with the opsonic index, he has only, in a tuberculous person, to inoculate somewhat smaller doses than are required and he will see the patient's condition improve and his opsonic index increase for a few days after inoculation, and then regularly fall away again before the next inoculation is undertaken.

I have hitherto always emphasized this generalization and said little about the exceptions, *first*, because in every new scientific departure our business is with the rule and not with the exception; and, *secondly*, because when it has once been stated that a measurement of the opsonic power of the blood is confessedly and in intention a partial evaluation of the antibacterial defences of the body, that statement inevitably brings it home to the thoughtful that there cannot then by any possibility be a perfect correlation between the opsonic power and the clinical condition.

I leave the matter there for your consideration. I would, however, point out to you that the difficult thing in this intricate web of things in

which we are entangled is to possess ourselves of the broad generalizations. It is no difficult task to alight upon an exception to a generalization which confessedly gives only the general rule. The man who, meeting an exception which might have been foreseen, straightway throws up the sponge is like the man "who encountered a corpse and retreated to bed, announcing that all life was contradicted." I suppose that not even the correlation that exists between the readings of the clinical thermometer and the condition of a patient is to be accounted a perfect correlation.

- (iii) *Question as to whether the Measurement of the Opsonic Index can be dispensed with, and whether there is any other Guide which can take its place.*

I have said elsewhere¹—weighing my words very carefully as I did so—practically everything I have to say on the question of the importance of controlling the dosage by measurements of the opsonic index. I pointed out there that in a large class of cases it is impossible within the short interval which normally elapses between one inoculation and another to tell by any clinical observation whether the preceding dose of vaccine has elicited a satisfactory immunizing response. We have in chronic tuberculous infections typical examples of this class of case, and there are also many obstinate cases of infection by other micro-organisms—cases of empyema, sinusitis, middle-ear disease, urinary infections, streptococcal infections of bone, &c.—where a definite clinical improvement can be hoped for only after a consecutive series of effective inoculations. In all these cases we have either to work entirely without a guide or to rely upon the opsonic index as our guide. I have also emphasized that even where we have more or less definite clinical symptoms to guide us at the outset there will, if the patient improves, inevitably come a time where the clinical symptoms will fail us as a guide, but where the inoculations ought to be continued for the purpose of extinguishing the infection. Here, again, the opsonic index is our only possible guide. And we cannot dispense with it if we are to diagnose our obscure cases, to take accurate stock of the progress of the cases we have under treatment, and to satisfy ourselves that we have extinguished the infection and that we may suspend our inoculations.

¹ "Studies on Immunisation," pp. 434-9.

If any of these statements are controvertible, it would be well that they should now be controverted. For, up to the present, what I have urged in favour of the importance of controlling dosage by the opsonic index has been met only by insistence that the correlation between the opsonic index and the clinical condition is not a perfect one—if this were a reason for dispensing with the opsonic index, it would also be a reason to dispense with the thermometer—and by the iteration of the formula that the clinical signs give to the clinician sufficient guide in the regulation of his dose. When I find a speaker obsessed with this formula; when I find him ignoring the fact that there are cases where no guidance can be obtained from the clinical symptoms; when I find that he refuses to face the problem as to how in such cases the dose of vaccine is to be regulated; when I find him citing cases which he has inoculated with success under the guidance of definite clinical symptoms, and adducing these as proof that the opsonic index can be dispensed with in cases where guidance cannot be obtained from the symptoms, I ask myself whether I am not perhaps listening to “one of those sages whom a man should understand less as he heard him longer.”

While I have insisted, and continue to insist, that there are many cases where we are not doing the best for the patient if we are not controlling the effect of our inoculations by the opsonic index, I have from the very outset recognized that vaccine therapy can in many cases be carried out with success without its aid. I recognize that more fully every day, and I rejoice, with all those who understand what vaccine therapy may mean to the world, that it should be so.

Let me briefly describe to you what our practice is in connexion with the control of inoculation by the opsonic index in the case of the out-patients and in-patients in the Inoculation Department of St. Mary's Hospital. In an ordinary case of localized streptococcus or staphylococcus infection we practically never have recourse to the opsonic index. In connexion with these infections we know the appropriate doses of vaccine, and the clinical symptoms furnish any further guide that may be required. The same holds true of acne. It holds true again of croupous pneumonia.

Where we have to deal with a case of staphylococcus infection, such as sycosis, which has obtained a firm hold upon the patient and which offers considerable resistance to the treatment, and which we can only hope to overcome by a succession of effective inoculations, it is often necessary to regulate the dose by means of estimations of the opsonic index.

The same holds true of the very chronic streptococcus infections which are associated with tuberculous disease of bone. It holds true again of the chronic coliform infections.

In the cases of tuberculous infection we make a distinction. We make it a practice in every case of phthisis to control the effects of the inoculations by the opsonic index, but employing, as we do in the case of phthisical out-patients, only doses which give no negative phases, we find it sufficient to determine by blood examination, undertaken on the day before the patient returns for inoculation, whether the dose has been adequate to keep the opsonic index up to the normal. In the case of phthisical patients who are treated in the wards, more frequent examinations are undertaken. In the case of tubercular adenitis and other localized forms of tubercular infection we limit our opsonic examinations if satisfactory progress is being made. As a rule, we undertake these only where the question of increasing the dose presents itself. In cases which do not make such satisfactory progress the opsonic index is estimated much more frequently.

In cases of septicæmia and in cases of advanced phthisis, and, in short, all cases where the condition of the patient is undergoing constant and rapid changes under the influence of continuous auto-inoculations, we find that the measurement of the opsonic index does not render any very valuable services.

In conclusion, I may mention, in connexion with the question as to whether the temperature in a pyrexia case can be taken as a guide to the opsonic index, that we have over and over again verified that, except in those unfortunately more or less rare cases where a pyrexia infection is being definitely got under by inoculation, we do not find any of that inverse correlation of temperature to the opsonic index which is illustrated in some of our published charts¹ and which Dr. Latham, generalizing apparently from very few cases, has alleged to constitute the general rule. The temperature cannot therefore be depended upon as a guide in immunization.

I pass on from the consideration of the limitations of vaccine therapy to its results.

(II) VALUE OF VACCINE THERAPY.

It would clearly be an impossible task to attempt here even a summary of the results of vaccine therapy. All that I would propose

¹ "Studies on Immunisation," pp. 404 and 407.

to do is to suggest for your consideration certain general canons of criticism which ought, I think, to be kept in view when we set ourselves to appraise the results of any therapeutic procedure.

The question as to how we are to give our verdict upon the success or failure of vaccine therapy in the individual case ought obviously to take precedence over the question as to how, when we have passed our verdict upon the success or failure of vaccine therapy in a series of cases, we can bring these separate verdicts together into the form of a general verdict.

Let me then begin with the former of these questions. Now I would put it to you that we have in connexion with vaccine therapy to consider two entirely different classes of cases.

We have, first, the simple and unambiguous case. This is the case where the treatment consists of a single inoculation of vaccine, and where the verdict takes into account only the results of that one inoculation. We may take as an example the case in which the vaccine therapist sets himself the task of aborting a sty on the eye, or of arresting a streptococcus infection in a poisoned wound. To abort the sty and to stop the streptococcus infection promptly is to succeed—for these things do not happen of themselves—to do less than this is to fail. The game consists here in the winning of one trick, and there can be no two opinions as to whether that trick has been won or lost.

We come now to the more intricate case. This is the case where the treatment comprises a whole series of inoculations, and where what has to be adjudicated upon is the success or failure of the whole series of operations. Consideration shows that the conditions which here present themselves may be compared with a game which consists in winning, not, as in the case last considered, a single trick, but a whole series of tricks. Among the problems which here present themselves there is again a simpler and a more difficult one.

Let us begin with the former. It is clear that if the patient gets steadily worse under inoculation, the case must be counted as a failure to vaccine therapy. And if the case gets steadily better and has ended in the extinction of the infection, it must be classed as a success to vaccine therapy, *if* it is conceded that the case offered no prospect of a spontaneous cure. If that is not conceded, the case becomes, for those who have either a bias in favour of or a bias against vaccine therapy, a case for wrangling over. For the judicious and unbiased person it becomes a case which is to be set down as a more or less probable success for vaccine therapy. In other words, if the game is

won it may be a matter of dispute whether it is the vaccine therapist or another who has won the tricks, and the dispassionate man will decide on the probabilities.

I pass to the really difficult cases. We have such a case where the vaccine therapist begins by winning a series of tricks and then begins to lose, and the game is broken off. We have again such a case where the vaccine therapist wins a series of tricks and it is assumed that this wins the game, and then the game is broken off, and then, after abandonment of treatment, there comes a relapse. And we have again such a case where the game is never definitely won, but where the vaccine therapist reinoculates whenever the condition of the patient requires it, and each time temporarily ameliorates matters.

In these cases the judgments that are passed are often absolutely reckless. It is here that the man who is blinded by a bias in favour of inoculation claims credit for winning the whole game when he has won only a very few tricks. It is here that the man who is blinded by a bias against inoculation contends that the game has been lost when only one trick or a very few tricks have been lost.

I will leave it to others to illustrate the effects of the bias in favour of inoculation. I think the following verdicts will illustrate the effects of the bias against inoculation. They relate to cases which were treated by me, which then passed out of my hands into the hands of others, furnishing to them material for controversial uses:—

The first was a case of tuberculous epididymitis. An eminent surgeon had arranged to operate in this case, and the day had been fixed. On the advent of that day he, however, found that the disease had progressed so rapidly that the operation had to be abandoned. The patient was then referred to me for treatment by vaccine therapy. For a long time the patient made very satisfactory improvement under vaccine therapy. He then lost ground. If I remember aright, the epididymis began to break down. He then went back to the surgeon, and the operation for amputation of the testicle, which had before been abandoned, was undertaken. The case was then controversially cited as an example of the failure of vaccine therapy.

I do not demur. I merely point out that this was a case where, in the language of my metaphor, I had won a series of tricks; I then began to lose, and the fact that I had failed to bring about a cure was the only fact which was taken into account, although, if I appreciate the case aright, the success which attended vaccine therapy had made it possible to undertake the operation with a prospect of success. But I ask

myself what would be the verdict of the judicious upon such a case. Would *they* pronounce it a failure or a success?

The second case was that of a patient who had been suffering for several months from a chronic oedematous inflammation of the pharynx and soft palate, which had been treated unsuccessfully by an eminent laryngologist. I was asked to see the patient, and found that the cause of the trouble was a mixed pneumococcus and catarrhalis infection. A striking improvement manifested itself immediately after the inoculation of the first dose. The patient was easier and the oedema and cyanosis of the affected parts had markedly diminished. A few days later, however, a small perforating ulcer made its appearance in the central line of the soft palate, and inoculation-treatment was discontinued. The case was published by the laryngologist who had been in charge of the case as a failure for vaccine therapy.

Again I ask myself what the verdict of the judicious would be. It would perhaps have been that one trick had been won by vaccine therapy, or perhaps—in view of the development of the ulcer—that one trick had been lost. But I think the decision would not have been that the game had been played to a finish and that vaccine therapy had proved a failure.

The third case was that of a patient with fairly advanced phthisis who was treated as an out-patient in the Inoculation Department of St. Mary's Hospital. Considering the fact that she was a frail little woman and had a very considerable distance to come for treatment, this patient had, we thought, made very fair progress under vaccine therapy; and she, of course, assured us that she had. Some time in the late autumn of last year she fell seriously ill, discontinued her attendance, and saw in consultation with her medical attendant an eminent physician. By his advice she was placed upon continuous inhalations of an antiseptic. A letter published by her medical attendant in one of the medical journals early in this year recounts the brilliant success of this method and the failure of vaccine therapy.

Only two or three days ago that patient was admitted to St. Mary's suffering from pneumothorax and in a very serious condition.

I do not know what the commentary of the judicious would be upon this. He might, of course, decide that the case was a success for vaccine therapy, and a success also for the method of the continual inhalation of antiseptics. Or he might decide that it was a failure for both methods. But I think he would not decide that it was a failure for vaccine therapy and a success for the method of the continuous

inhalation of antiseptics. I think he would remind the letter-writer that "with what measure you mete it shall be meted to you again."

I have suggested all these difficulties to you. I confess I do not see my way out of them, unless perhaps we could content ourselves, in cases like those which have been cited above, to abstain from pronouncing a verdict on the summarized result of the whole. In such cases we might, it seems to me, content ourselves with giving a verdict on each successive movement in the game.

If I have succeeded in making you see eye to eye with me in this matter, if I have succeeded in making clear to you how in many cases almost insurmountable difficulties stand in the way of a final decision on the results obtained in the individual case, it will not be necessary for me to emphasize the fact that it must be hopeless to attempt to summarize our verdicts on vaccine therapy in any statistical form.

I have, in conclusion, only one or two passing remarks to make in connexion with the question of the mode of administration of the vaccine.

(III) MODE OF ADMINISTRATION OF THE VACCINE.

Probably to those who are familiar with Dr. Arthur Latham's work the issue as to whether the administration of vaccine by the mouth is an improvement over the method of hypodermic inoculation will be the first issue to present itself for consideration. For all of us, however, who approach it from the standpoint of the laboratory, this issue was already *res judicata* before it was brought into prominence by Dr. Latham. I had satisfied myself long ago — and the results of my experiments are embodied in my "Short Treatise on Anti-typhoid Inoculation"—that, though typhoid vaccine may be absorbed by way of the intestinal canal, it is only badly and incompletely absorbed, and above all that its action is uncertain. My friend and successor at the Royal Army Medical College, Sir W. B. Leishman, has carried out far more extensive and more careful experiments in connexion with the same question, and has arrived at the same result. He finds that inoculation by way of the alimentary canal is an extremely uncertain process. I do not think it is necessary to go any further than that, for science never sanctions a more complicated and more uncertain method being employed where a simple and certain one, such as subcutaneous inoculation, is available. And I would submit that the idea that a *via media* can be found between the antique system of

prescriptions, with doses taken t.i.d., before or after meals, and scientific applications of bacteriology, and the idea that that *via media* can be found in the administration of vaccines by the mouth, ought steadily to be put away from us. The new wine of bacterial vaccines cannot with impunity be poured into the old bottles of ancient medicine.

There is, in conclusion, just one other issue which I should like to put before you for consideration. The problem has been before my mind for a long time, and I understand that it has also suggested itself to others.

Let me introduce it to you by recalling to your mind the mental picture which I dwelt upon at the outset of this discourse. You will remember that I suggested to you that the rationale of vaccine therapy was to be found in the exploitation of the unexercised immunizing capacities of the uninfected tissues. In other words, I suggested that the antibacterial substances which are elaborated in the organism in response to inoculation are elaborated by the tissues into which the vaccine is introduced. Now inasmuch as we may make our inoculation into any part of the subcutaneous tissue, it would, upon the theory that antibacterial substances are produced at the site of inoculation, seem to follow that we ought, by inoculating in a series of different places, to get a summation effect. The idea that such a thing might be opens up whole vistas of therapeutic possibilities.

But at present the achievement of a summation effect from a series of simultaneous inoculations undertaken in different parts of the body belongs, like the achievement of a summation effect from a series of consecutive inoculations undertaken each after the previous one has evoked its immunizing response, to the realm of unrealized possibilities.

There lies before us here a wide and very difficult and unexplored field of work.

"Something lost behind the Ranges. Over yonder.
Go you there."

Dr. CHARLES SLATER: It is with considerable reluctance that I take part in this discussion, and I shall not detain the Society more than a few minutes, as I wish to confine myself to emphasizing the necessity which exists at this stage of the inquiry for great care in selecting the evidence which is to be used in support of vaccine therapy. There is no need to do more than refer to the solid basis for this method of treatment which was laid by the work of the older bacteriologists, and we appreciate the more recent additions due to the labours of Sir Almroth Wright, Sir William Leishman, and their co-workers.

No doubt in many inoculation departments a large body of evidence based on well-observed and well-authenticated cases is being accumulated, but as yet not much of this has been published. In the meantime judgment as to the value of the method of treatment is being formed on the basis of cases which are not of well-defined clinical characters, and whose bacteriology is even more indeterminate. It must be remembered that this system of treatment claims not only to alleviate or to cure, but that it is a scientific treatment, depending for its effect on the use of specific materials counteracting specific infections or intoxications. Consequently something more in the way of evidence is needed than improvement after the administration of a vaccine; every trade circular advocating a new drug contains that kind of evidence. How many of the cases on which judgment is being formed are cases of disease of the nose, throat, air-passages, intestinal and genital canal—diseases of ill-defined character, often very chronic, and liable to very considerable variations in severity? Of the clinical side I do not wish to speak, but on the bacteriological side I would point out that there is often very slight *evidence* that the vaccines employed have any real connexion with the disease; it is frequently a case of presumptive evidence. The relation between the pathological condition and the vaccine rests very often solely on the numerical preponderance of a particular germ either in preparations or in cultures made from materials in which a very large number and variety of organisms are present. Now every bacteriologist knows that there is often a very great discrepancy between organisms as seen in the preparations made from such material and in the organisms as found in the cultures made from the same material, and that it would be very unsafe to assume pathogenic importance on the basis of numerical preponderance in preparations, and still less safe on numerical preponderance in culture where so much depends on the culture medium and other conditions.

Not infrequently selective culture media are employed, which makes the argument still less cogent. The connexion is strengthened when preparations and cultures agree, but this is very frequently not the case—indeed, I should say is generally not the case. Practically, since the vaccine must be grown, the evidence of the culture is usually allowed to outweigh the evidence of the preparation. That this difficulty is felt is shown by the fact that further evidence is adduced by observations on the opsonic index, and that organism, from a number, is picked out as the most important which shows an abnormal opsonic index when tested against the patient's serum. This, again, I hold to be a very frail thread. I do not deny that its usefulness may be great sometimes, but not when we are considering evidence in support of vaccines. Even the much more definite agglutination tests, if used for the purpose of fixing the pathological importance of an organism in a case of doubtful bacteriology, would lead us to some strange conclusions.

In many cases reported the characters of the organism used are indifferently defined. Organisms such as *Micrococcus catarrhalis*, *Bacillus segmentosus coryzæ*, and *Micrococcus paratetrageus* are freely mentioned, but their characters rarely stated to have been tested. The former is by no means easy to secure in pure culture, and is especially liable to be mixed with organism having fermentative powers, and I have noticed that varieties are spoken of and admitted in some investigations. It is not an organism which lends itself to the opsonic technique; at any rate, some varieties are difficult to work with, and occasionally a strain which lends itself to the formation of a workable emulsion is used for testing the patient's index instead of the one actually isolated. The criticisms I have made above apply with equal, if not greater, force to many of the cases of intestinal infections which are recorded, and the *Bacillus coli* is so easy to find that it must always be suspect to a bacteriologist unless there is very clear evidence of its connexion with the disease which it is supposed to cause.

These criticisms are made solely in the hope that evidence of doubtful value, which does not become more valuable because it is multiplied, should be rigidly set aside, and that it will not be necessary for some future investigator to go through the records, as has recently been so brilliantly done by Dr. Bulloch in his work on hæmophilia, and reject a large proportion of the work. At the present stage of the matter, cases with well-marked clinical characters whose bacteriology

is definite, or in which the proof of the connexion between the disease and the vaccinating organism is complete, should alone be admitted as evidence for or against the value of vaccine therapy as a scientific treatment. These views may seem ultra-conservative, but it must be remembered that vaccine therapy has a commercial as well as a scientific side, and it by no means follows that all the cases treated are necessarily such as contain even the elements of scientific accuracy. I am speaking as the friend of this method of treatment, and not as an opponent, when I urge that the cases quoted in proof of its efficacy should be rigidly selected.

Dr. L. COLEBROOK: Sir Almroth Wright has anticipated that there will be some barriers raised across the path which he has taken, and he has asked me to bring forward some evidence on one or two issues which are certain to come up.

The first of these is the relation of the temperature to the immunizing process. The contention that one could control inoculations just as well by watching the temperature as by taking the opsonic index was raised by Dr. Latham before this Society a year or two ago, and Dr. Latham brought forward several charts which showed clearly an inverse correlation—i.e., a high temperature coinciding in time with a low index, and vice versa. Since that time there has accumulated much evidence along this line, and in Sir Almroth Wright's wards at St. Mary's Hospital we have taken a good deal of care to establish whether, or not, we can rely as well on the temperature as the index.

Taking, first of all, some cases where the temperature is keeping steadily along, or near, the normal line, we find that following a slightly excessive dose of vaccine there occurs, *almost* invariably, a rise in temperature in association with, or slightly preceding, the "negative phase" in the blood. Turning, however, to the more serious and also the more difficult class of cases, where the temperature is not keeping steady, it has been a much less easy task to unveil a general law. To this end we have studied some cases where we thought there was only one microbe concerned. Firstly, two cases of advanced tuberculosis of serous membranes—pericardium, pleuræ, peritoneum, where there was usually a temperature variation of 3° F. or 4° F. in the twenty-four hours. Sometimes, in these cases, the index followed the excursions of the temperature; sometimes it went in the reverse direction.

Again, we studied a case of puerperal septicæmia of long standing, doing three or four indices a day, but that yielded us nothing in the way of a general law. On some days our charts showed curves like Dr. Latham's—i.e., high indices concurring with low temperature, and vice versa; on other days the reverse relation. Again, I would refer you to three charts bearing on the same point in the case of glanders. They relate to some periods in the illness of our late colleague Dr. Wells. This chart (I) needs a word of explanation: the temperature was keeping fairly normal, but Dr. Wells had a quiescent focus in the calf of his leg, and we did not believe the infection was finished with. For a month before the period recorded on this chart his blood had not been below 1.4; then, for some reason, it dropped below the normal.

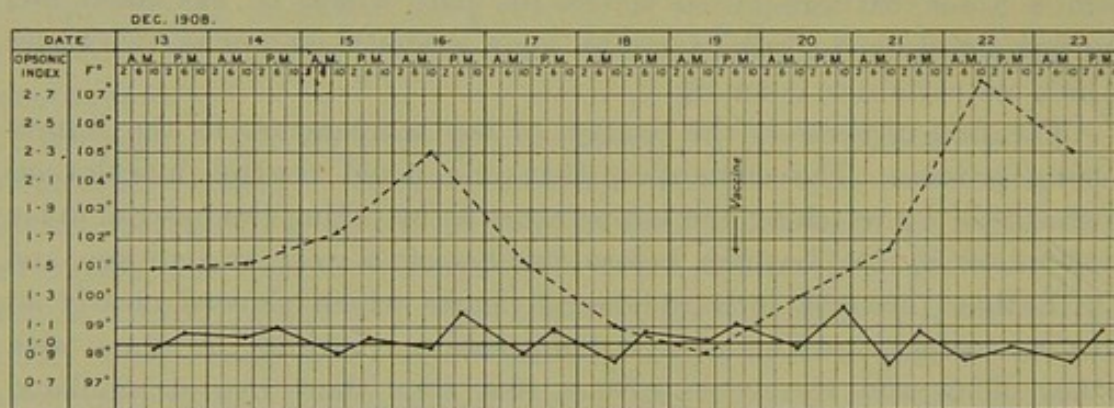


CHART I.

Glanders. ---- Opsonic index to *Bacillus mallei*.

There was no indication from the temperature that one should inoculate, but from the index there manifestly was. Similarly there was no considerable temperature phenomenon corresponding with the marked rise in opsonic power after the dose. Turning now to Chart II, you see both types of correlation more or less distinctly. There had been no inoculations at about this time, but at this point ($\frac{M}{\downarrow}$) the record tells us that he walked to his bath and massaged the calf of his leg. The temperature rose to 102° F., but at the same time the index went steadily up also, being examined every day. If one had been using the temperature above as an indicator one would have inoculated at this point, but from the point of view of the investigator of the immunity

it would have been the wrong moment. It would seem from this piece of chart, as from a considerable amount of other evidence that will occur to you, that the temperature is to be regarded as an intoxication effect rather than an immunity effect. The third chart from the case of Dr. Wells (III) will show you again both types of correlation. Our ultimate failure to save Dr. Wells, in spite of constant observations of

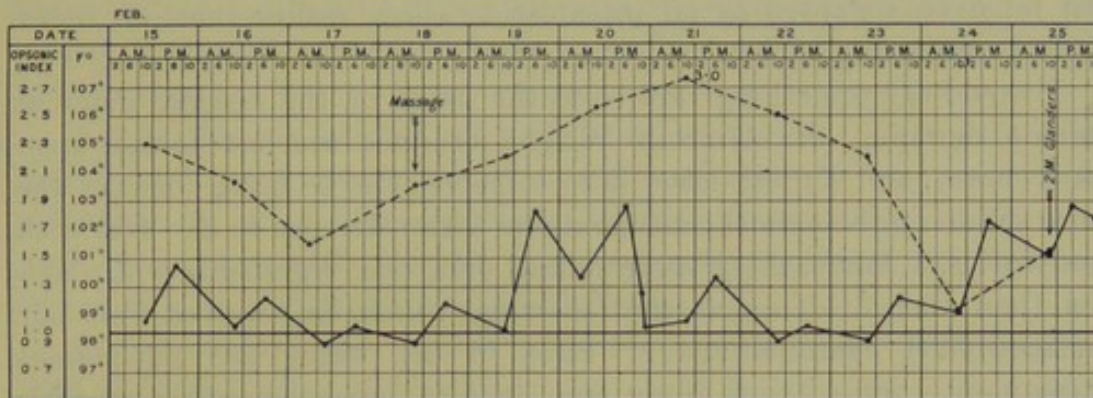


CHART II.

Glanders. ---- Opsonic index to *Bacillus mallei*.

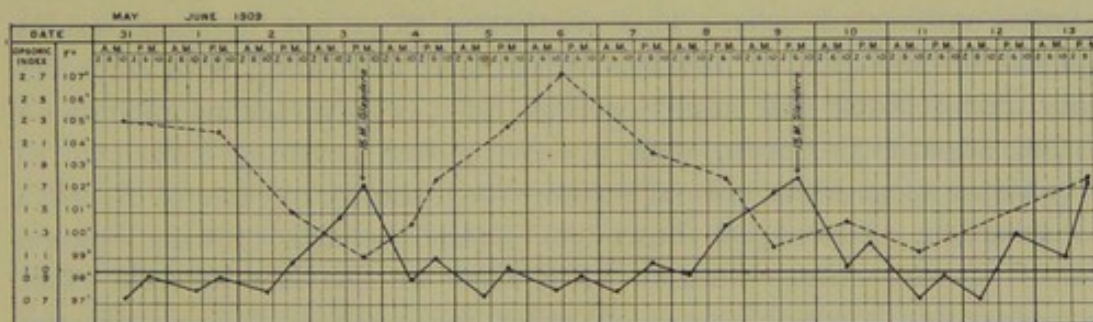


CHART III.

Glanders. ---- Opsonic index to *Bacillus mallei*.

his immunizing efforts (opsonins and agglutinins) and every kind of dose of vaccine, brings home to us the most important of the limitations of which Sir Almroth Wright has spoken—viz., our deficient knowledge of the immunity processes.

What conclusions emerge from this study of the temperature question?

First: It seems that where the temperature is steady, along or near the normal line we may get *some* valuable indications as to dosage—that is to say, we may detect even a slight *excess* in dose, of vaccine—but that is all; we shall get no evidence to guide us as to whether a given dose is the optimum or something less, and that guide we want, to get the best result of our treatment. Where, on the other hand, the temperature is irregular it will not serve as a reliable guide to us and must be regarded as an intoxication effect rather than an index of the immunizing effort.

I would say something now as to the value of the opsonic index in vaccine therapy. Sir Almroth Wright has not touched to-day upon its accuracy, and I must leave it to someone else to bring forward the more subtle mathematical considerations with reference to it. But with many of us, I fancy, these more refined data and arguments will weigh less than such evidence as the following, which has evolved from our routine blood examinations of cases in the wards and out-patient department, quite apart from any definite investigations upon this point; treatment being the only question at stake when the “bloods” were tested. The contention has been urged by some that all sera will be found equal in opsonic power (i.e., every index will come out normal) if enough trouble is taken to perfect technique, and especially to count a large number of cells. This contention does not demand serious thought on the part of any one accustomed to dealing with microbes other than tubercle and staphylococcus, for it is by no means uncommon to find a patient's serum with opsonic power anything from two to forty times as great as normal serum—for instance, in cases of *Bacillus coli* infection. I have just shown you glanders charts showing opsonic indices of three times normal. But when we consider tubercle cases the contention is possibly more in order, inasmuch as here we are not accustomed to nearly such large variations in the blood, and one can understand the worker, perhaps, with limited experience, saying that, if one's technique is good, all sera come out within normal limits.

In this connexion I would cite to you the following case: A woman with afebrile phthisis was in our wards six months, and during that time her index was recorded two or three times per week, and showed only the small range of variation usual in such cases when at rest—i.e., between 0·7 and 1·3, the majority being closer to normal, either a little above or a little below. Suddenly she developed pleurisy, which proved to be a mixed infection of pneumococcus and tubercle, both

microbes being found in the effusion. That process served as an auto-inoculation, and while her temperature was still elevated, 100° F. to 101° F. We recorded twelve consecutive indices during a fortnight, ranging from 1·10 to 1·60 (1·14, 1·25, 1·10, 1·19, 1·34, 1·38, 1·22, 1·43, 1·53, 1·59, 1·20, 1·10). Of seventy-two indices previous to this attack of pleurisy there was not one above 1·30. Synchronous with this maintained high level of immunity was an equally striking clinical improvement, associated with an almost complete cessation of the output of sputum, which had been a troublesome and obstinate feature for two years.

Nor is this an isolated example; our records at St. Mary's could furnish many similar series of maintained high or low level, some extending for much longer periods than the above, and these, if there were really a tendency for all to be normals, could not be explained except on a very violent assumption of coincidence.

One more case may be cited here: A child came to "casualty" with a tender mass of glands in the neck, and an index of 1·47 to tubercle. All through the following two weeks she continued to have high indices, three times above 1·40, and the glands were decreasing rapidly in size. Apart from its bearing on the point at issue here, this series of high indices taught us two things of value in treatment—viz., that the infection was tuberculous, and therefore to be regarded seriously, and that, for the present, nature was doing well enough without any artificial aid. After three weeks the child's index came down to normal and we inoculated, the glands having almost entirely disappeared. She has had no recurrence at all during eight months.

Here I would leave the consideration of the accuracy of the index, and say something of its current value in diagnosis and treatment. Sir Almroth Wright has referred you to a chart which may serve well as an example of our method of using the index in diagnosis, when it is a question of deciding which of two or three known pathogenic microbes is responsible for a given lesion, say an arthritis. In another class of cases we have used the index for diagnosis where the problem is somewhat different—viz., to pick out the one or more microbes which are acting as pathogenic agents in an individual case, when many varieties are present in the infected area. Such a problem faces us in dealing with colitis, and this method of attacking it (viz., by isolating a few of the possibly pathogenic microbes from a stool and testing the blood to find out to which of these there is an abnormal resistance) has

been largely used by Dr. Matthews in his work on the application of vaccine therapy to this disease.

Chart IV illustrates an extension of this process for diagnosis—viz., an attempt to bring to our aid an auto-inoculation experiment analogous to that used for the arthritis case, as shown in Sir Almroth Wright's chart. To this end calomel was administered, and, some four hours later, massage of the thickened colon was employed. Samples of blood, taken before the primary administration of calomel, and at intervals after the massage, were tested to five coliform microbes

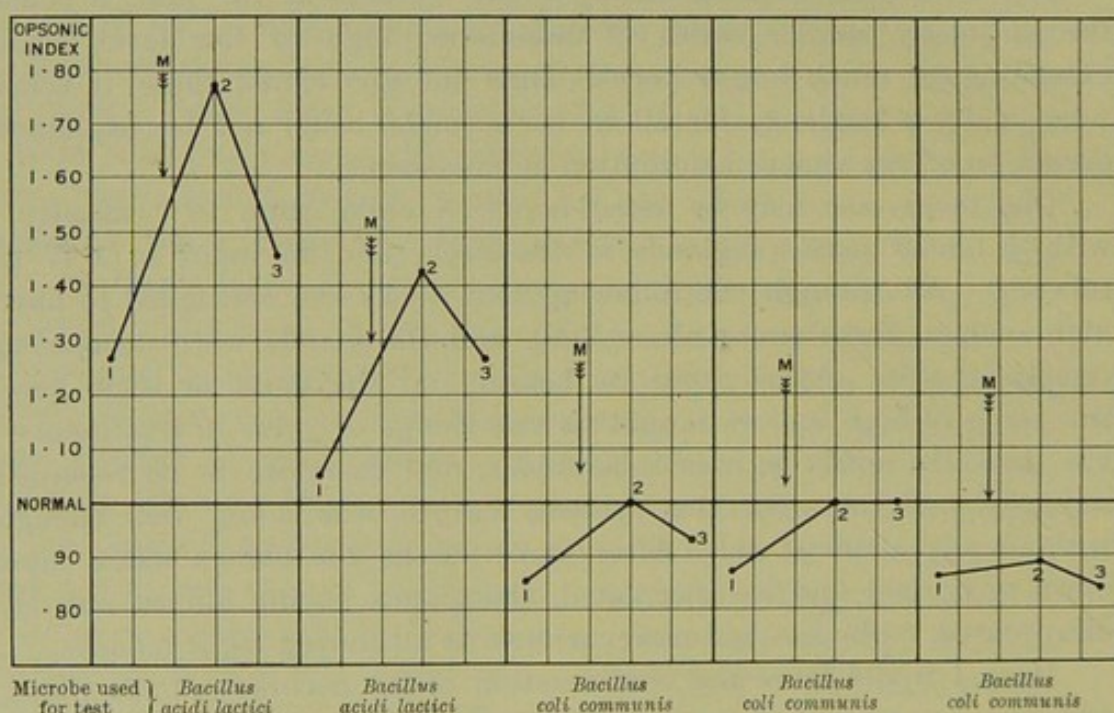


CHART IV.

Mucous colitis. Experiment to determine the causal organism. Auto-inoculation by calomel and massage, \downarrow Blood specimen 1, before calomel; blood specimen 2, half-hour after massage; blood specimen 3, four hours after massage.

isolated from the stool. With three of these microbes only slight variations in the opsonic indices were recorded, while with the other two the range of movement was greater, and this was adduced as evidence that these microbes were playing a pathogenic rôle. On more complete bacteriological examination of these two microbes it

was found that they were in reality identical, giving the reactions of *Bacillus acidi lactici*. This diagnosis of the causal organism was sufficiently confirmed later, by the marked improvement of the clinical condition which followed the use of the vaccine, having previously resisted other measures for three years.

Before leaving the subject of the value of the opsonic index for diagnosis, I would remind you, as Sir Almroth Wright has done, of the importance of making a complete diagnosis, which should include, not only the detection of the offending microbe(s), but also an assessment of the auto-inoculation processes obtaining under conditions of rest. Particularly is this of importance in cases of phthisis, where it is notoriously difficult to form an accurate conception of the extent and intensity of the infection from physical signs alone, and where, too, the ultimate result is more closely connected with this matter of auto-inoculation than with any other factor in the disease.

I may, then, pass over at this point into the domain of treatment, and consider briefly the current value of the opsonic index there. I would claim for it that it enables us, with the least delay, to arrive at the dose best suited to any given patient, either at the outset or at any point in the subsequent treatment of the infection, if we have reason to reconsider the propriety of our dose. This statement, balanced against what we know of the labour and expense involved in the determination of the index, is practically equivalent to saying that it demands and justifies its application in treatment to the more difficult and serious cases, in the conduct of which we can ill afford to lose (in Sir Almroth Wright's phrase) a single "trick."

I will now submit to you some concrete examples illustrating such advantages as I have claimed for the use of the index:—

Case I.—A woman was admitted to Sir Almroth Wright's wards with a very acute tuberculosis of hip, intensely painful, with considerable swelling, and an irregular, raised temperature. A succession of high indices to tubercle determined a verdict against a pyogenic infection of the joint, but the index soon fell and the question of dosage of tuberculin came up for consideration. The index showed us that only a very small dose, $\frac{1}{20000}$ mg., was, at that time, appropriate. Gradually pushing the dose, during two months of extremely satisfactory progress, we were surprised to find that, following $\frac{1}{20000}$ mg., the indices remained low (0.80), although there had been no temperature reaction and malaise following the dose. A further increase, to

$\frac{1}{15000}$ mg., sufficed to provide slight temperature reaction, with headache and continued low indices. Going back in dose, to $\frac{1}{30000}$ mg., we obtained satisfactory immunity and continued improvement. Here was a difficult case because of unusual susceptibility to tuberculin, even at the time when the focus was quiescent. I think it very probable that, if such a case had been treated without the help of the opsonic indices, larger doses would have been employed all along, and the case regarded, ultimately, as a failure of vaccine therapy.

There was in the ward at the same time a small boy, aged 7, with a chronic tuberculous infection of bone (lumbar vertebræ) and sinuses which were infected with staphylococcus and streptococcus. An irregular temperature chart did not help us in establishing dosage, nor did subjective phenomena, on account of the boy's small mental stature, so we had to fall back on the index, and, with this guide, pushed the dose of tuberculin to $\frac{1}{2000}$ mg. before we reached the optimum—a larger dose than any adult in the wards was having; and not until we had arrived at this dose could we control the excursions of his temperature.

To cite one more case: A country practitioner told me that he had been inoculating several cases of urinary tuberculosis with satisfactory results, but, in contrast to these, he had one case which was not doing well on a similar plan of dosage. I suggested that there was perhaps some other organism in addition to the tubercle bacillus playing an important part. This, however, proved not to be the case, and so some four or five determinations of the index were made. The blood was found to be keeping low, but on reducing the dose considerably, it rose, and a few weeks later I heard that the clinical improvement had been very marked.

The last two cases have been adduced in illustration of the value of the index in *difficult* rather than urgently serious cases, and before leaving the subject I ought to say a word upon these latter cases. The question has often come up for discussion, as to whether or no we may place any reliance upon one index per day when the temperature chart is showing irregular and large variations. Although we have found the excursions of the index to be, on the whole, less distinct than those of the temperature within twenty-four hours, yet we must, I think, answer the above question in the negative. We may, at the same time, wisely reserve as a method of choice in difficult cases of this kind, the practice of examining two or three specimens of blood in the twenty-four hours

preceding, and following, an inoculation. Such a method of choice must, however, remain, for the most part, impracticable.

I would now bring before you a few cases of real, or apparent, failure of vaccine therapy which have come under my notice. Into Sir Almroth's Wright's wards during the past year we have admitted several cases which have been segregated from our out-patient department, by the fact that they were not doing so well as the majority of the cases, and we have instituted special investigations to determine, in each case, the reason for such non-success. I think a short series of such gland cases will be of interest to you.

The first case is that of an adult woman (N. S.), who had received inoculations during two years, for a large mass of glands on one side of the neck, of which the clinical characteristics were held to be more those of tuberculous than of a lymphadenomatous infection. In differentiation between these two infections the index has not served us, since in both it is abnormal to tubercle bacillus, and although in some lymphadenomatous cases improvement has followed tuberculin treatment, the larger number have refused to yield to it. In this case the surgeon cleared up our difficulty by removing the mass of glands, which proved to be typically lymphadenomatous. Here, then, was only an apparent failure of tuberculin.

The second case is very similar, an adult woman (B. H.), with a large mass in the same situation, who had been under treatment for eighteen months without diminution of the chief tumour mass, although some outlying glands had decreased and disappeared. Skilful clinical fingers were unable to agree as to the presence or not of fluctuation, but a sac full of sterile pus was all that was found by the surgeon, who was considerably surprised at the complete absence of any other infected glands. Here, then, was a real failure to remove by vaccine a collection of pus—a failure which will surprise none of us.

The third case is that of a small boy (J. J.), with large masses of glands on both sides of the neck, in the anterior and posterior triangles, which had diminished satisfactorily in size during the first eighteen months of his tuberculin treatment, but in the last six months had made no headway, increasing, in fact, in size, on one side of the neck. On admission his temperature chart showed an abnormal range, up to 100° F. or 101° F. at night. To account for this, we searched in vain for any other focus of disease, until a slight discharge from the ear, which we had previously missed, was detected by Mr. Warren Low.

After some preliminary treatment of the ear his temperature fell, almost to normal limits, and Mr. Low, to whom we are indebted for all the surgical work in this group of cases, removed the most superficial of the glands. These glands yielded, on culture, pyogenic microbes similar to those obtained from the ear discharge. Suspecting such secondary infection, Mr. Low decided not to do an extensive operation, as would have been necessary for complete removal of the glands, but to return to this later, if necessary. Since that time, however, the boy has made very satisfactory progress during six months on inoculation treatment, and we anticipate that no further extirpation will be required.

The fourth case is that of a girl, aged 15 (L. B.), who was sent to us by a surgeon for a large mass of glands in both sides of the neck. A higher index confirmed his diagnosis of tuberculosis, and treatment was continued for six months without any improvement, but rather the reverse. On admission, a portion of gland was removed for histological examination, and Dr. Spilsbury reported it to be an endothelial type of sarcoma. In this case I have no explanation to offer of the anomalous tuberculo-opsonic indices, for although a series of bloods taken before and after massage of the glands gave but a small range of variation, and did not therefore confirm our previous opinion that the glands were tuberculous, we have as yet had no reason to suspect any other focus of disease in the body, of a tuberculous character, to account for the anomaly. Failing such a finding later, the case must remain on record as affording a rare exception to the rule of the value of the index in diagnosis. Here, again, there was only an apparent failure of tuberculin treatment.

My fifth and last case is of a different nature again. An adult woman (M. G.) was under inoculation treatment twelve months; during the first nine months, of which progress was of a negative character, the glands increasing slowly in size, and only during the last three months beginning to improve, also slowly, although her general health has kept remarkably good. At no time was there any tendency to softening of the glands. Here index and clinical features had, again, pointed to tuberculosis. Mr. Low recently advised operation, in view of slow progress, and on section of the glands we found that 80 to 90 per cent. of their substance consisted of firm caseous material, without evidence anywhere of pus formation. As regards the gland tissue remaining, Mr. Low expressed the opinion that it was of an unusually

tough fibrous character, which condition, he thought, was certainly traceable to the tuberculin treatment. This case presents us with a problem to which I can give at present no adequate answer—namely, why some such cases readily form pus and others do not. Until we get to some understanding of this and other problems connected with tuberculous glands, we shall probably continue to treat some of these cases without success.

Dr. STCLAIR THOMSON: The very brief contribution I have to make to this discussion will be founded on my experience of vaccine therapy in affections of the upper air-passages. I can further circumscribe my remarks by dealing chiefly with two disorders—lupus of the nose and throat, and suppuration in the accessory sinuses of the nose. Yet these two infections—one chronic specific and the other chronic pyogenic—would appear to offer a good field both for beneficial results and for fairly obvious observations. Lupus is readily recognized on the mucous membrane, and pus in the accessory sinuses of the nose generally makes its presence only too disagreeably evident. Still, “right here,” as our American cousins would say, I would offer a protest against accepting the evidence of cure of either disorder, except from a trained expert after a complete examination. Such loose statements as that “lupus nodules ceased to appear” or “the nasal discharge ceased” are valueless. Lupus of the mucous membrane will not only improve under various treatments, but it will heal up and remain cicatrized for years in some cases under no treatment at all. A mucous membrane may, to the uncritical eye, appear free from lupus, and yet the trained rhinologist, aided possibly by the use of adrenalin, as I have suggested, may detect minute pin-head deposits beneath an intact epithelium. Again, in regard to nasal suppuration, we must first rule out of court recent infections. The large majority of cases of acute sinusitis get perfectly well without anything more than symptomatic treatment, and I would lay stress on the point that by a recent case I mean any case within some months of its origin. I have published the records of carefully observed instances in which pus has persisted in a maxillary sinus for three months, and then disappeared spontaneously and permanently. And in the case of undoubted chronic sinusitis, we must not forget that it is not uncommon for the suppuration to become so latent that the patient

may think he is cured, and the pus may escape detection except by those specially trained and interested in this work, or that it may only be intermittently present in one sinus, or may cease to collect, and yet go on smouldering in another cavity, from which more generalized multi-sinusitis may take place from time to time.

I have to apologize for the scantiness of the actual *pièces justificatives* which I have to submit to the Society. Most of my work has been carried out in the stress and strain of the out-patient department, where scientific observations are so frequently lost from the inability to take careful notes. I cannot give the exact number of lupus cases which were treated by tuberculin; there were probably five. I have fairly complete notes of one (L. C.), who, between October 29, 1906, and February 19, 1907, had ten injections of $\frac{1}{800}$ mg. under opsonic control. Fresh crops of lupus deposits occurred after each injection, so that the patient begged to be allowed to abandon them and to return to the intermittent treatment with the galvano-cautery, which has kept her malady in check for ten years. Other lupus cases gave very similar results. No case was even improved, and some of them even appeared to be aggravated.

Of cases of suppuration in the accessory sinuses I have notes of six in which it was tried. In one case, and one only, was it associated with improvement, and this was a post-operative case. Ten days after operation on ethmoidal and maxillary sinusitis there was thrombosis of the internal saphenous vein, with foetid crusting in the operated nostril, and double suppurative otitis media. The nasal pus showed the pneumococcus in large numbers, and the patient received the stock pneumococcus vaccine (25 to 150 millions). But it is right to point out that this patient on her return to bed after operation had a profuse hæmorrhage from the operated nostril, requiring plugging with gauze and adrenalin, saline injections, and strychnine. The risks of septic absorption after nasal plugs are so well known that they are never used if they can possibly be avoided; but, still, such complications as those described, have occurred before nasal operations, and have quite disappeared without vaccine treatment. But in the other five cases, of which I have fairly complete notes, there was not even a trace of any objective improvement. Patients were vaccinated with staphylococcic, streptococcic, and pneumococcic vaccines. Some received the treatment before operation, and other cases were given it after drainage of the sinus had been established but had failed to check suppuration. In both

classes the results were equally disappointing. In one case of multi-sinusitis in which the frontal and maxillary sinuses were operated on successfully, but pus continued to be secreted by the ethmoidal and sphenoidal cavities, cultures carefully collected from intranasal pus sometimes showed a growth of streptococci in pure culture, on other days a pure culture of pneumococci, and on repeated occasions the inoculated media remained quite sterile! Now surely such an observation as this should give us pause. It refutes the excuse often made for vaccine therapy in nose and throat work that it is the mixture of infection that accounts for failure. It indicates that suppuration in a sinus may one day be entirely associated with one organism, on another day with an entirely different coccus, while the same cavity may on a third secrete a pus which is germ-free. It would look as if the organism, the original enemy, had in these chronic suppurations become a mere casual camp-follower. If the bacteriologist is to be the diagnostician, as Sir Almroth Wright suggests, this patient is in a parlous state. He might be told one week that he had a streptococcic sinusitis; the next week a pneumococcic sinusitis; and in the third week, although his nose was full of pus, he might be told he was quite well!

It is a difficult and a thankless task to prove a negative; but, as we have been invited to-day to discuss the limitations of vaccine therapy, I think it right to record that in rhino-laryngology my own experience is so disappointing that we cannot yet preach its value as a truth to those that eddy round and round. This is important; for, unfortunately, many of both the profession and the public are so pleased with the attractive theory of the method, and so delighted with the short cut it promises to both diagnosis and treatment, that sound and reliable clinical procedures are being neglected. I come across old patients of mine with purely neurotic vasomotor rhinitis who have passed through the inoculation phase simply because their medical attendant sent a swab of nasal mucus to a laboratory which reported the presence of staphylococci—an organism present in the vestibules of every nose in this room. Cases of suppuration in a maxillary sinus disappear from my ken to pass under the needle of the vaccinator; they return uncured, and in the time lost in neglecting surgical relief the pyogenic process may have spread to other cavities. Infections of the lower air passages, solely due to the stagnation and putrefaction of nasal secretion from merely mechanical causes, are submitted to a vaccine treatment which

may be longer and more tedious, and is certainly more uncertain, than the methods we already possess. If cases do not return because they are cured by vaccine therapy in other hands, no one would more gladly hear of them than myself; for the disappointing recurrences in lupus, and the anxieties associated with sinus surgery, would make simpler and surer methods most gladly welcomed. Surgical methods are at present not only more effective but generally more speedy than vaccine therapy. Patients cannot afford to keep a medical gardener permanently to look after their nasal flora; what they want is a plumber, who will put things in order with a greater chance of permanency. It is a delight to hear of its success in other departments of medicine; in that of laryngology, my only regret is that if it is to be, it is not yet.

Royal Society of Medicine

May 25, 1910.

SIR WILLIAM S. CHURCH, K.C.B., President, in the Chair.

Discussion on Vaccine Therapy: its Treatment, Value, and Limitations.¹

DR. W. HALE WHITE: My experience of this subject is entirely clinical, and it is limited to some sixty patients, excluding sufferers from tubercle. I propose this afternoon to say nothing about those suffering from tubercle, not because I have not used vaccine methods for that disease, but because it is a malady about which it is particularly difficult to arrive at conclusions, for usually tuberculosis is a slow disease, and, further, the subject is so large that it is well to limit oneself to one part of it. I may say, before I go any further, that in none of the sixty cases have I been aware that the use of a vaccine has done the patient the slightest harm. Whenever possible the vaccine treatment has been combined with other treatments which previous experience has taught us is likely to do the patient good: for instance, abscesses have been opened.

Out of the sixty cases in which vaccine treatment has been used, in eight or ten it has certainly done no good, although it has done no harm. In some others, although it did no harm, I admit there is no proof of good; but in many of these there is a considerable probability of benefit from it. Taking those in which benefit was undoubted, I will first tell you of some in which we obtained the most strikingly good results—namely, those in which the infecting micro-organism is the gonococcus. As I said, I propose that what I say this afternoon should be entirely clinical. Here is the case of a woman, aged 49, who had a multiple

¹ Second meeting (adjourned from May 23).

gonorrhœal arthritis for nine months. No treatment that she had had during those nine months had done her good. She was treated with gonococcal vaccine, and after only three injections the arthritis entirely subsided, and she was discharged at the end of a month quite cured, and has remained cured. Here is another case: A man, aged 36, had had gonorrhœal arthritis for two months. He was vaccinated with a vaccine prepared from the gonococcus derived from himself. He was given four doses, after which he was discharged quite cured, and has remained cured ever since. A very striking case is the next, and it is one to which I particularly wish to call your attention, because I think every one in this room would have admitted when he saw this woman that she would in all probability have died; and I can only say that my own opinion, standing at the bedside, is that the vaccine treatment saved her life. It is that of a woman, aged 30, who came in for very severe septicæmia, with a temperature of between 104° F. and 105° F., and had rigors. On trying to discover the cause of the septicæmia we found she had a profuse purulent discharge from the vagina. Streptococci were cultivated from that, but no gonococci were found. As the index to the gonococcus was three, it was thought probable, and I think there could be no doubt, that the original infection was gonorrhœal. So she was vaccinated with gonococci and streptococci, and the improvement was most striking. The temperature fell, and in a few days, from being a woman whom anyone would think must die, recovery set in and she was discharged perfectly cured. Another very striking case was that of a woman, aged 25, a patient of Dr. F. K. Holman, who was eight months' pregnant. He asked me to see her for multiple arthritis affecting both knees, both ankles, and several fingers. The right ankle was discharging pus, and she had fever. Considering the suddenness of the onset, and that one of the joints had broken down, I thought it was probably a pneumococcal infection; but examination of the blood made it more likely from the opsonic index that it was gonorrhœal. Ultimately gonococci were found in the discharge, she was vaccinated with gonococci, and was rapidly and completely cured. The gonococci in that case were cultivated from the pus which came from the ankle-joint. There are among my notes many other cases, but these I have given are good examples of the benefit done by vaccines in gonorrhœal cases. I am sure everyone here will admit that gonorrhœal rheumatism is frequently so intractable that when we can bring forward such cases as these it shows that the treatment has been of use.

Other genito-urinary cases which I should like to mention are some

in which the infecting organism was a coliform organism. For example, here is a good example, which again is one to which I want particularly to draw your attention. I saw the patient with two doctors well known to all of us, and I can only say the opinion of all three of us was that, when seen, the patient was a dying woman. The case was that of a lady, aged 45, who had pains and swelling in many joints, obviously severe septicæmia. The ears and the bridge of the nose were swollen, and she had double conjunctivitis, severe cystitis, blood and pus in the urine, a high temperature, and pain over both the bladder and kidneys. She was very ill and was vomiting, probably because of the double pyelitis. She was almost pulseless and had a high temperature. The urine was examined at once, and the *Bacillus coli* was found. A vaccine was prepared, and again the improvement was immediate and permanent. Thirty-six hours from the first injection the temperature fell, and she completely recovered. All the joints subsided, and when heard of a year afterwards she was perfectly well. The next example I shall select was also that of a coliform organism causing very severe cystitis and pain in the right kidney region. A vaccine was given, and, after only three injections, the patient recovered; the pain subsided after the first injection. Another case which I may trouble you with, without going into details, was one in which a young man had severe pain in his kidney, and pyuria. It was proposed to explore his kidney; I did not agree with this suggestion, for the urine contained a coliform organism. He was cured by a vaccine, and there was no operation.

Leaving the genito-urinary group, I now come to alimentary cases. One of the most interesting was a man who was invalided home for an abscess in the liver. He coughed up enormous quantities of pus, many gallons of it. He improved up to a certain point, even doubling his weight—he was practically a skeleton when he arrived—but the expectoration of pus did not cease until the micro-organism was discovered. In his case it was the *Streptococcus pyogenes longus*. A vaccine was given, and then at once, although he had been under treatment months before, the amount of expectoration diminished, and then ceased, and he is now perfectly well and earning his living. The next alimentary case is very strange, and if any one has had a similar experience I hope it will be published. The patient was a woman who had seen many doctors, and it was proposed to explore the abdomen. She had repeated attacks of vomiting, associated with high temperature. The stomach contents were examined, and were full of coliform organisms. A vaccine was prepared, and after several injections she got well. She never has

an attack now, she has gained considerably in weight, and is perfectly well and healthy. It is very unusual to find such cases due to the *Bacillus coli* or any allied organisms in the gastric contents. Under the vaccine treatment the coliform organisms disappeared from the gastric contents.

This case impressed me very much. A young man, aged 17, lay in bed, thin and wasted, having suffered from ulcerative colitis for many months. He had been seen by many physicians in London, and I think he had had every form of treatment but opening the appendix and vaccine treatment, so that we could contrast the effect of vaccine with other treatments. We did not open his appendix, but from the commencement of the vaccine treatment the temperature fell, the motions became more normal, the passage of blood ceased, and he is now well, of normal weight, and earning his living. I have vaccinated several patients who suffered from ulcerative colitis. The results are not so striking as in this case. The disease is very tedious at best, and very often several means of treatment have to be carried out simultaneously. Often it is difficult to be sure which is the offending micro-organism; so, although I believe that often the vaccine treatment has helped these patients very much, I cannot bring forward such precise proof as I have tried to do in the cases which I have already mentioned.

I have already described a patient who coughed up a liver abscess and was very much improved by vaccine treatment, and other cases of discharge of pus from the lung have also been much benefited by this treatment. One of the most convincing, on account of the unfavourable conditions, was that of an old man in an asylum. He had been an inhabitant there for many years, and he had pneumonia. When I saw him it was four months from the pneumonia, and he had signs of an empyema at the left base and was coughing up some pus. The offending micro-organism was *Streptococcus lanceolatus*. Under vaccine treatment the expectoration soon ceased; that is two years ago, and he is now well and still in the asylum. I mention this case because everyone will admit that an old man, an inmate of an asylum, is not a very promising subject when he has an empyema. Another case in the same group, of empyema being coughed up, was that of a woman, aged 34, who came into the hospital on account of expectoration of pus. Physical signs and the X-rays showed that the empyema was just over the upper part of the right lung. Although she had been coughing up quantities of pus, it diminished very rapidly under treatment. A coliform organism was cultivated from the pus, vaccines were given, and the

striking thing was that after the first injection with the vaccine the temperature began to fall and she never looked back. She was discharged perfectly well, no surgical interference having taken place. When she went out it was easy to see with the X-rays that the empyema had shrunk up and was virtually cured.

I have tried this method of treatment in some cases of bronchiectasis. Considering how difficult they are to cure; even under the best circumstances, it would be very welcome to us to be able to help them by any method. Unfortunately, I have not had any successful case. The experience of others may be different. This failure no doubt is largely due to the fact that the flora of the bronchial expectoration is very varied indeed, and possibly we have not succeeded in isolating the offending micro-organism.

Two instances in which patients seem to have been snatched from the grave are two puerperal cases which I should like to mention to you. One was that of a woman aged 27. I saw her for general puerperal septicæmia and septic pneumonia. She was so near death that it seemed probable that she would not live until the offending organism could be isolated and the vaccine prepared. But we did get some sputum, which was sent to the laboratory, and a coliform organism and a pneumococcus were cultivated. She was vaccinated with both, and the improvement was immediate and remarkable, because before we began she certainly appeared to be dying. After the first injection the temperature soon became normal, and, as far as I know, she is perfectly well to-day.

Another case was that of a woman, aged 30, who had puerperal septicæmia with acute nephritis and blood in the urine. From the catheter specimen the *Streptococcus aureus* was cultivated and a vaccine given. But she did not get better, and then coli organisms were found in the vaginal discharge; she was vaccinated with that also, and again the response was immediate, for the temperature in a few days became normal, she made an uninterrupted recovery, and she is now well. Those cases illustrate the benefit which may occur in puerperal cases.

The last case I shall mention was very dramatic. The patient was aged 30, and had been seen by many physicians. She was taken ill on February 24, with arthritis in the right shoulder, and a temperature of 105.6° F. It soon became clear that she had general septicæmia, following upon a small scratch on the hand. She rapidly developed severe septicæmia; there was arthritis in many joints, the

temperature was raised, and remained at 103° F. to 104° F. for a month; she had various swellings about the body, and at the end of a month a swelling appeared in the middle of the right arm. It was incised, and much serum oozed from it. This contained a pure culture of *Streptococcus pyogenes*. A vaccine was prepared, and, although her temperature had previously been raised for a month, within forty-eight hours of the first vaccination the temperature fell, it never went up again, and she is now well. Her husband, a doctor, writes: "The immediate good result after using a special vaccine ought to convert the most hardened sceptic."

I am not myself a bacteriologist, and I am a sceptic, so I think I have approached this subject with an unbiased mind. I can only say I have come to the conclusion, after using vaccines pretty largely, that, given in the doses which are now employed, I have never seen harm follow. I have sometimes seen cures when other modes of treatment have failed, and in some of the cases I have mentioned the patients seem to have been literally saved from death by vaccination. I am sure it sometimes helps other modes of cure; and sometimes, unfortunately, in some of the cases in which we should like most to use it, it is inapplicable, because the offending micro-organism cannot be found. But that, I think, should not deter us from trying to find the offending micro-organism by every means which the bacteriologist can devise; and when he has found it, we should use a vaccine where previous experience has taught us that some good is likely to follow.

I have selected these seventeen cases to relate to you, for I wished to bring forward examples in which the benefit following vaccination appeared so soon after vaccination, and was so great that all who were watching the cases were convinced that the improvement was due to the vaccine.

Dr. J. W. EYRE: I take it that Sir Almroth Wright, in his opening remarks, gave such a comprehensive survey of the principles of vaccine therapy that those who follow him in support of the views he put forward are relieved from the necessity of dealing with the general principles, and are free to devote themselves to contributing to the discussion observations which have occurred in their own experience, and which have struck them as being of importance. There is one thing I would refer to before mentioning my own impressions, and that is with regard to the relations existing between the clinician on the one side and the bacteriologist on the other. Sir Almroth Wright

explained that the bacteriologist was now "coming into his own"; in other words, that the bacteriologist was taking a definite place in the treatment of disease as well as in diagnosis. But I do not think the opener wished to imply that the bacteriologist was competent to take entire charge of the patients, at this early stage since his emergence from the seclusion of the laboratory. It seems to me that for the present, at all events, and until the new generation of students who are now being trained have grown up and come out into the world, that the clinician is as essential to the patient as the bacteriologist, and vice versa. That is to say, the presence of the clinician is essential to the patient because of his experience in the treatment of symptoms, for the bacteriologist has not yet had time to accumulate clinical experience of the human subject; and although it is from animals that we have derived most of our knowledge of how to apply vaccine therapy to the human subject—for the work which has culminated in the treatment of man by vaccines has been based upon exact experiments on animals in the laboratory—there are many respects in which the laboratory animal differs from man besides size and weight.

I do not propose to say anything about the value of vaccine therapy, because that seems to me to be a self-evident proposition; and, although there are still some conservative members of our profession who adopt a sceptical attitude in the matter, their number are decreasing rapidly, and one or two are being converted every day.

The point, however, which particularly impresses me is the way in which vaccine therapy is being applied in the special branches of medicine. Dr. Hale White has given you his experiences in a wide selection of cases in general medicine; but, in addition to the cases which are met with in general medicine where vaccine therapy has proved of such value, if one turns to some special department of practice, such as ophthalmology, we have a notable example of the superiority of imitating Nature's method of cure over the methods that have been in use in former times, when the removal of diseased tissue was attempted by drugs and operations. Take, for example, tuberculosis of the conjunctiva—a condition in which I have been particularly interested for many years, and which, in spite of operations repeated time after time and all sorts of local medicament, one could never hope to cure permanently, at any rate without considerable distortion. In the past two or three years seven or eight cases of tuberculosis of the conjunctiva have come under my notice, and have been treated with tuberculin, and with tuberculin alone. In every instance the

result has been splendid; and the whole of the diseased tissue has been removed naturally and without distortion. After six to eight months' treatment in each instance a normal conjunctiva, with no trace of disease, has been obtained. In every case it may be mentioned that the diagnosis has been made absolute by bacteriological methods, including inoculation. Again, in the old days one used lotions of various sorts for simple conjunctivitis. Some of the patients went on for months and even years, but now in chronic cases, due to the *Diplobacillus lacunatus*, very rapid and complete recovery is insured by the help of vaccines. In acute streptococcic conjunctivitis vaccine therapy is by far the most useful agent we can employ; whilst gonorrhœal ophthalmia, which formerly had such terrible results, can be efficiently controlled by vaccines, and practically by those alone. But here a word of warning is necessary: unless care is used and the injections controlled by the estimation of the opsonic index in gonorrhœal ophthalmia, definite harm may ensue. I have a very vivid recollection of a case of gonorrhœal ophthalmia which I treated with gonococcus vaccine, but one injection of the vaccine was given at the wrong moment, and practically all the cornea was lost, so that in the end the result was as bad as if the case had been treated in the ordinary way by lotions and drops. Another class of case in ophthalmological practice, to which my attention has been recently drawn, is orbital cellulitis associated with proptosis. In the old days this condition was usually said to be due to specific disease. Mercury and iodide of potassium were given, but often with no obvious results. Upon the investigation of these cases by bacteriological methods, and the recognition of the fact that there may be cellulitis or periostitis of the orbit, due to bacterial infection, the aid of vaccines is invoked, and it has been found that one can influence a large number of these cases in a favourable way, and the improvement in some of them is very striking indeed.

Another special branch of medicine in which vaccine therapy has scored heavily is dentistry. Goadby and other workers have investigated such conditions as pyorrhœa alveolaris, and have shown that even vaccine alone is capable of doing a large amount of good of a lasting character—much more than local surgical measures, long continued, are capable of effecting—while the combination of vaccine therapy and local treatment achieves results little short of marvellous. This is the more striking because pyorrhœa alveolaris is a condition which is exceedingly chronic, and after local treatment is liable to bad relapses.

In genito-urinary diseases vaccine therapy has come to stay: some instances of its application have already been detailed by Dr. Hale White. Puerperal septicæmia, as you have already heard, is a condition which has, on several occasions, yielded to vaccine treatment after the failure of antitoxic sera. In such a severe infection, where the case is not usually seen until late in the disease, it would not be surprising if vaccine therapy failed, because one of the chief limitations to vaccine therapy is the one which Sir Almroth Wright had on the board as the fourth—namely, that imposed by the resisting power of the patient. That is to say, if the resisting power fails, and especially if it falls to such a point that it no longer responds to the stimulus afforded by a vaccine, obviously vaccine therapy is of no use in that case. Often we do not see cases of puerperal septicæmia until the resistance of the body is at its lowest. But the fact that we are able to obtain a measure of success in this fatal form of disease is another instance of the success of vaccine therapy in a special department.

Again, in throat diseases, such as tuberculosis of the larynx, there is a notable yielding to treatment with tuberculin when intelligently carried out. But here is a point which has been forced upon me in many cases, which may be common experience, or may be noted only in isolated examples; but I have found that in tuberculosis of the larynx this local focus will clear up and the patient get a respectable voice again, and yet when, as so often happens, the lungs are infected as well, the tuberculous process in these organs will go on more quickly than before. In other words, the local resistance is improved, but the general resistance is lowered. One notices the same thing in joint diseases associated with phthisis. When the patient is suffering from a tuberculous joint and tuberculous infection of the lungs, very frequently the joint clears up completely; but the lung condition, so far from being favourably influenced by the tuberculin, actually progresses.

Finally, a word with regard to vaccine therapy in colitis. I have paid considerable attention to the disease, and I was rather surprised by a remark of Sir Almroth Wright's with regard to diagnosis—and by diagnosis I mean, of course, the recognition of the offending organism from amongst those isolated from the case. His suggestion was the administration of a cathartic and the estimation of the opsonic index to the various bacteria before and after an action of the bowels; for as his diagrams showed, very often one gets only small movements of the index with many organisms, and it may be necessary to carry out

an extended series of estimations before sufficiently widely divergent indices are recorded to enable any particular bacterium to be picked out as the offender. It seems to me that, in any but very mild cases, such a method is quite out of the question, because of the danger from hæmorrhage which may follow such a proceeding. The diagnosis of the infecting organism can, I believe, best be carried out by searching for specific agglutinins. In many of these cases the organism at the bottom of the trouble is either the colon bacillus or a member of the same group, and in all the infections I have met with so far, where such has been the case, there has been developed a sufficient amount of agglutinin in the patient's serum to enable one to pick out the required organism with certainty. But in other cases other organisms have been responsible, such as streptococci and pneumococci. These, however, usually present no difficulties. Again, with these colitis cases the necessity for an exact and absolute diagnosis, from the clinical as well as the bacteriological standpoint, is one of the very greatest importance. Given a case of simple bacterial infection of the colon causing colitis, the results to be obtained by vaccine therapy are simply wonderful. But many cases of colitis are really due to some condition which may escape observation if not thoroughly investigated. One such case occurs to my mind. The colitis, although secondarily bacterial, was undoubtedly primarily due to chronic constipation resulting from a band across the colon, which was only demonstrated during an X-ray examination. Vaccine therapy might have been carried on in that case for years with no real benefit, while the operation for the removal of the band resulted in the disappearance of the constipation, and the colon quickly recovered its normal condition.

Dr. HAROLD A. DES VŒUX: It is very difficult for an ordinary practitioner to make up his mind, as he often has to, in a hurry as to the value of a new method of treatment. Our patients, who worry us on so many subjects, are always most urgent and insistent that we should give an opinion within five minutes on every subject. They want to know whether this treatment or that is the right thing, and they add, "Surely you can tell." And we are in the position that, if we want to keep any practice at all, we must pretend to know much more than we do. I do not think that is maligning the profession, and I know it is true of some of the men whom I come across. I once said to a lady to whom I was almost a stranger, "I do not know," and her answer was, "Well, I had better get somebody who does know." I

became rather angry and left the house. She sent for another doctor—perhaps wisely. He of course knew. We have to make up our minds on these questions, and even with time and thought it is difficult to do so; yet we are often driven into a corner and are bound to give hurried opinions. We are very apt to judge of the value of a treatment by the first cases in which we see it tried. We may see a sudden and remarkable result, or we may come across cases in which the treatment has been tried in the last stages of a disease and the patient has gone from bad to worse. For instance, we may have seen a vaccine employed in a hopeless case of tuberculosis, which would incline us to say that the vaccine treatment was no good. We may have tried unsuccessfully a vaccine in Malta fever or acute septicæmia, and we would have formed an opinion accordingly; and once a man in our profession has committed himself to a statement, whether favourable or unfavourable, it is difficult to retract. It does not do to change an opinion. I heard one man say he never changed his opinion; and perhaps he was wise, for he was very successful.

There are two groups of cases in which the vaccine treatment has been used—in one very successfully, and in the other more or less unsuccessfully.

In the first group—of which staphylococcic infections of the skin (boils) are a type—inoculation is most successful. The results obtained by so many practitioners in that kind of case have had much to do with the more extended use of the treatment in other diseases. I have treated over one hundred cases of boils with vaccines, and since doing so my method of treating them has altered completely. I shall not go into statistics, but before I took up this treatment my ordinary practice, on seeing a patient with a hard, brawny, painful boil, was to advise early and free incision under an anæsthetic. On the whole it was a successful treatment, but disagreeable and sometimes prolonged. Since I have taken up the vaccine treatment I have never had to give an anæsthetic. But even now, when I find a boil in a softened condition, I make a small incision into it to evacuate the liquid pus, and in this detail disagree with Sir Almroth Wright. I will only mention one of the cases I have seen. A man came to me from Chili in June, 1908. He had been suffering from very bad boils for four years, they having followed an attack of typhoid fever. He came to me immediately after the voyage and said he was much better, but he wanted vaccine treatment. I said, "You had better wait to see whether the voyage has cured you." He said, "I have only six months in England, and I want to be cured."

However, he waited, and after three weeks he developed a boil—an enormous one, $4\frac{1}{2}$ in. by 3 in. Over a certain part of his body he had quite a Clapham Junction of scars from old incisions. He had three doses of vaccine only, and was cured. He had no further attack in England, and went back to Chili in the following September. In August, 1909, he had a slight relapse, for which he again employed vaccine. I received a letter from him this week, in which he reports that he has been well ever since. That may be a coincidence, but I think there is something more in it. It may be regarded as a coincidence of time, but my own belief is that it was a sequence of treatment and result.

I now come to the other group of cases, in which the disease is generalized from the first. Dr. Colebrook showed you on the last occasion the charts of the opsonic indices in a typical case. That patient, a young physician working in the laboratory of St. Mary's Hospital, came under my treatment when he developed that dreadful disease of which he died—glanders. He was suffering from fever of a mild type, he was not very ill, and I thought that his disease was influenza. The patient himself made up his mind from the first what was the matter with him, and after a few weeks the diagnosis was made from his blood. There was no focus of disease and no local symptom for nearly two months after the beginning of his illness, and then there was pain in the spleen. He had the advantage of the help of all his colleagues in the laboratory, and everything possible was done for him. His index was taken every day, his temperature recorded every four hours, a close watch was kept on his condition, and he was treated on the best advice procurable in London. I think one can truly say that the vaccine treatment had no effect on him from beginning to end. The disease varied a great deal. Sometimes he was much better, and, for a period of a month or two, he seemed to be nearly well. Still the disease kept breaking out, and he lingered for eighteen months; his spleen slowly enlarging throughout, his only focus being a small inflammatory patch on the front of the leg, which cleared up after incision. Those are two extreme types of cases. What is the difference between them? The boil from the first may be severe, but is a local infection; the other may be mild, but is a general infection. The disease in one case cannot stimulate the blood to create sufficient antibodies to destroy the microbes, and what antibodies are formed cannot reach the disease, because the boil as a rule forms a wall round itself, which prevents due interchange between it and the circulation. A

vaccine in such a case introduced into a healthy part of the body will immediately stimulate the creation of antibodies, and what blood does reach the boil will be powerfully destructive of germs. In the case of a general infection, germs are introduced almost direct into the circulation and distributed all over the body, and therefore stimulate all the tissues they reach to create antibodies. But in that case what seems to be wanting is not stimulation to create antibodies, but a lack of power of the tissues to create them. Therefore it was reasonable to expect that a vaccination treatment will not be so successful in that type of case as it would in the local disease. It does succeed in certain cases, but in some it fails.

I am watching another case which I believe is very similar, but of milder type—namely, one of chronic staphylococcic poisoning. The patient is a delicate woman who has been treated by different physicians, including myself, for many years. Some said that she was probably tuberculous; but there are no signs of it, and her blood when examined was normal in reaction to tubercle. She has attacks of malaise, nausea, giddiness, and very slight rises of temperature to 99° F. or 99·5° F., and with these attacks there is often an outbreak of minute acne, like pustules on the face. Dr. Matthews kindly tested her blood against staphylococcus, and found that she had an index varying from 0·5 to 1·3, and under vaccine treatment she improved slowly for a time, but she is now as bad as ever. At present she is under the treatment of a well-known dermatologist, who is convinced that her trouble is due to disorder of digestion. After six weeks' treatment she tells me that she was worse last week than she has ever been before. After a very long day of fatigue she had a very severe attack, and was compelled to keep to her bed, and felt the same sensations as she experienced after an inoculation; then she rapidly improved, and her spots suddenly disappeared. I think that was a clear case of auto-inoculation, due to over-fatigue; during the negative phase she was forced to keep to her bed, and during the positive phase she rapidly recovered. To-day her complexion is natural, and I think that if I treat her carefully, watching the opsonic index, I shall eventually cure her; but it is a very difficult case, and will require great attention to details, the neglect of which accounts for my previous failure.

I attended a boy two or three years who had very acute attacks of middle-ear disease, high fever, great pain, delirium at times, a sudden discharge from the ears, and then relief. He had five or six of these

attacks every year. I took him to an eminent aurist, who thought the attacks were due to adenoids, and that if they were removed he would recover. They were taken out, and the boy remained well five months. After that the attacks came back, and he had three or four acute ones in six weeks. Then the late Dr. Wells saw him with me in one of the attacks. There was a clear discharge from the ear, in which there was a pure growth of streptococcus. He was vaccinated with that germ, and has remained well ever since, though the treatment was commenced two and a half years ago. That, I believe, was not a coincidence in time, but a sequence of events.

I have treated about twenty cases of chronic bronchitis, and a striking case was that of a lady whom I attended in her fifty-fifth year for a very severe attack of measles. During that attack she developed acute bronchitis, and made a very slow convalescence; but she never was quite rid of her bronchitis, except for short periods in warm weather. In February, 1908, I asked her if she would allow me to treat her with a vaccine, confessing to her that I had never treated bronchitis previously in the same way. She said "Yes," she was willing to try anything. We got her sputum, a vaccine was made from it by Dr. Freeman at St. Mary's Hospital, and I vaccinated her. Within three days she was very much better, and in a fortnight she was cured. There has been no other treatment. That was nearly two and a half years ago. Last winter she developed acute influenza, but no bronchitis. I gave her, however, a dose of her vaccine as a precautionary measure. Again, is this case a coincidence of time? Am I unjustified in calling it a sequence of events?

I will now relate an interesting case of appendicitis. I thought it would be instructive if I could, during the attack, find out the offending organism. So, following the method which has been employed in colitis, I obtained a specimen of fæces containing mucus, which was examined by Dr. Fleming. Several germs were isolated, but there was one coliform germ to which this patient's blood was continually on the move; sometimes a high index, sometimes a low one. A vaccine was made from it, and I put it to the patient whether he would have vaccine treatment as an experiment, or whether, as this was his second attack, he would have the appendix removed. I advised him to have it removed. He agreed, and Mr. Arbuthnot Lane operated. At the operation Mr. Lane said there was a smell at the seat of trouble which made him suspect that it would suppurate, and he took the precaution of inserting a drainage tube. The appendix was placed in a sterile bottle, and in it

Dr. Fleming discovered in pure growth apparently the same coliform germ. The wound did suppurate, and acute fever developed. The vaccine being ready, no time was lost, and there ensued another coincidence of time! It is interesting to speculate whether a course of vaccination could have cured the appendicitis without operation.

I will contrast that with a case which I have at the present time under my care, that of a lady from whom a fibroid of the uterus was removed five or six years ago. She was concurrently affected with what was thought to be Paget's disease of the nipple, but, as it seemed to dry up with simple treatment, we did not take very much notice of it. Three months ago she came with an evidently malignant growth of the breast, which was removed. I thought it would be interesting to find out what germ was associated with Paget's disease, so, under aseptic precautions, I obtained a piece of the breast not involved in the disease, placed it in a sterilized bottle and sent it to Dr. Matthews, who examined it. It produced a tremendous growth of streptococcus. Unfortunately, I did not have a vaccine made, as I did not anticipate danger; but in a few days there was a fearful explosion—high fever and suppuration of the whole wound. She is still ill, although ten weeks have elapsed since the operation. There has been a profuse discharge of pus, and the wound was reopened four weeks ago from end to end. But even a fortnight ago suppuration broke out again in a new spot. I contrast that strongly in my mind with the previous case, and ask whether, if I had had a vaccine made for it, she would not have made a rapid recovery? It has taught me a great lesson, and I shall never miss the opportunity again.

I should now like to speak of influenza. I have been vaccinating cases of influenza for nearly three years, and, as far as the treatment of the acute influenza is concerned, it is very difficult to say anything about it. We have for many years tried different treatments—antipyrin, bicarbonate of potash, salicin and aspirin, &c., &c.—and have obtained very much the same results whatever we tried. Most cases recover in a few days, but some few have had distressing symptoms and complications, and some were simply tedious and long. I do not think we can foretell which cases are going to do well and which will do badly. So I commenced by vaccinating only in the prolonged and unsatisfactory cases, and obtained some very good results and some which were doubtful.

The usual effect of vaccination is that there occurs in a few hours a negative phase in which the previous symptoms are exaggerated and

accompanied by a rise of temperature. And I am fairly certain that, if an effective dose of vaccine is given and no response follows, the case is not one of pure influenza. In fact the vaccine is diagnostic of influenza as tuberculin is of tubercle. It took me some little time to discover what was the effective dose, and I finally came to the conclusion that 15 to 20 millions was right in most acute cases.

In the cases where no response occurred I began to have the sputum carefully examined, and found that many of the cases which did not do well were not influenza, not due to the specific germ, but were apparently due to some other germ or germs (mixed infection). I can mention two cases of that type which occurred to me in one week. Both cases occurred in ladies well past middle life, who were subject to influenza and thought that their present attacks were influenza. One of them told me that the day before she was taken ill she stayed at a small inn where there was a disagreeable smell. She had what seemed to be typical influenza, with a temperature of 103° F. to 104° F., and was very miserable and depressed. I gave her 20 millions of influenza vaccine, but it had no effect. I obtained some sputum and a swab from the throat, and a pure streptococcus was found, but no influenza bacillus. The other case was very similar. She was suddenly taken with very acute pain and fever one night at half-past ten. She believed she had influenza, and so did I. On seeing her next morning I gave her 18 millions of influenza vaccine, but the day following her condition was unaltered, and a swab and sputum showed nothing but pure pneumococcus. I gave her 15 millions of pneumococcic vaccine (stock), her temperature being 102.8° F. The effect was marvellous. She had a severe reaction for about three hours. After a rise of temperature to nearly 105° F. her pains began to go, she fell into a beautiful sleep, and next morning she awoke with a temperature of only 99° F. Again, was this case a coincidence of time?

I have used influenza vaccine in a few chronic recurrent cases, one of which I will mention. A man, aged 53, came to consult me in October, 1908. From 1900 onwards he had yearly six to eight attacks of influenza with slight fever, great prostration of strength, and severe mental depression with suicidal tendencies. In the spring of 1907 he gave up all work and travelled in the East for a year, remaining well while away. Returning to England in June, 1908, he was ill with influenza in less than a fortnight, and reported three further attacks before I saw him. He was then just recovering from an attack, and I vaccinated him with ten millions. This made him ill for three days; so

much so that he was reluctant to have another dose. He was afterwards regularly inoculated, and has remained in good health, although he thinks he has had one or two very slight attacks. He has been able to resume all his work and his former life in every respect. Unfortunately it has been impossible to obtain bacterial proof of his disease.

I always have by me a stock pneumococcic vaccine, but, until I came across the following, I have thought my cases of pneumonia were too mild to need it. But this was a typically severe pneumonia. On a particular Monday evening a man, aged 42, began to feel ill. He was a heavy drinker, and therefore a bad subject. On Tuesday midday his doctor saw him and found him with a temperature of 104° F. and a pulse of 130, and he was very ill. I saw him next day at three in the afternoon; his temperature had not gone below 104° F., nor his pulse lower than 130. The liver was below the umbilicus, and the skin of the face was congested and had a yellowish tinge. There was loss of resonance over left lower lobe, and fine crepitation and commencing tubular breathing. His tongue was dry, and altogether it was a very bad case. He was given 20 millions of the vaccine on the spot, and in two hours he felt better. His temperature again never rose above 103.5° F., and in three days he was practically well. There are many people who will say that was another coincidence of time; I feel almost inclined to say it myself, but surely it was more a sequence of events. Here was a pneumonia only commencing in a patient of a bad type, in which the crisis occurs on the fourth day; not a complete crisis, for the temperature rose for a few hours to 103.5° F. on that day, but was never over 100° F. after.

If those cases were coincidences of time, there was nothing in the vaccine treatment; if they were a sequence of events, then in each case there was a wonderful effect from the treatment; and I could, did time allow, relate many more striking cases. I can vouch for the facts; I have watched all the cases. I am convinced, after watching these and other cases for the last four years, that the vaccine treatment has come to stay. I was extremely interested in Dr. Hale White's cases, and the only difference between us is that I think we ought not to postpone vaccine treatment until every other treatment has failed. My own belief is that we should try it in every case which we think will be severe, and try it at once. It is not fair to try it only where the patient is *in extremis*. We do not postpone operation until a patient is dried up and moribund: if we think a patient will get acute peritonitis, we operate at once; if we suspect diphtheria, we inject the serum before

we are sure of our diagnosis. If we are to make a success of vaccine treatment we must begin early, and do it faithfully, with great attention to details, carefully watching the effects of each dose. It is not always an easy treatment; in fact there are many difficulties as to size and spacing of doses; some patients are very susceptible, and will only bear small doses, whereas others not only will stand but require enormous doses.

MR. H. W. BAYLY: As Sir Almroth Wright has pointed out, the value of vaccine treatment for staphylococcic infections seems established, and also the prophylactic value of antityphoid and antiplague inoculations seems considerable, though not nearly as absolute and complete as in the case of vaccination against smallpox. It appears to me a remarkable thing that, after seven years of very extensive trials all over Europe, the opinion as to the value of tuberculin treatment of tuberculosis is still so divided. It is obvious in a disease like tuberculosis, so prone to sudden changes either for better or worse, that the result of any method of treatment must be scrutinized with the greatest possible care.

Four years ago I had the privilege of working for several months in Sir Almroth Wright's laboratory, and shortly afterwards Dr. Latham was kind enough to appoint me his clinical assistant at the Brompton Hospital for Consumption. One day a man applied for admission to the Hospital. He had a five-lobe infection, and the larynx and one hip-joint were also involved in the tuberculous process. He was obviously an unsuitable case for hospital or sanatorium treatment, and death appeared inevitable in a very few months at longest. I was unsuccessful in obtaining his admission into a Home for the Dying, but a charitable lady of my acquaintance kindly offered to support him in a cottage in the country till such time as I could obtain his admission into a Hospital for Incurables. Within six months he had put on 3 st. in weight, and now, after more than three years, my charitable friend is still supporting him, for though a different man, the disease is not eradicated, and he is unable to undertake hard work. He has never had tuberculin treatment. Sir Almroth Wright said that improvement in desperate cases might be taken as evidence as to the value of treatment, and therefore I imagine that this extremely desperate case, if he had been subjected to tuberculin treatment, would have been triumphantly brought forward in proof of the value of such treatment.

I only quote this one case of many similar ones in order to emphasize Dr. Slater's remarks as to the extreme importance of a critical and

unbiased examination of all evidence. In any investigation of the value of vaccine treatment one should obviously take every precaution not to confuse *post hoc* with *proper hoc*. Personally, I am a firm believer in the value of therapeutic inoculation, and have seen excellent results follow the vaccine treatment of staphylococcal, streptococcal, gonococcal, pneumococcal, *Bacillus coli* and *Bacillus influenzae* infections. I have not been so impressed with the value of tuberculin as with the other vaccines that I have mentioned.

May I mention two cases in which it appeared to me that the improvement was almost certainly due to the vaccine treatment? One was an old gentleman, aged about 80, who had an acute coli infection of his bladder. Rigors were frequent, and the patient appeared to be *in extremis* when I first saw him, and indeed the medical practitioner in charge of the case did not expect the patient to live many hours. I considered that the case had gone too far for vaccine treatment, but was urged by the relations to give the patient the benefit of a forlorn hope. I had previously prepared a vaccine from an atypical *Bacillus coli* isolated from the urine. After the first dose of vaccine the temperature came down, and no rigor occurred for three days. Then I gave a second inoculation, and a week later a third. No rigors occurred after the second inoculation, and the patient recovered. The other was a child, aged 12, in which phthisis was suspected. There had been cough, expectoration, languor, and loss of weight for several months, getting progressively worse. The sputum was examined on six occasions. Tubercle bacilli were never found, but large numbers of influenza-like bacilli were always seen. A vaccine of this organism was prepared and inoculated, and after the first dose the child was decidedly worse. I had some difficulty in persuading the father that this probably indicated that we had got hold of the right organism, but the wrong dose. My advice to give the vaccine another trial was, however, taken, and the dose was reduced. After six inoculations at weekly intervals the child was completely cured. With streptococcal septicæmia and gonorrhœal rheumatism recovery has followed the vaccines and has apparently been due to them.

In regard to the comparative value of the administration of vaccines hypodermically or by the mouth, it is, I think, generally accepted that it is much easier to immunize animals hypodermically than by the mouth. That some toxins are destroyed by the digestive juices seems certain, and the amount absorbed during passage through the alimentary canal seems to vary greatly, and it is difficult to calculate how much will be absorbed.

There seems to be no possible advantage in the by-the-mouth over the hypodermic method from the point of view of the immunizator, and, in view of the greater accuracy of dosage obtained by hypodermic inoculation, the slight advantage from the point of view of the patient's comfort obtained by oral administration seems hardly worth considering. I think that perhaps better results may be obtained with vaccines sterilized by an antiseptic rather than by heat.

The medical world seems still to be divided on the question of the value of the opsonic index as a guide to the patient's resistance to the organism against which his serum is tested. One would hardly expect that the complex riddle of immunity, in which so many varying factors take part, should be completely cleared up by the examination of the serum alone. Surely the cell is the beginning of things, and the protective bodies being produced by the cell, the cell itself, and not the product of the cell, must be the ruling factor. In view of the fact that fatigue is well known to lower resistance to infection, whereas several observers had stated that fatigue had no effect on the opsonic index, I undertook two years ago a short series of opsonic indices in women at the conclusion of the second or third stage of labour. In each case I took the tuberculo-opsonic index twice, using for one examination the patient's own cells, and for the other my own cells. I found that in nearly every case the opsonic index was normal when my own cells were used, but below normal when the cells of the fatigued woman were used.

I think that it has been shown that toxins and poisons generally exert an inhibitory action on the phagocytic power of the cell. The opsonic technique is such that it is extremely difficult to entirely eliminate all sources of error, and personally I am not, after considerable experience in the method, satisfied that my results are always consistent or reliable. And I have taken every care, and have done my best. My results with the pneumococcus, gonococcus, and *Micrococcus catarrhalis* have been most unsatisfactory. I consider small excursions of the opsonic index as entirely valueless for diagnosis or as a means of controlling treatment.

I can but admire and envy the technical skill of the workers in the laboratories of St. Mary's Hospital, which enables them to obtain the excellent results that they have shown us; but surely a method of examination of serum that is beyond the power of any careful laboratory worker ceases to be a practical test, although still remaining an interesting laboratory phenomenon.



Royal Society of Medicine

June 1, 1910.

Mr. A. PEARCE GOULD, Vice-President, in the Chair.

Discussion on Vaccine Therapy: its Treatment, Value, and Limitations.¹

Dr. WILLIAM BULLOCH: In rising to take part in the discussion on the administration, value, and limitations of vaccine therapy, I feel some difficulty in deciding to which of these questions attention should be mainly directed, as it is plainly impossible in the time at one's disposal to deal effectively with all three. It seems to me, however, that one of the principal questions refers to the *value* of the method, especially as there is a difference of opinion as to how the value is to be judged and who are to be the adjudicators. From what is being widely said, there appears to be a certain degree of resentment on the part of many of those who practise medicine among their fellow-creatures that others should enter the domain which, rightly or wrongly, they consider to be their perquisite, and should enter it especially in a spirit of commercial competition. And I take it that there are two classes to be considered—viz., the clinician and the scientist. The conflict or antagonism between these two is nothing new, nor is it confined to this country. For hundreds of years the clinician has relied on his unaided five senses to carry him through his life-work; but the last twenty years has witnessed remarkable developments, which show that this simple state of affairs can no longer obtain. To many of us, evidence appears lacking that occult things which are revealed to the majority only by the aids of chemistry or microscopy are revealed to a few by means of

¹ Third meeting (adjourned from May 25).

their unaided five senses. To these unaided senses medicine is, as was stated nearly two thousand years ago by Celsus, "a conjectural art," and one of the chief problems is whether it is to remain a conjectural art or not. Scientific medicine has sunk deep foundations on which a great superstructure of facts has been raised, and it is now known, although not always admitted, that two or more things which look identical to the unaided senses may have causes essentially different. The discovery of these causes has been brought before the notice of the practitioner of medicine by the medical scientist in nearly every instance. A glance at the history of medicine shows that in the evolution of medical knowledge we have passed through various epochs. At first the concept of disease was symptomatological only, and when this was found inefficient, an attempt was made to lay a basis on pathological anatomy. In turn this has had to give way to the ætiological concept. The end and aim of all medical research is that we may create a scientific theory of disease on the basis of which a rational can be substituted for an empirical treatment. All this work, however, shows that medicine and disease are much more complicated than was formerly believed.

Now the attitude of the practical man of medicine has at first been almost invariably one of indifference to the advances of science, and often, indeed, one of hostility. If the scientific method is not of easy application it has been said to have no "clinical" value, and in a large number of instances the clinician has delegated it to some other person. In this way a large number of people have arisen to whom the clinician has delegated a considerable portion of his work. Bacteriological work, chemical work, microscopic work, is now undertaken in laboratories at the request of clinicians, and for them. In recent times the physiologist has also tended to invade the field of practical medicine, and to him is largely due the advances which have been made on the subject of blood-pressure and variations, physiological and otherwise, in the heart. Chemists and pharmacologists are hard at work in the discovery of therapeutic remedies which are ultimately exploited by the practitioner. We frequently hear the clinician assert that the work of physiologists applies to the dog, but not to man. When the physiologist shows that blood-pressure can be accurately determined and recorded in man by scientific instruments of precision, he is told that, although this may be true, his method is not "clinical." Although a sphygmomanometer is accurate, it must be subservient to the highly-trained physician's finger, because the physician cannot carry an instrument with him

and because the sphygmomanometer is not clinical. I should like to raise the question what a "clinical" instrument is. The concept of "clinical" seems to be one of inches. If an instrument cannot go easily into the waistcoat pocket it is not clinical. A "clinical" thermometer is something less than 4 in. long. If it is a foot long it may be much more accurate, but it is not clinical. A hæmocytometer is apparently not yet a clinical instrument because Zeiss has not yet chosen to make it go easily into the physician's pocket. Personally, I cannot see why this should be so. The surgeon has emancipated himself from this sartorial tyranny, and does not hesitate to take with him any instrument he requires, even in the shape of a real clinical instrument, an operating table. From a practical point of view this makes a considerable impression. What, for example, can be more impressive than the arrival on the scene of labour of a relatively small obstetrician with a very large cephalotribe? If he produced from his pocket a clinical instrument in the form of a gimlet, I imagine he would be discredited in the eyes of his patient.

Coming, in particular, to the question of infective diseases, it appears to me that physicians have been studying these for hundreds of years without making any material advance. I know no instance where the contrary can be urged. We have, on the other hand, very extensive bacteriological research leading to the elucidation of the causes of a large number of infective diseases. These causes have been isolated, their effects and life-histories have been studied, and a great deal is now known about them. Hecatombs of animals have been immolated to determine their effects, and methods of prophylaxis and cure have been worked out. On the basis of all this knowledge, which has been accumulating for thirty years, the bacteriologist has at last said, "Let us try whether these results can be applied to man." What is the answer of the clinician? "No, *you* ought not to do this: you must demonstrate anew to us the grounds for your suggestion. We shall determine for you the value and limitations of this method." The question may, however, be asked: Has the clinician the requisite knowledge and experience to adjudicate in this matter? This is very largely the problem which has led to this discussion. To many practical physicians it seems illegitimate that a bacteriologist or experimental pathologist should have an opinion on a matter concerning man, who is assumed to have an organization entirely different from the animals which the experimenter uses in the course of his work. On the other hand, it cannot be denied that observations on animals can be carried out with

much greater precision than in the case of man, who is only partially open to experimental methods.

Now the immunity problem is one which has been very carefully studied in the case of animals, and I would submit that the bacteriologist and immunizator possesses very special knowledge with reference to infective disease. In spite of this, however, he has hitherto been classed as an appendage to the physician or surgeon. That this is not merely the point of view of the bacteriologist may be seen if one refers to the opinions of certain clinicians on this question. Thus I turn to the address in medicine delivered before the British Medical Association in 1908 by Dr. Kingston Fowler,¹ a man of wide experience and known temperate judgment. He says: "The bacteriologist, in some at least of the general hospitals, is now regarded as the servant of the physician, who orders that certain investigations shall be undertaken. This is not, I submit, the position to which he is entitled. In important cases in which his advice and assistance are required he should consult on equal terms with the physician at the bedside, and the investigations to be made or the treatment to be adopted should be the joint result of their deliberations. That any person professing ignorance of clinical medicine should independently attempt to treat disease is a position so unsound that it needs but to be stated to be condemned." My own experience would lead me to regard Dr. Kingston Fowler's views on this subject as advanced. There is still much of the spirit which moved Chassaignac to exclaim, with regard to Davaine's experiments, "Laboratory results should be brought out in a circumspect, modest, and reserved manner as long as they have not been sanctioned by long clinical researches, a sanction without which there is no real practical medical science."

With regard to the methods advocated by Sir Almroth Wright, it may be said they are not clinical. They presuppose knowledge which is not revealed to the unaided retina or the organ of Corti. They are complicated and difficult methods. I think, however, that they have been embarked upon in a very light hearted manner in many instances. Writing on this subject five years ago, I suggested that before vaccine therapy was launched on the public it should be carefully worked out in hospital practice under conditions not readily obtainable in private practice, and when its value and limitations had been decided it might be applied as a practical method. This is the way we have tried to conduct this problem at the London Hospital. Cases are sent to us to treat, and

¹ *Brit. Med. Journ.*, 1908, ii, p. 253.

when our investigations are at an end, these cases are referred to the clinician for his opinion on the value of the treatment. It would appear, however, that this cautious mode of advance has not been followed everywhere, and the fact that considerable commercial possibilities were likely to accrue from the practice of vaccine therapy at once led to the appearance of a large number of persons who, in spite of a very limited knowledge of bacteriology, began to exploit the method practically. Instead of passing through the moultings necessary for the bacteriologist, they emerged as fully-fledged imagines, to sip with the physicians and surgeons from the flesh-pots. If rumour is to be credited, some of them have sipped so deeply that the physicians and surgeons have been perturbed. The contributions of these pseudo-immunizers to medical science are trifling and cannot well be criticized, as they avoid the bacteriological arenas of discussion. Their commercial aptitude would appear, however, to be in the inverse ratio to their bacteriological ability. From what they write they appear to consider that the whole problem of immunity to infective disease is solved by the injection of a vaccine which has been prepared from some morbid product. If one vaccine does not answer, another is tried, liberal payment being demanded all the time. The pseudo-immunizer extends his operations still further to prophylactic courses of inoculation against diseases which leave a trifling degree of immunity, the durability of which is evanescent. Instead of administering vaccines subcutaneously, a short boom was created by the exhibition of antigenic substances *per os*, although numerous experimental data were opposed to such a method. Indeed, the whole problem of vaccine therapy seems to have become so complicated that the value and limitations of the method are difficult to determine. In estimating the value of any therapeutic method the elimination of chance is of fundamental importance. There should be parallel series of cases, those with and those without the treatment in question; and it is only when this is done on a big scale that the true value of vaccine therapy will be known. At present we do not appear to possess accurate data of this kind, and thus we have to rely only on the personal impressions created in the minds of medical men who have witnessed the treatment of infective disease by different methods. It must, however, be clearly borne in mind that the medical man is not infallible, and he is subject to frailties common to other members of mankind.

So far as I have been able to learn, the profession can be resolved into four groups with regard to the question of the value of vaccine therapy. There is, first, the clinician, who boldly and publicly asserts that as a

result of his experience he is unable to subscribe to the view that the results of vaccine therapy are better than those obtained with other well-tried methods. This group appears to be small. There is a second and much larger group, who allege this in private, but, for various reasons, do not assert it in public. This seems to include a large number of clinicians. A third and small group condemn vaccine therapy by word of mouth, but practise it by hand. I feel sorry to refer to this group, and I only do so because I know it exists. Lastly, there is a group, in which I reckon myself, who consider that results can be achieved by vaccines which have not hitherto been obtained by other and older methods.

It must be remembered, however, that most of the cases which have come into the hands of the inoculators have been thoroughly submitted to other methods of treatment before. We may thus subdivide the cases treated into those that are chronic, severe, desperate, moribund, and dead, for in several instances the patient has died before the inoculator arrived on the scene at all. Had he inoculated, I have no doubt that the result would have been ascribed to a failure of vaccine therapy.

I believe we have hitherto seen the worst of vaccine therapy, and better results will be achieved when it is recognized that this method is not to be looked upon as a *dernier ressort*. Even in desperate cases, however, cure has been brought about in some instances. The attitude of the clinician is nevertheless remarkable. If a desperate case gets well on vaccines, it is alleged to be a question of chance; if it does not get well, the case but confirms the unfavourable opinion which the clinician expressed. Were this kind of logic applied to other methods of treatment, therapeutics would soon be discredited altogether. I have no doubt in my own mind that many cases which have been ineffectually treated over long periods by the most competent in the profession have been cured by inoculation at the end; but it seems very necessary to collect data on a much wider scale and much more accurately before the final value of the method can be determined. We need more science in our profession and fewer clinical impressions.

SIR WILLIAM B. LEISHMAN: Although I felt it an honour to have been invited by the Council of the Society to take part in this discussion, I had considerable reluctance in consenting, for the reason that my personal experience of the clinical side of vaccine therapy is so limited. From the laboratory side, however, I have a large experience of phagocytic work in connexion with the typhoid bacillus, and my remarks will be mainly in connexion with this organism.

I should like, however, in the first place, to put in a plea for a wider trial of the method of estimating the phagocytic index which I first introduced. This method I still think presents some advantages as compared with the modification of Wright and Douglas. These are (1) that the technique is simpler, takes less time, and requires no special apparatus; (2) that phagocytosis goes on in the medium of the fresh blood plasma, instead of serum, and the conditions therefore approximate more closely to what occurs *in vivo*; (3) I believe that it is better to test the power of the patient's own leucocytes instead of employing those of another individual; (4) in this method the cells are not exposed to repeated washing and centrifuging, processes which I cannot but think must damage them to some extent. At the same time I fully appreciate the value of the modification which was introduced by Sir Almroth Wright and Captain Douglas, and no one realizes more than I do the enormous importance of the work which has been founded upon it. I only suggest that the older method might be worthy of more extended trial for the reasons I have put forward.

On thinking over the work which I have done in connexion with typhoid vaccine, there are three points which I wish shortly to bring before you:—

First, in our efforts to improve typhoid vaccine—if that were possible—we have experimented with a large number of alternative vaccines, and, to judge of the effects of these vaccines, our principle has been to inoculate a group of rabbits, to pool their blood, and then, over a period of weeks or months, to institute examinations every day or two for the various protective substances. We have done that work for some years now, and have come more and more to the conclusion that the phagocytic index of these animals is the most reliable test of the value of a particular vaccine; more reliable, for instance, than that which is furnished by the bactericidal substances or agglutinins. I may add that we have to some extent confirmed this by a series of observations on cases of enteric fever and on convalescent patients who have recovered. We worked out an average curve, showing the course of the various substances, and those concerned in phagocytosis remained at a high level longer into convalescence than the others.

Secondly, in Sir Almroth Wright's eloquent introduction to this debate he alluded to a method which has been suggested many times—that is, the ingestion of vaccines as being a possible alternative to inoculation. Our typhoid work has given us some experience in this direction which may be of some interest. Sir Almroth Wright will

remember his own earlier attempts at immunization by the mouth by the swallowing of sterilized broth cultures of typhoid, and the results which he has recorded are very similar to those which we got in our experiments. The latter we conducted, however, on different lines. My colleague, Major Harrison, endeavoured to guide dead typhoid bacteria past the dangers of the stomach into the intestine, and, to do this, administered to various volunteers—our brother officers—pills containing dead typhoid bacteria suspended in a matrix consisting of fat and stearin. These were given at various intervals, and sometimes were continued for three or four weeks. Another series of experiments was done by enclosing bacteria, suspended in lard, in gelatine capsules. We analysed samples of the blood of these various volunteers, and concluded that it was certainly possible to modify the amount of protective substances in the blood by giving vaccine in this way by ingestion. But the results were extremely irregular. In one case, in a man who had been previously inoculated a year or eighteen months before, there was a remarkable initial rise in the bactericidal power, this lasted only a short time, and was followed by a fall to below the normal, which persisted until treatment was abandoned. In one or two cases there was no obvious effect at all, while in others a negative phase was apparently induced. In one case, in especial, considerable gastric disturbance was set up by the use of these capsules; and as the officer concerned was one who holds both the Victoria Cross and the Distinguished Service Order, we may believe that he held out longer than most. Generally speaking, the results of these experiments showed we had no control over this system of immunization. It might modify the substances, but we could not prophesy what would happen, and there was danger of producing bad effects in the shape of a negative phase.

The third point, which is more directly concerned with the subject of your debate, is the use of typhoid vaccine not as a prophylactic but as a therapeutic agent in enteric fever. That has been suggested often, and has been tried in various places—in Germany, America, and in India. Our own efforts in this direction arose in this way: I was very much struck by hearing Chantemesse's account of the results of his serum therapy in enteric fever, and these results he attributed to opsonification. He gave extraordinarily small doses of his serum, and claimed that the good effects were due to increased phagocytic power. If that is so, I thought we ought to do the same, or better, by the use of vaccine; and we have therefore treated some cases with our ordinary

prophylactic vaccine. So far, we have only got a comparatively small number of cases, but they are, I think, distinctly encouraging. On talking it over with Captain Smallman, who was shortly returning to India, I asked him if he would undertake this vaccine treatment, and, when he got back to Quetta, which used to be a hotbed of the disease, he carried it out in a series of cases of enteric fever. As we were working in the dark we had to go cautiously with regard to dosage, but we had found, previous to this, that inoculation of very small doses of typhoid vaccine, up to 50 millions, produced no evil effects at all. It was equally certain that there were no good effects from such small doses. On raising the dose, however, up to 300 or 400 millions, and repeating it every fourth or fifth day, better results were obtained. If the dose is given in the morning there is a reactionary rise of temperature of 1° F. or $1\frac{1}{2}^{\circ}$ F. above what one would have expected on that evening. That is followed next day by a considerable drop in the temperature, which remains comparatively low for two or three days after the inoculation. After that it begins gradually to rise again. If at this moment the injection was repeated there was the same sequence of events, and after three or four inoculations the temperature fell to normal and usually did not rise again. There appears to have been no doubt of the great improvement in the appearance and general condition of the patients. In the ward in which these cases were treated I was told there was complete absence of the typical typhoid *facies* in the patients; they were rosier, seemed in good condition, and felt better. It is remarkable also that in several instances the men asked for the inoculations to be repeated, while, in the case of an officer, he said that in spite of the rise in temperature which followed his inoculation, he felt from that moment a definite change for the better, and never afterwards looked back. Captain Smallman treated thirty-six cases, of whom two died; but he noted an unusual freedom from relapse and complication in the remainder. The system has also been tried, but not on such a large scale, in a few other stations at home and abroad. Five places I have now information about, and the results generally are certainly encouraging. Some of the five officers who tried it started in a spirit of profound scepticism, and were converted, and are now anxious to try the method in other cases. I cannot give you information about the behaviour of the opsonic index of these cases. Captain Smallman was going to investigate that during the next enteric season at Quetta, but owing largely, I believe, to the extended use of anti-typhoid inoculation, he has not had sufficient material to work with.

My experience of vaccine therapy on the clinical side is so small as to make any general opinion of mine hardly worth listening to. Still, such as it is, I give it to you. I believe vaccine treatment to be the greatest step forward that medicine has made of recent years, and that it has immense possibilities before it. One of the most important keys to successful treatment I believe to be the question of dosage, and I do not see how we can arrive at the appropriate dosage in the absence of frequent estimations of the opsonic index.

Professor HEWLETT: I believe Dr. Bulloch is a Scotsman; I do not know whether he is a member of the Church of England. At any rate, his attitude towards vaccine therapy very much coincides with one of the sentences in the preface to the Book of Common Prayer—namely, he keeps to the *via media*, he avoids the extremes. And I think that it is very much my own attitude with regard to vaccine therapy. There is, I believe, immense value in vaccine therapy, and immense possibilities; but undoubtedly it has its limitations. I do not propose to deal with diseases treated by vaccine therapy, as this has been gone into fully by previous speakers. One has, of course, seen striking results in a number of various diseases. With regard to pulmonary tuberculosis, I must confess that I am very uncertain as to the value of vaccine therapy. I think pulmonary tuberculosis can be divided into three classes of cases. There is one class which, even if the conditions are but moderately good, tends to do well. There is a second class which, if very well looked after and well treated and put under good conditions, also tends to do well. There is a third class which, do what you will, goes downhill. And in this last class there are cases which run a very long course—ten years, perhaps twenty years, with remissions. So it seems to me extremely difficult to be sure as to whether tuberculin treatment is of service in pulmonary tuberculosis. Similarly as regards tuberculous glands. If they are of any size, it seems to me a dreary process to treat them only by vaccine therapy. To my mind the treatment to be suggested is immunization, or treatment for a period with a few injections of tuberculin, and then excision (of course I am only speaking generally), followed again by treatment with tuberculin from time to time to try to keep up immunity. As regards the mode of administration of vaccines, I was rather sorry to hear Sir William Leishman's results as to the uncertainty of oral administration, because I cannot help thinking that if oral administration could be adopted it would have many

advantages over subcutaneous inoculation. Personally, I should prefer to take a medicine rather than have it injected, and I think probably *prophylactic* vaccination would be much more extensively adopted if we could get over the inoculation difficulty. Moreover, with inoculation, accidents have sometimes happened, which make one wish that oral administration could be adopted.

Then there is the question of failure of vaccine therapy. Failures do occur, as I imagine everyone will admit. It cannot be expected that any form of treatment will cure every case, and the peculiarities of the person infected with the microbe must always influence the result. Early treatment also is always conducive to success with any form of treatment, and vaccine therapy should not be considered as a *dernier ressort*. Admitting these factors, however, we are still face to face with cases which we believe ought to do well—we may be mistaken in that, of course—and yet they do not do well. After all, I take it that vaccine therapy is a somewhat clumsy imitation of Nature's methods of curing disease. The fact that the culture is sterilized by heat, for example, must necessarily destroy properties which are possessed by the living microbe. I have suggested that probably microbial endotoxins may be more potent than sterilized cultures, and I think that their use is at least worth a trial. Again, there is Besredka's method, which, according to him, is extremely successful for *prophylactic* vaccination, at any rate; and it appears to me it is a possibility that it might be extended to vaccine therapy—namely, the treatment of microbes before injection with an immune serum—in other words, sensitizing the microbes. He claims that *prophylactic* vaccination by this method gives results which are superior to the simple injection of bacterial cultures. Again, as Dr. Hort has pointed out, in all probability the disease complex is due not only to microbial products, but also to toxic products of tissue disintegration. And it seems to me there is a very great deal in this suggestion. By vaccine therapy we can only hope to combat the one portion of the infection, the microbial one, leaving the somatic portion unaffected, as it were. Therefore I consider that auto-inoculation as a means of treatment has at least a sound theoretical basis, although I appreciate the difficulty of applying it in graduated dosage. Finally, by vaccine therapy we rely practically entirely on the responsive powers of the body; and, personally, I am still of opinion that, if we only knew how to apply it, serum therapy is the ideal method of fighting the bacterial part of the infection. And the results obtained by Flexner and others in the treatment of cerebrospinal fever with an anti-serum suggest that we

are not by any means yet at the end of our resources as regards serum therapy. And, lastly, there is the question of the opsonic index, which has not been touched on very much. The work during the last two or three years shows the extreme technical skill that is requisite for obtaining a true index. Such a technician as Sir Almroth Wright is perhaps able to obtain results which are to be relied on and which serve as a guide to treatment; but I think it is questionable whether the opsonic-index method is going to be generally applicable. It also seems to me that in a great many cases at least it may be dispensed with by carefully noting the general clinical condition, and so on. I quite appreciate that it is due to the opsonic method that the proper dosage of vaccines has been arrived at through the work of Sir Almroth Wright and his collaborators and their masterly technical skill. Having obtained those data, I think that, to a large extent at any rate, we may be able to have vaccine therapy without the opsonic control, though I admit it is desirable to have it. But if you are going to have it, it must be done by someone whose technique is beyond reproach.

Mr. K. W. GOADBY: In contributing to the discussion I wish to make some remarks on the treatment of those diseases which affect the mucous membrane of the mouth and the gums. A large number of diseased conditions of the mouth have, and are, often included under the generic term pyorrhœa alveolaris, although the symptoms may be as diverse as profuse discharge of pus with destruction of the tooth sockets, and infection of the alveolar process, and loosening of the teeth, or a diffuse gingival or even periosteal inflammation associated with rarefying osteitis of the alveolar process, but unaccompanied by any discharge of pus at all. Between these two extreme variations any combination may exist.

A point already referred to by previous speakers is perhaps truer of disease of the mouth than of any other part of the body—namely, the incompleteness of our knowledge of the bacteriology, owing to the refractory nature of the organisms so far as obtaining cultivations are concerned. Some of them, such as the *Bacillus fusiformis*, described by Ellermann, and the common spirochæte of the mouth cultivated by Mühlens and Hartmann, are strict anærobæ; a number of others require an environment of carbonic acid; others again are highly sensitive to the reaction of the medium in which they are growing, and anyone who has had experience of the bacteriology of the mouth knows to his cost what

a limited number of the bacteria which may be actually seen existing in oral pus can be ultimately obtained in pure cultivation. It is not surprising, then, that two main classes of oral disease caused by bacteria may be observed clinically. Firstly, there are acute infections, more often than not engrafted upon a chronic infection, in which some well-known, or even rare, pathogenic organism is the causative factor, producing general disturbances of the whole body with acute symptoms, often septicæmia, pyæmia, or toxæmia. Secondly, there are the chronic cases of long-continued and insidious mouth suppuration in which the products of bacterial activity slowly find their way into the body either through the gum margins direct or via the gastro-intestinal canal.

For some time I have had the opportunity of observing from the bacteriological standpoint, and, further, of treating by means of vaccine therapy, a considerable number of cases of mouth disease, and I can unhesitatingly say that, in my own experience, vaccine therapy has never produced any direct or indirect ill-effects upon the patient so treated, and that, at any rate coincidentally with the use of vaccine therapy, symptoms which up to the time of the use of vaccines had resisted treatment were ameliorated, and the local suppurative conditions improved rapidly and ultimately entirely disappeared. The following two cases are good examples of acute symptoms caused by disease of the mouth:—

The first, a lady aged 65, subsequent to a slight attack of appendicitis, from which she had entirely recovered, began to exhibit symptoms of chronic toxæmia, culminating in an acute alveolar abscess, for which two offending teeth were removed, but with no amelioration of the symptoms, and in fact the temperature, which before had oscillated between 99° F. and normal, rose irregularly until it had reached 102° F., varying between this and normal in the usual manner in chronic suppuration. All kinds of local treatment of every nature had been tried, but without avail, and the patient became so ill that no hopes were entertained of her recovery. At the point marked on Chart I (*see* p. 88) a vaccine prepared from the organism—a staphylococcus obtained from her own mouth—was injected. It was followed by an immediate fall of temperature within twelve hours, the temperature never again rose above 99° F., and after a further series of inoculations the patient made an uninterrupted recovery, and has now, two years later, had no return of her symptoms and is perfectly well. It will be seen on reference to the chart that the opsonic index as taken during the process of inoculation rose against the temperature, but the slight oscillations did not give any indication on the opsonic curve.

The second case was that of a lady who was taken suddenly ill with shivering and pain in her mouth. The gums in the upper and lower jaw were turgid, oedematous, and purple, there was no previous history of any disease of the mouth, the temperature rapidly ran up to 103° F., and on one occasion touched 104½° F. Careful examination of the blood and of the mouth showed the presence of staphylococci and streptococci in the mouth together with a large number of other bacteria, and the blood on the third examination showed a limited number of streptococci. These streptococci were isolated and subsequently compared with the ones obtained from the mouth, and gave the identical

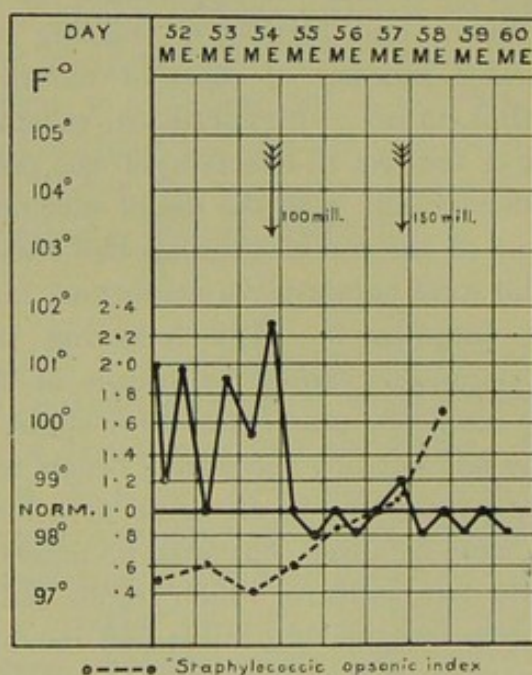


CHART I.

cultural characteristics, resembling closely that form of organism, a streptococcus, described by Andrewes and Horder as the *Streptococcus faecalis*. A dose of 100 million of a streptococcal vaccine, made from her own streptococcus, was injected as indicated, and was followed by a slight temporary fall in temperature (Chart II). The opsonic index was shown to be distinctly rising, and a further dose of five million streptococci was given. The index continued to rise, although upon one occasion the temperature showed another rise to 102° F.; but after this point no further rise in temperature above 99° F. was recorded, and the patient made a gradual recovery, in the course of which three abscesses

and around which considerable quantities of pus were to be found. The offending teeth and crowns were removed, and were followed by a smart exacerbation of his symptoms. Cultivations were made at the time of the removal of the teeth of the pus from the gum margins, and a streptobacillus, of which I shall have more to say at a later time, obtained. The symptoms did not entirely disappear, although they were considerably ameliorated by the surgical interference, and accordingly a vaccine was prepared from the organisms obtained from his mouth, and to which alone of the organisms present he showed a varying opsonic index. Immediately on the injection of the vaccine his condition began to improve, and he is now able to walk about without the use of his sticks, and he continues to make improvement.

The second case was that of a young woman, aged 32, who had an attack diagnosed as subacute rheumatism, followed by a very prolonged convalescence. As soon as she was able to be moved she was sent to Bath, where, after some three months' treatment, she was able to hobble about with the aid of two sticks, and she then returned to town, the symptoms showing no further signs of abatement. On examination, her mouth was found free from pus, but there was considerable thickening of the alveolar processes in the upper and lower jaw, and exploration with a sharp probe showed that the alveolus in many places was distinctly thinned, and that it was undergoing rarefying osteitis. A streptobacillus was isolated from her mouth, and, the opsonic index of her blood showing distinct variation towards this organism, a vaccine was prepared. Some exacerbation of her symptoms occurred after the first injection, but I persuaded her to continue, and I received a letter from her this morning, saying that she had discarded the use of her stick and was now able to go about her ordinary avocation with comfort.

The third case was a rheumatic type similar to the last, but in this instance the infection had not proceeded so far as to cripple the patient in walking. She had, however, swelling and tenderness of the extensor tendons on the back of the hand, attacks of pain frequently at night in her knee- and ankle-joints, from time to time swelling took place in the knee-joints. A similar bacillus to the one noted above was obtained from her mouth. In this case considerable suppuration existed. Inoculation with the vaccine was immediately followed by an improvement in the condition, no exacerbation taking place, and the patient made practically an uninterrupted recovery.

I should like to refer to two further points. Firstly, the value of the opsonic index in determining the infecting organism in any given

instance. In exploring a dark cave a source of light is of first importance, and the more brilliant the lamp, naturally the more advantageous to the explorer. But he would be a rash explorer who, because he only possessed a farthing dip and not an acetylene lamp, would prefer to blow out his much inferior light and trust to finding his way in the dark. Similarly, then, granting that the knowledge given us by the opsonic index is but meagre and by no means as adequate as we could wish, it is yet better than no guide at all. Where a number of organisms, sometimes eight or nine, are isolated, as from suppuration about the jaws, I have found that the organism most likely to be associated with the disease is the organism which shows variations in its opsonic index to the patient's serum. The organisms which may be termed the adventitious ones show very little variation, except those well within the limits of experimental error; but if either massage or other treatment be applied to the infected area in the mouth, and the opsonic index taken subsequently, the organisms which show variation in the index are invariably ones that are associated with the disease. As treatment progresses, the variation in the opsonic index towards the organism used as vaccine diminishes until the inoculation is followed ultimately by very little excursion of the index. If at this time the diseased condition has not entirely cleared up, it is not necessarily due to the fact that the vaccination by the organism in use has failed, but that other organisms are producing concurrent infection. In this my own work agrees with that cited by other speakers.

Finally, I have experimented with the effect of digestion upon a vaccine. I prepared a strong vaccine of the *Bacillus pyocyaneus*. This I divided into two portions, one of which I digested at 37° C. with pepsin and hydrochloric acid for two hours, and the other portion was untreated. At the end of the two hours the digested sample was carefully neutralized with sodium carbonate. Two sets of animals (guinea-pigs) were injected with the vaccine, two with the digested vaccine and two with the normal vaccine. Each animal received two doses at intervals of five days; the third animal was unvaccinated. At the end of a fortnight all three animals were injected with a fatal dose of a living culture of the *Bacillus pyocyaneus*. Both the vaccinated animals recovered, but the unprotected animal died in twenty-four hours. A second series of animals were treated in the same way. Both the vaccinated animals again recovered, and the control animal died.

It would seem, therefore, that two hours' digestion in the presence of pepsin does not entirely destroy the immunizing value of pyocyaneus vaccine, but it by no means follows that the absorption, via the stomach, will create immunity in a similar way to that produced by injection.

DR. HENDERSON SMITH: Just as in the last few years there has been an attempt to introduce the practice of giving sera by the mouth, so also in vaccine therapy the oral administration of vaccines has found support. In the case of sera there is readily accessible a very large mass of evidence wholly against the efficacy of such a method, but the general use of vaccines as a curative procedure is comparatively so recent that no great body of results can be expected. There is, however, a considerable amount of evidence, the result of experiment on animals, to be found in the literature; and, as the question is one of considerable importance in practice, I propose to bring before you briefly the conclusions which that evidence forces upon us.

As you are aware, when bacteria are injected into the subcutaneous tissues, the recipient responds by the production of not one substance only but of a whole series of antibodies. These various reaction products doubtless have different values in the mechanism of protection. Some, such as the phagocytic and bactericidal antibodies, have an obvious direct influence in the scheme of defence; the importance of others, such as the agglutinins and complement-deviating bodies, may be doubtful or denied. But we are hardly yet in a position to assign to each of these substances its true relative value in the total defensive response which follows an inoculation of bacteria, or to safely reject any of the various means by which the organism acts upon its invader. Now, when killed bacteria are given by the mouth, it has been found that, as a general rule, one does not obtain the full response which is obtained after subcutaneous inoculations. There is certainly in most cases some response: the recipient does usually react to the dose of bacteria. But the reaction is nearly always imperfect. There is a difference not only in degree, but of kind. For example, after feeding with paratyphoid, or with typhoid, or with dysentery of the Shiga type, one may obtain some appearance of agglutinins in the blood, but no protection; or again, one may obtain some protection and bacteriolytic substances, but no agglutinins. There is no certainty as to the result which will be obtained in any given case. This was the experience of Sir William Leishman and his colleagues when they administered

typhoid vaccine by the mouth to men, and it is the usual experience of those who have experimented with the lower animals. The oral route is one which commonly fails to elicit from the patient the full reaction which we are entitled to look for and are endeavouring to produce.

Further, the degree of response is markedly less after oral administration. The amount of reaction, in such cases as we can estimate it by measuring the reaction products or by determining the protection conferred, is relatively quite small. This is probably to some extent a question of dosage—i.e., a question of the amount actually absorbed from the intestinal canal; not, of course, of the amount swallowed. In vaccine treatment what one is endeavouring to do is to stimulate the patient to produce his own protective substances; and one tries to do so by introducing into his system certain specific substances contained in the bacterial bodies. It is only when these substances reach his system that they are effective; and the effective dose after oral administration is merely the quantity absorbed unchanged from the intestine. In the case of bacteria, as in the case of serum, this amount absorbed bears no constant relation to the amount swallowed. The active substances are contained in the bodies of the bacteria. Before absorption can occur they must be brought into solution. (It is true some of the bacteria may be absorbed intact possibly, but the frequent absence of agglutinin formation is against the probability of this occurring regularly; and even if it did occur with fair frequency, it would simply be an indirect and unreliable method of doing what one can do directly by subcutaneous inoculation.) To effect this solution the action of the digestive ferments is required, and this very action is largely destructive of the active substances we are endeavouring to introduce. The attempt has been made to neutralize the digestive juices by administering sodium carbonate and by coating the bacteria with fat or keratin; but these measures, in so far as they are effective, would seem necessarily to delay the solution and so to retard resorption, which is in any case very slow, and must vary with the rate of peristalsis and the condition of the intestinal contents. No practical method of regulating the quantity absorbed has as yet been devised which gives fairly consistent results.

In the case of vaccines this question of dosage is all-important. Those who support oral administration have urged that it is possible to immunize animals against tubercle by oral administration of killed bacilli, and the same thing has been done with other pathogenic

organisms; but these animals were previously normal animals, where the effective dose may vary within comparatively wide limits without doing serious injury. But the case is very different if the animal is suffering already from the disease; then, as Sir Almroth Wright insisted on in his introduction to this discussion, accurate dosage is of the first importance, and this is what oral administration cannot yet give us. It is possible that repeated administration by the mouth, of which the advantages are obvious, might prove of very great service in prophylaxis, but as a therapeutic measure the evidence of experiment is against it. The efficacy of vaccines, as indeed of sera, depends so largely on factors which we cannot yet fully estimate, and their action even in the most favourable conditions is so uncertain, that it would seem premature to give up the method which admittedly allows of the greatest accuracy and control in administration.

Dr. WHITFIELD: In my opinion vaccine therapy has already been proved to be a method of great value in many cases, and I believe the number of diseases which may be successfully treated by this means will be increased as time goes on. It is, however, very important that we should review from time to time our method of procedure, and discard any part of it that proves either useless or fallacious. This brings me to the question of the value of the opsonic index. For the purpose of discussion the use of the opsonic index may be divided into two parts—namely, its value in diagnosis, and its value in regulating the frequency and dose of the inoculation.

As regards its value for diagnostic purposes, I may say at once that I am thoroughly convinced of its utility. What I may call an ultra high, an ultra low, or a variable index may be regarded as a sure sign of infection, though it may not be the prime cause of the disease. Further, if the index be taken on one or two occasions, an inoculation of the suspected organism be given, and the index be found to exhibit a sharp fall, followed by a rise, we may be very positive that we are dealing with a case of infection with the organism inoculated. This reaction I am in the habit of describing as Lawson's reaction, as I believe it was first discovered by Lawson, of Banchory, that the healthy person did not show a well-marked negative phase after inoculation. The absence of these variations in the opsonic index is not of equal value in negating the infection. I may give three illustrative cases:—

The first was a case of obstinate whitlow which began acutely but did not clear up. At first one finger only was affected, but this spread fairly rapidly to a second, and then very rapidly to several toes. The onset as a whole was not at all like that of tuberculosis, nor was the local lesion in any way characteristic, the lesions rather resembling chronic staphylococcic infection. Dr. Emery carried out Lawson's reaction with a positive result, but the course seemed so utterly unlike that of tuberculosis that I began to have doubts as to its accuracy. I therefore gave a diagnostic injection of old tuberculin, causing a sharp constitutional reaction, and corroborating the opinion given on the result of Lawson's reaction. The second case was a child with a small chronic abscess on the cheek. Such abscesses are often staphylococcic in origin in very young children. The pus from the abscess was almost purely polynuclear under the microscope. Lawson's reaction was negative, and the index was always within normal limits according to Dr. Emery's estimation. A diagnostic injection of old tuberculin was, however, followed by a sharp febrile reaction, and a little later by healing of the abscess. This shows that the negative result with the opsonic index is unreliable. In a case of very early and doubtful lung trouble I worked out the opsonic index as follows: Before injection 1.28 and 1.25, given $\frac{1}{2000}$ mg. new tuberculin, index 0.9 and 1.32. The case was watched for three months and, as, the lung did not clear, was sent to sanatorium, where complete healing occurred in a comparatively short time. This case was seen so early that, although Dr. Beddard, who saw the case, suspected its nature, the expert at the sanatorium had to ask which lung was affected.

I now turn to the use of the index in treatment proper. I may say that, owing to the fact that the frequent estimation of the index is a laborious proceeding, the conscientious worker is apt to think that it is his duty to estimate it, and that he is neglecting his patient by not doing so. After three years' close application to the method in skin diseases, where in many cases one can see the actual changes taking place from day to day, I am in a position to make one or two statements with a considerable amount of assurance. In very severe acne the index, taken frequently, has generally proved high, though in mild cases it is often low. Again, it is a common experience that a patient who has got the better of the infection in the case of a severe boil which is healing may develop a new and virulent one at a distant part where the skin was apparently healthy and the blood supply unimpeded. I wish to lay especial stress on the fact that this is of frequent occurrence

and not at all exceptional. Such a patient has, in my experience, invariably a high index. If, then, the high index means immunity or high resistance, why this second boil? There is here no room for fantastic explanations based on the theory that the immunizing fluids cannot reach the infected site, as the skin was healthy during the time the index was high and at this time became infected. Further, it has been my experience on several occasions to give a dose in acne which raised the index satisfactorily after a comparatively slight fall, and yet was followed by severe malaise and aggravation of the eruption for several days. Here we have an opsonically correct dose which was clinically an evident overdose. This is not of great importance in acne, but in tuberculosis, where the clinical effects are not so well marked, it might be very dangerous. Yet it is especially in tubercle that the defenders of the treatment regulated by the index tell us we must always rely on this as a guide. I admit that I held this view for a considerable time myself, but this was in the earlier days of my opsonic work. Sir William Leishman has told us that in his investigations on the subject of typhoid inoculation he has found that the opsonic index is the most reliable guide as to the potency of a vaccine, but this is not the same as proving that the effect is directly an immunizing one, merely showing a lasting disturbance of the serum. I do not think that he has yet evidence proving that those vaccines which disturb the opsonic index most have conferred the greatest immunity. Lastly, I wish to deal with the statement that the doses that we use have been determined by the opsonic index. This is entirely erroneous. The first doses before any opsonic variations were noted as the result of injection were obviously not so determined, nor, as a matter of fact, were the subsequent ones.

When I began the opsonic work some years ago the usual dose of staphylococcus recommended by Sir Almroth Wright was from 1,000 to 2,500 million cocci, and these doses were used, controlled by the index, for some years. With such doses the negative phase is usually slight and transient, yet the doses now recommended are usually from 100 to 250 millions of the same organism—i.e., roughly one-tenth the amount that was formerly found correct by the opsonic index. I think therefore I am justified in saying positively that the present doses of staphylococcic vaccine have not been determined by the index, but by their clinical effects. I have also carried out an investigation of the opsonic index in a short series of cases which had been treated by the old method of giving massive doses of tuberculin R, and, although some of the indices were high and others low, none were strikingly either

high or low, and it was absolutely impossible for me to diagnose from my results which of the cases was doing well and which badly.

Finally, I should like to enter an earnest plea for accurate and patient work in the proof of the causal relationship of every organism before it is used as a vaccine. I feel quite sure that this must often entail a careful research by both a competent histologist and a skilled bacteriologist. In one disease two different cultures were used for making what purported to be the same vaccine, which I am quite certain were completely independent organisms. Theoretically nothing is easier than to separate organisms by means of plate culture and other methods, and to grow each separately on its own medium, but in practice it is often extremely difficult. Not a professional bacteriologist myself, I have had over ten years' experience in the work, and perhaps the most important fact that I have learned from my own researches is the enormous difference in dealing with infections made by the wonderful technique of the really high-class bacteriologist compared with that of the inexperienced and half-trained man, who differs only from the clinician in his lack of clinical knowledge.

Dr. JOHN FREEMAN: I wish to speak about some recent work on inoculating for whooping-cough. I shall speak of it not so much for the information I can give on the treatment of this disease as for the illustration the work affords of the difficulties we have to face in judging any method of treatment, and therefore of judging this method of vaccine therapy.

Bordet, about ten years ago, isolated a microbe from a case of whooping-cough which he considered was the cause of that disease. It is not necessary here to examine the evidence for and against his microbe, but it may be said that various people all over the world have isolated it from cases of whooping-cough, and I think the bulk of the evidence is strongly in favour of its being the cause of that disease. Bordet, having convinced himself that his microbe caused whooping-cough, made an ordinary killed vaccine from it and tried to immunize some children in Brussels against whooping-cough. He selected twelve healthy children and gave them prophylactic doses of the vaccine. Shortly afterwards chance sent a child suffering from whooping-cough into the ward where these twelve children had been placed. The result of this accident was distressing, for all twelve immediately caught the disease and had it very badly. This result was so dramatic that the mothers, who knew that

the children had been vaccinated, persistently believed that the disease had been produced by inoculating with the living virus. This result was interpreted by Bordet to mean that immunity could not be artificially produced against the microbe he had isolated. But to us here it seems to have a different meaning; we should say he had afforded the world the best possible proof that he was dealing with a microbe intimately connected with whooping-cough, and that he had produced the phenomenon known as a negative phase by giving an overdose.

The reasons for thinking this are as follows: With the vaccines that have been tested we know that different results follow from different sizes of dosage. Thus we know that a relatively small dose will produce a transient rise in immunity: a larger dose will give first a decrease in immunity, which we call the negative phase, and then an increase which we call the positive phase; and with a still larger dose the negative phase is increased at the expense of the positive phase, and may completely obscure it. If these phenomena follow from varying doses in the cases of a hundred tested microbes, we have a right to expect them with the hundred and first—i.e., Bordet's bacillus. And when we seem to have evidence that these children were more susceptible to whooping-cough after their inoculation, we naturally conclude that the dose of vaccine was excessive and had given a negative phase. If this is true, it is clearly of the highest importance to establish what size doses will be required to produce these different results.

There are two methods by which we can fix the dosage for any given microbe. First, we can test the effect of the vaccine by measuring the changes in immunity of the circulating blood. This is the method which has been employed for establishing the doses of practically all the vaccines now used in England; therefore when I started to work with Bordet's bacillus I naturally turned to this method. I found, however, that technical difficulties prevented me from testing the serum for immunity against Bordet's microbe. I could not measure the opsonic index. What Mr. Goadby has just called the light of a farthing dip was blown out, and I was left groping in the dark; that is to say, I had to apply the second method. This second method is the method of giving a dose and seeing what happens to the patient, the method of judging by the clinical result. It appeals to the medical profession, because on it has been founded nearly all the orthodox medicine of to-day. There is, however, an obvious difficulty, for we can only reach a sure conclusion by this method if we know whether a given change in the patient is the result of a previous dose or whether it is merely an accident. It has

been carefully pointed out in a previous paper that any improvement in a patient after a dose of vaccine is not necessarily the result of the dose; and, it might have been added, any grave symptoms following the dose may be in spite of, and not because of, that dose. Furthermore, if the patient gets perfectly well without any dose it is no evidence that a dose would not have hastened the recovery or made it more certain. All these accidents obscure the evidence as to the effect of the dose on the patient, and if we judge of a system of treatment case by case we are obliged to fall back on "The Clinical Instinct," that refuge of the puzzled practitioner, to decide between results and chance. As I have no great belief in my instincts, clinical or otherwise, I decided that half the cases must be set aside as controls to show what the vaccinated cases would have done without the vaccine. Therefore to every other child with whooping-cough that came to me I gave no vaccine at all, but only a little sterile salt solution under the skin, and I left the mothers in ignorance of the fact that I was in any way differentiating between the children. Lest any one should think that the control cases were unfairly treated, let me say that both vaccinated and controls got the orthodox medical treatment; that is to say, symptoms were treated and complications looked out for. After the children had been inoculated in the way I have described, I constructed statistics from the reports of the parents to see what effect, if any, had been produced by the vaccination. For this purpose the rambling remarks of the parents were reduced to one of five following simple statements: "Much better," "better," "no change," "worse," and "much worse." In doing this I quickly found I could not rely on my own impartiality. For instance, if the mother reported to the effect that the fits of coughing were more severe but not so frequent, I found that this statement tended to appear as "better" in the case of the vaccinated, and "worse" in the case of the controls! I adopted the obvious remedy of remaining in ignorance as to whether child was a treated or control case until I had got the result safely classified in my note-book. I am convinced that without these precautions the investigator will usually find merely what he expects to find.

In this way nearly 2,000 inoculations have been given, with doses varying from 2 million to 120 million bacilli. I naturally started with very small doses, as I did not wish to get any harmful result, and let me say at once that I have never had a bad effect produced by the vaccine; that is to say, I have found alarming symptoms to follow the saline injections of the controls rather more frequently than they have followed the injections of vaccine. It took about four months' work to convince me

that doses of 5 million bacilli gave better results than doses of 2 million. Since then, during two years, the dose has been slowly getting larger and larger, till during the last five months the average dose has been 80 million to 100 million. This dose has given much the best statistics so far with the comparatively few children who have had it. With the children who have come to me during the last few months, the average length of the disease has been 4·3 weeks with the vaccinated, and 7·4 weeks with the control cases—a clear gain of three weeks to the vaccinated cases. The longest vaccinated case with this higher dosage was for seven weeks under treatment before it was well; the longest unvaccinated case came to me for eleven weeks. Owing no doubt to the change of season, no new cases appeared during last month (May), and I have been in the comical situation of having to continue doses of saline to the control cases, all of whose vaccinated brothers and sisters had stopped coming because cured. I conclude, therefore, that this microbe of Bordet has some part in the causation of whooping-cough if it is not the only cause, and that 80 million to 100 million of the microbe make an efficient dose of vaccine, though possibly not the best of all doses. I understood Dr. Bulloch to say this afternoon that he advocated such statistical work as the basis of true medicine, but I doubt if it will be found convenient to employ it largely.

There is a quasi-statistical method of judging the clinical results, which consists in "giving the thing a fair trial" and recording your impression. This method has been well illustrated at these meetings. The disadvantage is that it only convinces the observer, and when he tells us of his conclusions, we are left speculating on his status in our profession and on his capacity for judgment; its advantage is that if any given man wants to know the value of any given treatment, this is the easiest way of convincing *himself*. It is the easiest way of testing vaccine therapy; first learn something about vaccines, then employ them. Most people who have done so have been convinced, I think, as to the value of this system of treatment.

It has been suggested to me lately that the curing of otherwise hopeless cases constitutes a third method of judging by results; if you cure your hopeless case, it is a score for your treatment. That sounds promising, but it is very disappointing in reality, because when you have cured your case people will not admit that it was a hopeless one. The first time that occurred to me will serve as an illustration. It was a case of pyæmia, seen in conjunction with a surgeon who thought, and thinks, that nothing but the knife will do much good; he had been

employing the knife freely on this patient, for all over the body had been cropping up abscesses which were forthwith opened. In spite of this the temperature remained up, the abscesses continued to develop, and the patient was getting more exhausted and was clearly dying. The surgeon said the case was so hopeless that vaccines could do no harm, and the case was handed over to me. I inoculated her with a streptococcus obtained from the abscesses. She immunized rapidly, as shown by the changes in the blood, and coincidently with this change the patient got rapidly better, and in a fortnight she was out of hospital and recruiting on a farm belonging to a brother. The point of the story is that I did not receive the congratulations I expected from the surgeon; he merely told me that pyæmias sometimes get well spontaneously. So this is an excellent way of convincing one's self of the value of vaccines, but it does not necessarily convince third persons.

In conclusion, I re-state my belief that the best reason for the use of vaccines and the best method of testing them lie in immunity work and the testing of serum reactions in the laboratory.

Dr. BUTLER HARRIS: I am compelled to preface my remarks by expressing my deep sense of gratitude to Sir A. E. Wright for his opening address on Monday. His arguments and illustrations were marshalled with a dialectical skill and a spirit of toleration towards his opponents, which at once marked this debate as something more than an ordinary medical discussion.

In approaching this subject primarily from the point of view of the general practitioner, and secondarily from that of one who has devoted several years of close study to it, I am at once aware that my point of view is, perhaps, apparently a somewhat different one from that of most of you here. It most nearly approaches that of the general consultant; it differs most widely from that of the regional specialist and of the pure bacteriologist. Vaccine therapy is to me another weapon fashioned for the use of the medical profession as a whole; the interest has been to realize how far its uses are defensive and offensive, and, if these have already proved sufficient, to retain it in our therapeutic armoury. No weapon, however, is of much avail unless the wielder knows his art. I have listened to most of the important debates on this subject, and I have had many discussions with men occupied in many diverse branches in the profession, and I regret to say that adverse criticism has usually been in direct proportion to the ignorance of the critic of what I will term, shortly, clinical bacteriology.

Amongst the present limitations to the development and use of vaccine therapy, I would place a want of knowledge on the part of the clinician of methods of bacteriological investigation; and on that of the bacteriologist a lamentable need of practice in clinical matters. The fault does not lie at the door of the individual, but at the scheme of medical education in respect to applied bacteriology. It is as important nowadays for the general practitioner to be able to work out the simple pathogenic infections, which occur every day in his practice, as to be able to set a broken arm. The possession of an oil immersion is more necessary to a proper understanding of the majority of cases than an ophthalmoscope. I would have every dresser and every clerk take to the bacteriological laboratory the materials from his cases, and there learn in the outset of his career the paramount necessity of such routine examination. Every bacterial infection has its definite clinical picture, with its recognizable changes. I do not think the supplementary position of the bacteriologist to the clinician is altogether desirable, either in the interests of medicine or the scientific advancement of the individual.

I have thought this preamble necessary to my argument because of the enormous importance vaccine therapy must assume in general practice in particular. The general practitioner sees the beginnings of things. If he is able to recognize at once, clinically and bacteriologically, the species of infection he is dealing with, he is far more valuable to his patient than the man who jobs out the investigation. If vaccine therapy is to take its right place as the handmaid to both medicine and surgery, every practitioner, whether specialist or general, must, of necessity, be expert in rudimentary bacteriological technique.

I have claimed vaccine therapy as of vast importance even in everyday medicine, for the reason that the majority of cases met with are those of bacterial infections. I have, however, assumed without proof, that vaccine therapy is the particular weapon wherewith to combat bacterial infections. I do not think it is for me to traverse again the road of subtle argument which Sir A. E. Wright has mapped out to you, but I may adduce as a general argument that in every succeeding year during the last four years I have more and more employed vaccines, to the exclusion of other methods of treatment; and that conditions which formerly we regarded as beyond human intervention, now yield in ever-increasing numbers to this form of therapy. I suppose that everyone will agree with me that many modes of treatment have from time to time been in vogue, and that, with the gradually awakening

sense of failure, they have gradually dropped into disuse and have ceased to be. Vaccine therapy, however, has done much for our education in the regions of diagnosis, prognosis, and prophylaxis, apart from cure, in that we are learning the true relationship between the pathogenic parasite and its host, in order to properly apply the remedy. In other words, our practice is stepping upwards from the pseudo-scientific empiricism of drugging to a laudable imitation of nature herself.

What are the infections most commonly met with in everyday practice? In my experience they are those of the staphylococcus, the pneumococcus, the coli bacillus, and the tubercle bacillus. More rare are those of the streptococcus, the gonococcus, and the diphtheria bacillus. The catarrhal infections of the upper respiratory tract caused by the bacillus of influenza, the *Catarrhalis micrococcus*, *Paratetragonus*, and *Bacillus septus* are amongst the most frequent, and are most complicated to treat because of the combinations of these organisms.

Of the staphylococcic infections, we are agreed as to the value of vaccine therapy in boils and well-drained abscesses. I have found the *Staphylococcus albus* in severe intractable eczemata; an autogenous vaccine has proved an absolute specific in these cases. This is probably not the same organism that is associated with suppuration. With reference to the pneumococcus, time will only allow me to refer to my own results published in the *British Medical Journal*, June, 1909,¹ and the work of Parry Morgan and Willcox, of which you will hear later. I found that 20 millions to 50 millions pneumococci might be given in pneumonia without harm; that usually a drop of temperature was produced in a few hours, but that more frequently it rose again, but not to the same level, and that it was often necessary to repeat the inoculation once or twice. I am convinced that usually a distinct reaction in favour of the patient is produced and that it is wise to inoculate before the nervous mechanism of the circulatory system suffers much inhibition. The use of a pneumococcus vaccine in the sequelæ of pneumonia, and other pneumococcic infections, such as certain recurrent catarrhs, is in my experience as sure as that of staphylococcus in boils. To condemn vaccine therapy in pneumonia because it is powerless to check a virulent invasion after the whole organism has been overrun is illogical and unreasonable. In the *Medical Record*, of New York, for February of this year, Craig² gives the details of eight cases of pneumonia in men over

¹ *Brit. Med. Journ.*, 1909, i, p. 1530.

² *Med. Record*, New York, 1910, lxxvii, p. 259.

70 years of age, mostly alcoholic, treated by an autogenous pneumococcus vaccine. The inoculation was usually given on the third day; this was followed by a fall in temperature, with a tendency to rise later. A second dose was given about forty-eight hours after the first, with the result that in every case except one the disease quickly aborted. I think this is a very remarkable series of results, and if you will compare his account of the clinical history of these cases with those obtained by Parry Morgan and myself, all working independently, you will find that the effects produced by bacterial inoculation in pneumonia are practically identical. I would go so far as to assert that every case of pneumonia should be, from the outset, regarded as possibly a fatal one, and I would suggest that a stock pneumococcus vaccine, derived from one or more virulent strains, should always be employed as early as possible in a dose not exceeding 20 millions; that, in the meantime, an autogenous vaccine should be made as an additional safeguard. I think the time is not far distant when results will show that the pneumococcus vaccine is to pneumonia what the diphtheria antitoxin has proved to be to diphtheria.

Simple gonorrhœal and coli infections appear to yield very readily after a few inoculations. Coli-bacillus infections of the uterus, as well as those of the urinary tract, appear to be secondary very often to disturbances in the large intestine, which may not be so pronounced as to merit labelling as colitis. Quite recently a woman has come under my care suffering from coli infection of the bladder and urethra. Her cystitis and urethral pain disappeared after the second inoculation. A month later she miscarried at the sixth week. Coli bacilli were found in the scrapings from the uterus. There were, however, no constitutional symptoms, such as rise of temperature following the miscarriage, and she has made a perfect recovery. The manufacture of protective materials as a result of inoculations elsewhere evidently has safeguarded her from a spread of the infection.

With reference to colitis, the majority of cases which I have treated by inoculation have been passing mucus and occasionally blood. The action of the bowels is irregular, with attacks of diarrhœa and pain. There is loss of flesh and sallowness; some have had recurring attacks of acute indigestion in addition. One man recently had had an appendicostomy performed some three months previously, from which he had derived much benefit; but, realizing that he was getting back into his former condition, essayed inoculation. His opsonic index being persistently low—0·5 to 0·6—a coli vaccine was made; and now, after six

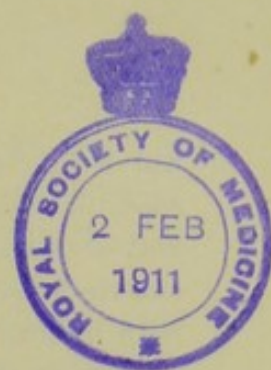
inoculations of 10 millions at weekly intervals, he has put on weight, passes no mucus or blood, and is better, he says, than he has been for years. The majority of these cases of colitis have the coli bacillus alone as the offending organism. Several of them are now well for over two years; two others, however, require occasional inoculation. The patients know when they are losing ground, and present themselves for inoculation. I venture to think that in severe cases of colitis, appendicostomy, followed by vaccine treatment, would be the most desirable course to adopt; certainly inoculation gives better results than washing out by the bowel.

Infections of the coli bacillus are constantly met with in everyday practice. In the urinary tract they appear to be not infrequently secondary to tuberculous or gonococcal infection; the results with a coli vaccine in these cases are certainly most encouraging. Where definite necrosis of kidney tissue has occurred in the tuberculous lesions, it appears necessary, unless the kidney is removed, indefinitely to continue the coli vaccine, but only at considerable intervals. It cannot be too fully recognized that certain infections cling to people for their life. We are familiar enough with the phenomena relating to the tubercle bacillus.

With reference to tubercle, my experience in inoculating in phthisis has not been encouraging. Though carried out under the most rigid conditions of opsonic regulation, I have failed to produce better results than occur with simply perfect resting conditions, such as Paterson has described. With regard to surgical tubercle, I have failed in lupus; but with non-suppurating glands and early hip disease during the past four and a half years it has not been necessary to resort to operation; and there is little doubt that the restoration of tissue in bone is very greatly accelerated by tuberculin. I find that Koch's B.E. works better than T.R., Denys's, or Beraneck's preparations.

I am inclined to think that the controversy about the opsonic index has been somewhat unnecessarily bitter. The clinicians deprecate it because it involves a good deal of labour, whilst the bacteriologists pin their faith to it because they distrust purely clinical methods. In my own work the practice has resolved itself into a compromise. I use it where it is necessary—that is, where clinical evidence is not conclusive. In tuberculosis, for instance, the diagnosis is often very uncertain, particularly in joint and bone infections; infection of the mesenteric glands in children is equally difficult to be certain about. A series of indices will usually settle the diagnosis. The first few inoculations,

both as regards amount and interval, must be regulated by a series of opsonic indices. The temperature and weight, and, where necessary, skiagrams, are sufficient guides for the future conduct of the case. The question of cure is answered by the results of another series of indices taken on the same day. In the acute infections, such as pneumonia, I have given up doing them. If inoculation is to be successful in this disease, it should be done early. It is much more important to know what the infecting organism is, and to make the vaccine. In many cases—such as staphylococcic infections of the skin—the local condition is a sufficient guide. In actual practice one finds that time and expense forbid the working of more than the actual series which I have indicated above. I admit that in the early days of bacterial inoculation it was very necessary to control each step by the opsonic index; and without a mass of carefully recorded results, the present, even imperfect, stage in the evolution of vaccine therapy could never have been reached so soon. But now those who have worked for some time at this subject, both at the bedside and in the laboratory, are able, I maintain, to recognize, from the clinical changes, the effects of their inoculations. The dosage and the intervals between the inoculations are, for the most part, now determined, so that the first barriers are swept away. I think it a thousand pities to limit the utility of so great a method of combating disease by making the process unnecessarily difficult and costly.



Royal Society of Medicine

June 8, 1910.

Sir WILLIAM S. CHURCH, K.C.B., President, in the Chair.

Discussion on Vaccine Therapy : its Treatment, Value, and Limitations.¹

Dr. J. KINGSTON FOWLER : I did not originally intend to take part in this discussion, as my experience on the main questions is insufficient to justify the expression of an opinion ; but important side issues have appeared in its course upon which I desire more particularly to speak. To the general question as to the value of vaccine therapy there can, I imagine, be only one answer. We are all agreed in recognizing the brilliant results which have followed the scientific researches of Sir Almroth Wright and his co-workers, and of the importance of the principle which he has established. I recall with pleasure that three years ago, on handing to him the Fothergillian Gold Medal of the Medical Society of London, which is given triennially for scientific work in connexion with medicine and surgery, I stated that it was fitting that a Society of which Edward Jenner was a distinguished member should be the first to publicly recognize the value of the labours of one who had made the immortal discovery of Jenner the basis of his work ; that, whilst faddists and politicians have been, and still are, endeavouring to prevent the people of this country from rendering themselves immune to smallpox, vaccination had gradually acquired a wider and wider meaning, until the principle underlying its action had become the basis of the most advanced medicine of the day. My own experience of the

¹ Fourth meeting (adjourned from June 1).

use of this method has unfortunately not lain in the observation of those cases in which the value is most obvious—viz., the various staphylococcal and streptococcal infections, and in the preventive inoculation against enteric fever—and I have consequently become perhaps unduly impressed with its limitations.

Vaccines have been used for a long time in my wards at the Middlesex Hospital in all cases in which their employment appeared likely to be beneficial, including malignant endocarditis, bronchiectasis, pulmonary tuberculosis, gonococcal arthritis, some pneumococcal infections, and cases of catarrhal affections of the bronchi. Elsewhere I have observed their use in Malta fever, in streptococcal infection, in infections of the urinary tract with bacillus coli, and in other diseases; but if I were pressed to produce from my personal experience the evidence upon which my belief in their value is founded, I fear I should be unable to do so. I have had more considerable experience of the use in pulmonary tuberculosis of tuberculin, both in the manner of 1890 and in the fractional doses used in recent times, but I have not yet seen a case of that nature in which I am sure that benefit has been derived. I hope, however, that I have still a mind open to conviction, for when that is lost it is time to retire to the country and grow cabbages. On the last occasion my story of Sir Andrew Clark's illustration of his dictum with regard to age was quoted, but I think the dictum itself was omitted. "No man is old until he ceases to be able to adapt himself to his environment." That, not one's years, is the real test of age.

There are possibly some here whose professional memory does not go back to August, 1890, when Professor Koch, whose great work we all recognize and whose recent death we all deplore, announced the discovery of tuberculin. Of that event some years later I wrote as follows: "The great interest excited throughout the world by this announcement is still fresh in our memories; the lamentable lack of judgment, of self-control, and of those critical faculties which should characterize the members of a scientific profession displayed by many upon that occasion may serve as a warning for the future. The history of medicine in still more recent times, however, appears to prove that the tendency to exploit for selfish purposes each new discovery in therapeutics, and to recommend it as a panacea for almost every ailment of mankind, is ineradicable from the minds of the weaker brethren."

In view of the fact that to-day patients may be roughly divided into those who are swallowing the Bulgarian bacillus, or rather who think they are, and those who are being injected with a vaccine—a fact highly

flattering to Professor Metchnikoff and Sir Almroth Wright, but not marking a great advance in the scientific spirit of the profession—I propose to let that paragraph stand, if another edition of the work is required.

I should like to take this opportunity of airing a belief to which I have often given utterance in teaching—viz., that the difficulty in estimating the value of a new remedy is greatly exaggerated, and that when a drug has been in use for a definite purpose for several years, and opinion is still unsettled as to its value, it is usually because it has none. Please, however, do not suppose that I am suggesting that vaccine therapy has no value. I base this belief upon the observation, with which you may or may not agree, that nearly all the great advances in therapeutics which have taken place in my own experience have been accepted within a comparatively short period. I do not include the period required to bring the method or the agent to a state fit for trial, and it may take long to render perfect the technique or to determine the dosage, but that its use does produce a definite effect for good or ill is quickly acknowledged. The first of such advances that I can recall was the introduction of salicin and salicylic acid for the treatment of acute rheumatism. A very brief trial showed that the effect in giving relief to pain was most marked, and that in spite of the fact that, owing to the impurities in some of the preparations used, nearly all the patients suffered severely from vomiting. I will not trouble you with an analysis of all such advances which have since occurred, but I believe that it would certainly prove my point. My belief, long held, is that if the time should arrive, and I hope it may soon, when we are in possession of a remedy having a decided influence upon the course of pulmonary tuberculosis, its effect will be quickly discerned and will be manifest from the altered course of the fever.

The advantage of a prolonged pathological and clinical experience is that thereby a knowledge is obtained not only of the ordinary course of a disease, but also of its rarer manifestations and terminations. By such a mind no geese are likely to be mistaken for swans. When a person thus equipped is engaged upon the trial of a new remedy, the first case in which some unlooked-for event occurs attracts attention; the second serves to fix the mind upon the observation, and a third brings conviction that one is in the presence of a fact new to one's experience, and worthy of close attention. It was, for example, only necessary to see for the first time a few cases of pulmonary tuberculosis which had been treated at Nordrach to convince anyone, no matter how great his experience might have been, that he was looking upon something which he

had never seen before. It was not that tuberculosis of the lungs had undergone arrest—that is one of the commonest events in pathology—but that with arrest there should be such a complete change in the appearance and capacity of the individual. I felt that in giving my support to the movement for the establishment of sanatoria I was assuredly on firm ground, and it is some satisfaction, in reviewing again in thought the road over which one has travelled, marked as it is by milestones, each one of which recalls some cure for consumption, to find that there is only one upon which the writing is still legible, "To the Sanatorium, one mile." That sanatorium treatment is a method incapable of producing arrest in many cases is no more to the point than that vaccine therapy, like every other therapeutic measure, has its limitations.

One of the important side issues which is involved in the discussion of this method of treatment is as to the person by whom it should be undertaken. In an address delivered in 1907 I referred to this point in the following terms: "Let us now pass on to consider the physician of the future. Sir Almroth Wright is of opinion that he will be an immunizator. We shall all agree in hoping that it may be in his power to afford immunity to his patients from as many diseases as possible, and we shall also agree that as a student and subsequently he must have received a careful and prolonged laboratory training. But I submit that he must continue to be in the future as he has been in the past, above all things a man of wide clinical experience. No matter how great the advance of science may be, there will never be a royal road to medicine; it will be the common road that all must tread who aspire to treat disease, and, after the class-room has been left behind, it will lie through the wards of the hospital, the post-mortem room, and the clinical laboratory, and will always lead back to the bedside. The physician of the future will have to deal with human nature as we have had to deal with it. Times may change, ideals may alter, but water and human nature will ever remain weak. They are the only two things in this world on which it is safe to stake one's last shilling." I might have added that in the future, as in the past, all mankind will die of some disorder, and that many will need a physician; if fewer die of infective maladies more will die of other diseases.

In the future, as in the past, the first and most important thing will be the diagnosis of the patient's malady. Once that has been accurately determined, the rest is comparatively easy. Some may think that, as medicine becomes more and more firmly fixed upon a sure basis of

science, the diagnosis of disease will gradually prove an easier task. It will become more certain in competent hands, but it will never be easy, for, as science grows, it will continually place new burdens upon the physician and the practitioner. I have had many opportunities of observing that the recent increase in the number of laboratory tests available is surely leading to the disuse of the older methods of investigation, the employment, that is, of all the senses with which Nature has provided us; and it is a physiological law that atrophy follows disuse. It must have occurred to every physician to be called to a case in which the condition of the blood and of every secretion that lends itself to examination had been carefully investigated; not once only but several times, and yet the diagnosis was as far off as ever, if not further off; whereas, an intelligent use of the old-fashioned methods of inspection, palpation, percussion and auscultation showed that it was literally staring one in the face. In so saying I shall not, I trust, be thought to undervalue the very great assistance given to diagnosis and treatment by the newer methods. I am only urging that the older should not be allowed to fall into disuse.

Dr. Bulloch was severe upon the clinician, but he was, I think, perfectly fair, and I am in complete agreement with his views. The great advances of medicine in recent years have been made by the bacteriologist and not by the clinician, and I, at any rate, am anxious that he should have his full share of the credit and the reward. But nothing will, in my opinion, ever fit a man for the treatment of disease but clinical experience. No man can shut himself up in a laboratory for years and then come forth equipped for the treatment of disease.

The practice of our profession is capable of giving an insight into human nature which no other training can give, and the physician may be required at any moment to focus the experience of a life-time upon the answer to be given to that which is often the most difficult of all questions, "Is this a case of functional disorder or organic disease?" That point can rarely be decided by a purely laboratory training. There are only two possible solutions of the situation. The clinician may become more of a bacteriologist, and the bacteriologist may become more of a clinician; but if this method of treatment is to be entrusted to one person, he must possess both kinds of knowledge. The clinician must keep in continuous touch with bacteriology; the bacteriologist must keep in continuous touch with clinical medicine. It is apt to be forgotten that the profession exists for the advancement of medicine and the service of the public. The public does not exist for the profession, and

will not pay for the services of two people when one is sufficient. For the younger generation of physicians there is no excuse if they have not undergone a prolonged training in a clinical and bacteriological laboratory. When they no longer lecture on materia medica, hygiene, forensic medicine, and like subjects, for the teaching of which they may have shown no special aptitude, they will have more time to devote to what is to be their life's work. For most of those who, like myself, belong to a pre-bacteriological age it is impossible to find time to master the technique of bacteriology; we must be content to accept the assistance of those who have done so, if we wish to practise this method.

I should like to take this opportunity of repeating that, in my opinion, it will aid in the solution of the difficulty to which the advent of this method of treatment has given point, and also will prove to the advantage of the physician and the consulting physician, that their relative positions should in the future be free from all ambiguity. The physician is now supposed from the beginning of his career to be a consultant. This is now and always has been a pure fiction, and the sooner it disappears the better. He is a man who has decided to attempt to attain a certain position, and in order to succeed has undergone a very prolonged training and has limited his practice to medical cases. He may be consulted by other medical men, just as a man in general practice may be so consulted; but he is, within the limits which he himself or the holding of some diploma has marked out, free to practise as he likes. Sidney Smith was once asked by an anxious mother what profession he recommended for her son. He replied, "Madam, I should bring him up to be a bishop: I have observed that it is a very respectable calling." But the bishop of to-day was once a curate.

I have often urged, and I now do so again, that some recognized means should be provided whereby a physician may be able, if he so desires, at some period of his career, to let it be known that he has become a consulting physician. The distinguishing feature of his practice should then be that he does not undertake regular medical attendance. I refrain from suggesting the exact means by which this change of status should be brought about—it would be analogous to that which a junior at the Bar undergoes on becoming a King's Counsel—but I am not advocating a measure which I have not myself adopted for many years, or one which there is any serious difficulty in carrying into effect. The claims of humanity and friendship will, of course, always remain paramount. I believe that by the adoption of this step the profession, which, like other professions, is judged from those near the top and not

from those near the bottom, would attain a higher position in the estimation of the public, and the general practitioner and the physician would thereby obtain an assurance that by reference to a consulting physician they could not possibly be supplanted in the confidence of their patients.

Dr. ARTHUR LATHAM: This discussion, so far as it has gone, shows that in the opinion of the speakers vaccine therapy has taken a definite place in our methods both for combating and, it may be added, for preventing disease. It is a great advance that such recognition should be forthcoming. Most of us from time to time are met with what may be, without offence, described as uninformed criticism of this method. It was for this reason that this discussion was suggested. The time seemed ripe for a "stock-taking," and there can be little doubt that the discussion will strengthen the hands of those who believe in the future of vaccine therapy. It is a matter for regret that many of those who do not hesitate to cavil at the value of this method in ordinary conversation should have resisted all my blandishments and refused to take part in our debate. It may be of interest to state that the reason given is that their knowledge of the subject is so limited.

My own experience justifies me in regarding Sir Almroth Wright's work as being one of the most brilliant and useful additions to our methods of diagnosis and treatment in my time. Vaccine therapy is a great addition to our methods of treatment, but that does not mean that it will displace the whole fabric of our clinical knowledge. We are far from knowing as yet all that there is to be known of the value of vaccines in the treatment and prevention of disease, and if we are conscientious observers we must recognize that, whilst vaccine therapy often achieves brilliant and lasting results, it is not infrequently attended with either complete or partial failure.

We must all recognize the truth of the saying of Hippocrates that experience is fallacious and judgment difficult. In spite of that I would say that from my own experience I am certain vaccine therapy does good, and I am equally certain it is capable of doing a great deal of harm if it is given in an unskilful fashion. I am in entire agreement with previous speakers in believing that a knowledge of bacteriology is essential to the clinician of the present day. I am equally of the opinion that the place for the bacteriologist without clinical knowledge is in his laboratory, and that he is out of place at the bedside.

In the experience of us all staphylococcic infections yield in most cases to appropriate vaccines, but even here failure sometimes occurs, and it may be added failure is more common if we confine our methods entirely to the use of vaccines. In *Bacterium coli* infections better results have been obtained as the result of vaccine therapy in combination with the usual clinical methods than by any other method; but here again a number of cases have failed, and will probably always fail, to receive any real or permanent benefit at the hands of even the most expert bacteriologist when unaided by ordinary clinical methods. There can be no question as to the value of vaccines in chronic pneumococcic and gonococcic infections. Our experience does not justify so dogmatic an opinion on the part likely to be played in the future by vaccination in acute pneumonia. In cases in which I have formed the opinion that in all probability the patient will recover under ordinary treatment, I have seen the use of a stock pneumococcic vaccine followed by the abortion of the disease on the second and third or fourth day in a sufficient number of cases to be certain of the value of the method. In severe cases—cases in old people or in alcoholics, cases which come under observation late in the disease, or cases which are associated with much bronchitis or a marked tendency to heart failure—my experience, as might be expected, has not been so satisfactory. There are obvious reasons for this, but one reason is our want of knowledge as yet of the proper dose in a given case. It is not sufficiently recognized that pneumococcic vaccines differ considerably in their virulence, and that we cannot always compare one particular vaccine safely with another. It is possible that the usual dose of 20 to 50 millions is far too large, for there have been several instances in which the employment of such doses by bacteriologists has seemed to be not wholly free from the responsibility of causing disastrous results. Apparently excellent results follow the use of doses of 10 to 5 millions, or even less, and I would urge a trial of the smaller doses. In my experience the use of appropriate vaccines—usually *Micrococcus catarrhalis* and pneumococcus, and occasionally Friedländer or streptococcus—in cases of recurrent bronchitis does much to relieve the patient and to lessen the frequency of the attacks. Again, I have seen a case of commencing bronchiectasis, due to the impaction of a small foreign body in one of the divisions of the bronchi, and in which the patient had daily expectorated 1 oz. or more of evil-smelling pus for over a year, relieved to the extent of losing all purulent expectoration by the use of *Micrococcus catarrhalis* and pneumococcus cultivated from the expectoration, and remain well to the present time, two years after

treatment. I have seen a long-standing case of bronchiectasis, in which 8 oz. of stinking pus were expectorated daily, lose all the odour of the expectoration, which became bronchitic in character, and the patient able to resume her work and to mix with her friends. She is not cured—there is too much damage to the lung—but her life has been completely changed by the use of vaccine therapy. In this case there were seven micro-organisms in the expectoration, and the appropriate one—a streptococcus—was discovered by the use of the opsonic index taken at rest and after exertion. I shall mention later a case of infective endocarditis associated with infarctions in which a streptococcus was isolated and used, with the result that the temperature became normal.

Tuberculin is a most potent remedy. At the same time it cannot be too emphatically stated that it is capable of doing irreparable damage if it is used without adequate knowledge and guidance as to dosage and spacing of doses. It is certainly more successful, or at any rate more rapidly successful, in non-pulmonary forms of the disease than in the pulmonary forms. I have seen what appear to be permanent "cures"—that is to say, "cures" which are maintained for two years and upwards—in most desperate cases. Thus three cases of acute tuberculosis under my care have recovered, in two of which there were no localizing signs, and in one of which the patient suffered from tuberculosis of the peritoneum, hip-joint, knee-joint, shoulder-joint and pleura, with fever to 105° F. In all the diagnosis was suggested by clinical methods and confirmed by means of the opsonic index. All three patients are without any evidence of ever having suffered from tuberculosis to-day, some two years or more after treatment. A case of glandular tuberculosis of the neck with secondary staphylococcic infection, and with a history of five extensive operations previously, and upon which two surgeons refused to operate again, was apparently cured and remains well. A waiter, suffering from long-standing tuberculosis of the knee-joint of such a degree that amputation was strongly urged, was given a movable joint of the same size as the healthy one, and enabled to resume his occupation. It is said that such cases sometimes recover spontaneously. That is true, but in my experience when a desperate case responds to vaccine therapy, recovery is much more rapid than when spontaneous recovery takes place; and, moreover, it is frequently possible to demonstrate the effect of the different doses. Tuberculin appears to be a specific for tuberculous peritonitis with effusion. I have seen fourteen consecutive cases, all associated with fever, in many of which there had been previous attacks, and in many of which there

had been an operation, lose all fluid and febrile disturbance and remain well. In the dry form of tuberculous peritonitis my experience is limited and is not so satisfactory, but these cases probably require very much smaller doses. Tuberculin appears to be a specific in any form of tuberculosis where there are no localizing signs, and merely the symptoms of the disease are present, the diagnosis being backed up by a positive finding with the opsonic index. Anæmic children suffering from lassitude, slight fever, and it may be slight enlargement of the glands, respond in most instances to a surprising degree.

With regard to pulmonary tuberculosis, my experience is that we are faced with more severe limitations for vaccine therapy than in the non-pulmonary forms. In long-standing cases with fever we usually fail in the great majority of cases to effect permanent good; in some we do harm. The same is true of very acute cases. In both classes, however, we see some striking instances of improvement which should be attributed to tuberculin rather than to coincidence. I have seen, in the last eighteen months, four cases in which sanatorium treatment—in two instances for more than two years—had failed in so far as there was constantly fever at night from 99° F. to 100° F., which was increased by exertion, but in which, after a course of treatment by tuberculin and absolute rest, the fever disappeared. All these patients were able to take active exercise to the extent of eight or more miles walking after a further period of sanatorium treatment combined with the continued use of tuberculin. In early cases of pulmonary tuberculosis, and in chronic cases without much fever, my experience is that tuberculin is most valuable, and bears out the experience of other observers on the Continent and in America. The most striking statistics in this connexion are those of Ritter, of the Edmundsthal Heilstätte, Hamburg, who, it should be mentioned, was using infinitesimal doses of tuberculin many years ago. Pottenger's experience—and he, again, is a man who, in many instances, used very small doses as the result of clinical experience several years before we did in this country—coincides with the above.

With regard to the use of the word "administration" in the title of this discussion, it is disappointing to find that it has been interpreted in so narrow a sense. We had hoped to have raised a more ample discussion on the question: How are we to be guided in the determination of the size of the dose and its appropriate time of administration? Is the opsonic index rather than clinical methods to be our guide as to the dosage and spacing of doses in the use of vaccine therapy in infective disease? That seems to me to be the most important question at issue,

and I will return to it in a minute. Let me say a few words first on the subject of the administration by the mouth. Many attempts like those described by Sir W. Leishman have been made to obtain absorption of vaccines of various kinds, but chiefly tuberculin, by internal administration, which have resulted in failure. In all these cases various devices, such as the employment of capsules, coatings of fat, &c., have been used in order to insure the passage of the vaccine through the stomach. It is owing to this fact that failure has occurred. One of the chief functions of the stomach is absorption, and the method I employ is to give the vaccine suspended in a fluid isotonic with the blood on an empty and healthy stomach. To insure this it is best to give the vaccine first thing in the morning. It is doubtful whether any appreciable quantity of gastric juice is brought to bear on a vaccine if it is given in this way, and, even if it is, Mr. Goadby's experiments suggest that no appreciable alteration occurs. None of those who have criticized this method have done so as the result of experiments carried out on exactly similar lines. Some have criticized them on the basis of experiments which are not comparable, others have condemned the method on a priori grounds; and certain bacteriologists, who inveigh against the want of the open mind of the clinician, condemn the method out of hand in the best "clinical manner."

There are certain grounds for believing that part of the immunity many of us enjoy against certain infections is due to small doses of the appropriate vaccine administered in this way by a beneficent Providence. Definite proof that vaccines are absorbed when given on an empty stomach is afforded by the following facts:—

(1) In any case of infective disease we can do harm, causing a rise of temperature and an aggravation of symptoms by giving too large a dose by this method.

(2) Vaccines administered in this way have the same effect on the temperature, the opsonic index, and the clinical symptoms, and yield the same results of treatment as when they are given under the skin.

(3) If we arrive at a dose which always has a definite effect when given by the mouth in any given case, a dose of rather less than half will have precisely the same effect when given under the skin in the great majority of instances.

(4) A case of malignant endocarditis with all the clinical symptoms, including infarction on more than one occasion, is at present under my care at St. George's Hospital. A streptococcus has been isolated on eleven separate occasions from the blood. A vaccine was prepared, and a dose of

one million streptococci given by the mouth. The temperature, which had previously been irregular, being raised to 99° F. to 100° F. at night for five or more weeks, has become normal, and the general condition has markedly improved. Dr. Hunt found that the patient's blood before the administration of the vaccine did not agglutinate the streptococcus. Within twenty-eight hours of the oral administration of the vaccine marked agglutination was present. Dr. Hunt's blood did not agglutinate the streptococcus, but forty-eight hours after taking a dose of the vaccine by the mouth his blood did agglutinate the organism. The same experiment was repeated on a laboratory boy with the same result. Further, at the commencement of the treatment, the streptococcus was present in such numbers in the patient's blood that it was successfully cultivated from a drop of blood taken from the finger. It is now somewhat difficult to cultivate from large quantities of blood.

It is stated that we cannot trust oral administration because absorption must differ from time to time, and that one and the same dose in a given case may at one time be too small and at another too large. In answer to this I would state that clinical experience proves the contrary. In many cases an effective dose is found, any slight increase of which does harm. For example, a dose of $\frac{1}{30000}$ mg. of tuberculin may for weeks have a good and definite effect, but the slight increase to $\frac{1}{25000}$ mg. will do definite harm. Again, I have known the oral administration of as small a dose as $\frac{1}{200000}$ mg. T.R. followed in a few hours by a rise of temperature to 102° F. to 103° F. in three or four instances. These clinical facts have been observed by too many practitioners to be swept aside on merely a priori arguments, and my contention has been confirmed by laboratory workers such as M. Calmette, Dr. Spitta, and Dr. Inman.

I do not restrict myself to this method of administration. I often use the hypodermic method, especially when the stomach is disordered and the tongue furred. The oral method undoubtedly has great convenience on its side for the use of vaccine therapy in large institutions or in general practice. It is often of service in the case of children who fear the needle, and I know of a number of such cases in which the hypodermic method became impossible and was given up owing to the child's distress, whilst later on a cure was effected by oral administration. Finally, this method has an advantage in that it makes many cases of vaccine therapy less expensive to the patient.

Let us turn to the "limitations of vaccine therapy." Some of these may be due merely to our want of knowledge, and may disappear or be

overcome in time. Others seem to me to be inherent. In my experience vaccine therapy is much less likely to be attended with success when we are unable to control the process of auto-inoculation. This is usually due to the fact that we cannot give adequate rest to the seat, or one of the seats, of the disease. For example, vaccine therapy has hitherto failed in infective endocarditis attended with high fever. One reason for this is that one of the seats of the infection cannot be kept at rest. Similarly, tuberculin therapy is of little, if any, avail in cases of pulmonary tuberculosis which are associated with constant harassing cough or with uncontrollable vomiting, and, owing to the necessary movements of the lung, tuberculin therapy is less efficient in many of these cases than in so-called surgical tuberculosis. Another limitation is that vaccines prepared from the patient's own organisms are more effective than stock vaccines, for there are many cases of infective disease in which it is not practicable, nor even possible, to cultivate the micro-organism. It is apparently probable that we shall soon be able to cultivate the tubercle bacilli of consumptives by an easier and quicker process. If that occurs we shall be able to use more often an autogenous vaccine, and we should have better and quicker results. Again, it is a limitation of vaccine therapy that we do not know how long immunity, when acquired, lasts, and that we are in the dark as to when a further course of vaccine therapy should be given. We are often, indeed, still in the dark as to when we have established immunity. We are told that when the opsonic index remains level, and within normal limits, we may be satisfied with the immunity produced. Can we accept this statement? Certainly in my experience relapses are much less common if the administration of vaccines is continued long after immunity has apparently been established. This is true of some cases of simple staphylococcic infections, and is especially true of tuberculin therapy, which in many cases must be carried out for as long as a year after apparent recovery if we are not to have a relapse. Another limitation of vaccine therapy is the fact that a real cure is seldom effected if any considerable quantity of dead tissue is present and is not removed by clinical methods. For example, vaccines cannot produce their full effect in cases of tuberculous glands or joints in which much necrosis or the formation of pus has taken place, until an exit is made for the dead irritating matter.

The greatest limitation of all would be the fact, if true, that vaccine therapy necessitated the use of the opsonic index as a guide. In this discussion, so far, the question of vaccine therapy has been regarded

almost wholly from the point of view of those who have great facilities for laboratory work, either carried out by themselves or deputed. We seem to have forgotten the enormous number of patients for whom such facilities are, for one reason or another, an impossibility. If the opsonic index is essential as a guide, then the application of vaccines must be greatly restricted. We will all agree that vaccine therapy requires a guide, even if we differ as to whether it should be the temperature *and* clinical symptoms or the opsonic index. We will all agree that the more forms of control we can have the better, and that if the opsonic index affords reliable information, and if the temperature and clinical symptoms afford reliable information with regard to the immunizing process, we should use them all if possible. In matters of diagnosis of certain infections I often use the opsonic index, and less frequently in treatment, in an endeavour to throw light on some difficulty, taking the opsonic index under different conditions, such as at rest and after exercise, or when the temperature is at the highest point of the day, and again at the lowest. In this way it is often possible to obtain most useful information, but it is necessary to restrict such questions to the most highly skilled bacteriologists, who can be trusted to devote their personal attention to the matter, and who are willing to share the responsibility for the answer given. It is not always wise to accept the findings then, if they are clearly at variance with the clinical features of the case, any more than it is wise to place a whole-hearted reliance upon the presence or absence of a Widal's reaction in a suspected case of enteric fever. For example, I saw last year a lady in the country under the care of Dr. Rich, who for weeks had suffered from high temperature and all the clinical symptoms, chiefly abdominal, of an infective fever. We said that a bacteriologist might help us to ascertain the organism at work, and so allow us to employ vaccine therapy. A most elaborate investigation was made, and the blood tested against any possible micro-organism. The bacteriologist had an absolutely free hand, but failed to give us any assistance. In spite of this, we stuck to our diagnosis that some micro-organism was at work. A few weeks later the patient passed an ounce or two of pus by the bowel, and made a rapid convalescence. The pus was almost a pure culture of the pneumococcus, but no bacteriological evidence had previously been forthcoming as to the presence of this micro-organism, although the conditions seemed ideal for the bacteriologist.

The first question is whether the opsonic index is a reliable guide in all infective diseases. In staphylococcic infections the determination

of the opsonic index is comparatively easy, and its reliability appears to be established. The same is true, though to a less degree, of tuberculous infections. When we come to the opsonic index of the pneumococcus, gonococcus, streptococcus, and *Micrococcus catarrhalis*, we find the skilled bacteriologist much less ready to swear to the correctness of his findings. We find one set of bacteriologists full of enthusiasm for the opsonic index of all organisms. We find others, perhaps in the same laboratory, who confess themselves unable to give a reliable reading for the pneumococcus or the *Micrococcus catarrhalis* or what not. Let me read an extract with regard to the opsonic index of the pneumococcus from the paper of two workers in the bacteriological laboratory of St. Mary's Hospital¹: "In many infections the appropriate dose of vaccine is indicated by the opsonic index, but in pneumonia certain difficulties arise. Sometimes the pneumococcus obtained was not susceptible to the action of normal serum, there being no phagocytosis under any circumstances, and then no opsonic index could be taken. In such a case one has to rely on indices obtained by using a suitable stock culture. Another difficulty is that of agglutination of the organism. This feature is seen late in the disease, especially in cases the course of which is protracted, and it causes great difficulty in the determination of reliable opsonic indices. We have found that sometimes the opsonic power of apparently healthy individuals to the pneumococcus obtained varies considerably, and thus there is difficulty in obtaining a reliable standard. This difficulty may be overcome by using for the standard a mixture of several serums from healthy individuals, or else by using in the same series of experiments serum taken always from the same individuals. In the present series of cases we have been unable to use regularly the opsonic index as our guide to dosage on account of the difficulties described. We have taken as our guide the clinical symptoms of the patient."

Again, in this discussion we have heard that Dr. Freeman, in the very able work he has done with regard to whooping-cough, was not only unable to rely on the opsonic index as a guide, but was compelled to use the purely clinical symptoms to establish the dose. The same sort of technical difficulties occur in our efforts to estimate the opsonic index of the gonococcus, *Micrococcus catarrhalis*, and other micro-organisms. In certain cases these technical difficulties can be overcome by highly skilled workers by the use of somewhat laborious methods,

¹ Dr. W. H. Willcox and Dr. W. Parry Morgan, *Brit. Med. Journ.*, 1909, ii, p. 1050.

but it is clear to any practical man that in a very large number of cases, probably an overwhelming number of cases, of infective disease, the opsonic index cannot be relied upon as a guide. This conclusion would confine the application of vaccine therapy to narrow limits if the opsonic index were the only reliable guide to the different phases of intoxication and immunization. But is it true that in any infective disease our only reliable guide to the different phases of intoxication and immunization is the opsonic index?

I have said that, in my opinion, vaccine therapy is the most momentous advance made in our therapeutics in the present generation. Criticism of the work of a great man often appears ungenerous, but I must state my opinion that Sir Almroth Wright is wrong in his contention that the opsonic index is the only real guide that we have for vaccine therapy. His contention may, indeed, retard advance in the subject. If so, it would not be the first time that an error in detail made by an inventor had retarded advance in the subject which owed its birth to him. When Sir Isaac Newton discovered the differential calculus, he, unfortunately, adopted an indifferent notation; and, as a result, advance in British mathematics was delayed for a number of years—until long after Newton died, in fact, and until the superior notation of Leibnitz was adopted in this country as well as in Germany. I think that case is analogous to the present one—that Sir Almroth Wright has adopted an inferior notation as a guide, and that, if he continues to champion it as he has in the past, he will do much to retard any further advance in vaccine therapy. Surely we cannot determine the doses of drugs or the doses of anæsthetics *in camera* by calculation for all cases of disease, and for all emergencies. In the same way, it does not seem possible that we can calculate the doses of vaccines in laboratories without regard to the clinical symptoms of the patient, or without regard to the personal equation of the individual; certainly not without grave risk of doing harm to the patient, or of bringing the whole method of vaccine therapy into disrepute. But is the opsonic index the only possible guide to the different phases of intoxication and immunization? Some years ago, when I considered this question, it seemed to me that when I dealt with a case of pneumonia, and it was found that at a certain period of the disease the temperature had fallen, the symptoms had improved, and the man was better, I was within my rights in making the deduction that a certain amount of immunity had been established. I asked myself: Why is it that the symptoms have improved? I said it was because there was a diminished amount of

intoxication. Why is it that there is diminished intoxication? I replied that there was a greater effort towards immunization. It seemed to me that as intoxication became less, the degree of immunization must be found to have become greater, because the lessening of the intoxication was due to an increase in the immunizing process. The converse appeared to me to be equally clear. In a crude way I took it that the immunizing process was comparable to an alkali, and the intoxication process to an acid. I thought that clinical observations might be compared to an indicator such as litmus paper, showing us when we were dealing with an excess of alkali or an excess of acid, or with a neutral fluid. I was told that the opsonic index was a better form of indicator—more reliable and delicate. I said to those who told me this that I thought that a clinician knew when his patient was getting well, that he knew when he was getting worse—he knew, in fact, whether the process of immunity or the process of intoxication was gaining the upper hand. But I was ready to learn and to put the matter to experiment. I asked Dr. Inman and Dr. Spitta to test it from the laboratory point of view in certain diseases, whilst I investigated it from the clinical point of view. I asked them to take the opsonic index frequently, whilst I recorded the clinical symptoms and the temperature.

When we plotted out the two sets of observations it was clear that there was a definite relation between the opsonic index and the clinical symptoms and temperature, and that both could be used as a guide to the immunizing process. We found that when the symptoms improved, the opsonic index had risen; when the symptoms were aggravated, the opsonic index had fallen; when the temperature was lowered or became flatter (even in subnormal temperatures), the opsonic index had risen; when the temperature was higher or fluctuated to a greater extent, the opsonic index had fallen. We found that, though we could not tell from clinical observation what the precise reading of the opsonic index was—whether it was 1·2 or 1·8—we could tell whether there was any marked variation in the height of the index, and whether it was rising or falling. I was gratified at this, and thought I could interpret the process of immunity by clinical observation in terms of the opsonic index. To my great disappointment, I find, in the course of this discussion, that two other skilled observers, Sir Almroth Wright and Dr. Colebrook, have since investigated the subject along the same lines, and that they state that the opsonic index has no definite relation to temperature or symptoms. One set of skilled workers says we are dealing with a black object, and the other that we are dealing with a white

object. Dr. Inman must deal with that question, but it is clear that when the opsonic index is asked to decide so comparatively simple a question, and we have two skilled workers giving us one answer, and two equally skilled giving us another, the only deduction to be drawn is that the opsonic index cannot be used practically on a large scale.

My experience convinces me that clinical observation forms a good, and in most cases an efficient, guide for vaccine therapy. A dose of vaccine which is followed within twenty-four hours by a rise of temperature or an increase in the fluctuation of the temperature, and by an aggravation of symptoms, is too large. A dose which has no effect on the temperature or the symptoms is too small. A dose which is followed by a lowering of the temperature, or a diminished fluctuation of the temperature (even in subnormal temperature), and an improvement in the symptoms, does good. When the effect of such a dose becomes less, the dose should be increased in size. These are simple rules, but they require careful observation and judgment. Occasionally one meets with a rise of temperature in the course of a specific infection which is not due to the specific organism. We are told that here the opsonic index is of great service, and it is true that it may be. It is, however, often quite clear from a careful consideration of the clinical symptoms that this rise of temperature is accidental. For example, suppose we are treating a case of joint infection and suddenly there is a rise of temperature. If at the same time the patient complains of a sore throat, it may be taken that the rise of temperature is unconnected with the joint disease. Numerous other and less crude examples will occur to any clinician. If we are in doubt, no harm will occur by waiting a day or two, as in the *majority* of cases the postponement of a dose of vaccine is a matter of no great importance. Again, we are told that it may be possible to be guided by clinical symptoms in simple infections, but we cannot do so when we are dealing with secondary or multiple infections. In most of such cases one infection is dominant, and must be dealt with before we can produce much impression on the others. There is no doubt that the treatment of a multiple infection is much more difficult than that of a simple one, but in most cases we can be guided by the clinical symptoms if we give the doses of the different vaccines on different days, and carefully consider the individual effects. Certainly the results obtained by the clinician with a working knowledge of bacteriology compare very favourably with those obtained by the bacteriologist.

Let us take another line of argument. Sir A. Wright has complained that although certain clinicians accepted the value of vaccine therapy in staphylococcic infections, they held that that was no proof of the value of vaccine therapy in other affections. He has argued, and I am not sure that his line of argument is quite sound, that if inoculations in one form of infection did good, inoculations in all other forms of infection must do good. When clinicians assert that it is possible to be guided in cases of staphylococcic infection by clinical symptoms, he agrees. He then goes on in the best "clinical manner" to say that that is no proof that we can be guided by clinical symptoms in other forms of infection. Sir A. Wright, however, holds that one case proves the whole, and, if we were prepared to accept that line of argument, the clinicians might rest satisfied with an easy victory. Let us examine the reasons why Sir A. Wright allows that in dealing with a boil on the neck we can dispense with the opsonic index. He says that in such a case we know what is going on, we can *see* when there is an aggravation of symptoms, and when there is an improvement. That is a remarkable admission, and means that when we know there is improvement or the reverse by a study of the case, we can dispense with the index. Is not it precisely the clinician's business to know whether there is improvement or the reverse, and is he not in most cases able to give a sound opinion? When we deal with pulmonary tuberculosis do not an increase in fever, increased expectoration, sudden onset of sweating, and a number of other symptoms tell us what we want to know, and cannot we gauge improvement in the same way? If we are treating a case of cystitis, have increased frequency of micturition, increase of pus, onset of hæmorrhage or increase of pain no meaning for us? The bacteriologist may be unable to make deductions from the clinical symptoms, and be restricted to the use of his eyes, but he is a poor physician or surgeon who cannot tell, by a careful consideration of his patient's case, whether a dose of vaccine has done good or harm or proved ineffective.

Vaccination by auto-inoculation is a more difficult business than vaccination by simple inoculation. We are told, and we accept it, that in the sanatorium treatment of pulmonary tuberculosis the physician in reality treats his patient by carefully graduated auto-inoculations. Here the clinician has been guided for many years entirely by the clinical symptoms. Are not the results of sanatorium treatment in early cases sufficient to show that auto-inoculation can to a large extent be controlled just as efficiently by a consideration of the clinical symptoms as by a study of the opsonic index? Does not this lead us to

the conclusion that treatment with vaccine therapy can also be controlled by similar methods?

Vaccine therapy is at present between two fires. On the one side we have the clinician, who is ignorant of the value of bacteriological methods; on the other we have the bacteriologist, who despises the clinician and undertakes the treatment of disease unequipped with clinical knowledge. The near future will show that the clinician must remain captain in matters of diagnosis, treatment, and prognosis. That does not mean that he will have to carry out himself highly technical laboratory work. It is impossible to undertake the laborious work of a clinician and at the same time to keep in constant touch with technical laboratory work. I gave up a year to bacteriological work; it was a year well spent. It does not enable me to carry out technical laboratory work now, but it does enable me, as a clinician, to keep in touch with bacteriological advances and to recognize the value of the bacteriologist.

Sir Almroth Wright used to hold that the bacteriologist would displace the clinician, whom he regarded as an effete product. Is not this view of the value of the bacteriologist due to some want of comprehension of all that clinical medicine means? Dr. Slater, in a recent address, when speaking on this subject, reminded us that a comparatively small object, held before the eye, would obscure the sun. We have been told by more than one speaker that the clinician must carry out his own bacteriology, prepare his own vaccines and the like, and not depute it to a laboratory worker. It is strange that bacteriologists who have strong views of the iniquity of clinicians in this respect should do everything they can to lead us into temptation by supplying the necessary vaccines to commercial chemists. But if we put that aside, what arguments can be brought forward to support this contention which do not apply with equal force to digitalin, hyoscine, and all the drugs of the Pharmacopœia? We recognize the value of the pharmacologist and of his work, and we depend on him for the preparation of our drugs and for information as to the dose of his preparations, which are carefully standardized. We do not, however, find that the pharmacologist seeks to magnify the importance of his work, or that he asserts that he is the only person who is competent to treat disease by drugs. The man who makes the gun is not the only man, and is seldom the best man, to fire it. It surely is a strange contention that the practical application of any science must rest in the hands of the expert in the science itself. It is, however, perfectly true, and I think realized by all the younger school of clinicians, that a working knowledge of bacteriology is a

necessity at the bedside. It is also true that in the future we shall have more exact knowledge of the part played by micro-organisms in a number of diseases which at present do not show any clear proof of being due to an infective agent. Sir Almroth Wright has modified his opinion, and now holds that the clinician of the future must also be an expert bacteriologist. Is applied bacteriology to be the only advance in clinical methods? Is there not some evidence of the value of applied physiological chemistry, and is this not likely to be of greater service in the future? Are electrical methods, including ionic medication, to receive no consideration? Is applied physiology not making great strides in clinical medicine to-day? Are the hard-fought lessons of pharmacology to be discarded?

If we accept Sir Almroth Wright's reasoning with regard to bacteriology, must we not also hold that the clinician of the future must also be an expert chemist, physiologist, electrician and pharmacologist, as well as a bacteriologist? Sir Almroth Wright is in this respect in the position of the trombone player in an orchestra who scoffs at the conductor because he is not an expert trombonist. A good conductor knows *all that is necessary* about each instrument, and a good clinician knows all that is necessary about the kindred sciences; he need not be a master of each instrument in his orchestra. The clinician may even be hampered by too intimate a knowledge of a particular science. Different qualities are required for scientific work in the laboratory from the judgment, experience, and intuition so necessary at the bedside. The learned professor of anatomy does not make the best surgeon, and similarly the bacteriologist does not make the best clinician. A general knowledge of chemistry, physiology, electricity, pharmacy, bacteriology, &c., will enable a physician to make a decision on a matter of diagnosis or treatment of much greater value than that of a scientific specialist whose main work is in the laboratory.

I am equally convinced that many of these necessary investigations cannot be carried out by the clinician without diminishing his value. The properly educated clinician is the only one who can correlate all these findings. The captain of a battle-ship must know much of navigation, engineering, electricity, gunnery, tactics, and other things. If he makes a speciality of one to the exclusion of others, his ship will often be in danger. I could give you a number of examples which have come under my observation in which the bacteriologist has failed, and sometimes disastrously, owing to his want of clinical knowledge. Let us take one. A young woman consulted a bacteriologist for a glandular

mass in the neck. The opsonic index was taken and tuberculosis diagnosed. No other examination was made. Tuberculin was given, and the opsonic readings were found to be well above the line, and the bacteriologist was satisfied. The woman, however, became steadily worse. A month or two later I examined the patient and found evidence of extensive pulmonary disease, and that the temperature was 103° F. The woman had lost her chance and she died. In febrile pulmonary tuberculosis the opsonic index is frequently always above the line. The bacteriologist, however, limited his examination to the glands, and, finding the index well above the line, misinterpreted the significance of his readings.

I have said that the clinician will remain captain at the bedside. Similarly the bacteriologist will be captain in the laboratory. The best results of vaccine therapy, or indeed of any application in clinical medicine of the allied sciences, must come from the properly co-ordinated work of the clinician and the laboratory worker. If we are to advance vaccine therapy the bacteriologist must recognize the value of the clinician, just as emphatically as the clinician who knows his business must recognize the value of the bacteriologist. We shall not advance our science if we throw stones at one another. To my mind it is obvious that we must work together, and that we must have at least a working knowledge of each other's subjects. There can be no real rivalry between us. We have each of us a part, and an important part, to play, and I trust that this discussion will do something to harmonize our respective fields of labour.

MR. MAYNARD SMITH: I confess I have suffered some disappointment in this discussion, chiefly from an inadequate representation of what I may call the opposition. Personally I am a strong believer in the merits of vaccine therapy, because I have been able to show, to my own satisfaction, that I have had better results in certain surgical lesions treated with the aid of vaccine therapy than I have had in similar cases treated on the previously existing lines, without the aid of vaccine therapy. That, put concisely, is my position in the matter. I had hoped I was to have heard in this discussion some of those who are counted as opponents of vaccine therapy, and then I felt I might have had something to discuss. This privilege has been denied me, and I therefore propose to confine myself to a brief account of an investigation I made into the results of treatment in a consecutive series of cases

treated in the Inoculation Department of St. Mary's Hospital. I have taken one type of case only, as better lending itself to investigation—namely, tuberculous disease of the joints. I shall tell you the results of treatment in this series. There were 72 cases written to who had been under treatment at the time these results were tabulated. Of these, 34 attended. From my experience in writing about other cases, I find about 50 per cent. of attendances is as much as one can expect in writing to hospital out-patients. Of those who attended, only three were treated by inoculation from the time they first came under the care of a doctor. All the other cases had been treated by other methods before they came to the Inoculation Department for treatment. Of these 3 cases, two were cured, with complete restoration of function. Let me say what I mean by that. I mean such restoration of function that an observer who did not know the case could not tell which had been the diseased joint. The third was cured, but there was some deformity and limitation of movement remaining. We are willing to accept the word "cured" in cases where the tuberculous disease is quiescent, but in which there may be left some limitation of movement in the joint. We have thus 31 cases left, and in 16 of them splinting, rest, and in some cases operations had been carried out during twelve months or less before they came under treatment by inoculation; that is to say, of the 31 cases, 16 had been under treatment for either twelve months or less. The results in those cases were: In 10 a cure ensued, with complete and absolute restoration of function, so that one could not tell by clinical observation which had been the joint affected; two were cured with slight limitation of movement; four were improved, but were still under treatment at the time this investigation was completed. The remaining 15 cases had undergone more than twelve months' treatment by splinting, by rest, by open air, by operation, and so forth, before they came under inoculation treatment. Of these 15 cases, two had only been under inoculation treatment for a couple of months; two cases had been under treatment for six and ten months respectively, but with no improvement. Of the other 11, six were cured, five were improved and remained under treatment. I ought here to make a point of the fact that these were out-patients; they had to visit hospital, as a rule, once in ten days. Complete rest was therefore often impossible, and, moreover, such advantages as seaside convalescent homes were not available whilst they were under treatment.

It is my belief as a surgeon that these are better results than are usually obtained in tuberculous disease of joints. I can say, certainly, that

TABLE OF CASES OF TUBERCULOUS

No.	Age and sex	Disease	Date of onset	Duration and nature of inoculations	Treatment previous to inoculation
1	16, F.	Tuberculous shoulder (confirmed by indices of 1.46 and 0.58 at intervals of four days)	June, 1906	August, 1906, to May, 1907; tuberculin	Nil
2	13, M.	Tuberculous knee	June, 1906	December, 1906, to November, 1907; tuberculin	Nil
3	21, F.	Tuberculous dactylitis and hip	1892	Has had inoculations for two months only; tuberculin	—
4	4, M.	Tuberculous disease of tarsus	Oct., 1907	October, 1908, until present time; still under treatment; tuberculin	Plaster case
5	38, F.	Tuberculous wrist (as a child, had tuberculous elbow and dactylitis)	Jan., 1907	February, 1907, to October, 1907; tuberculin	Nil for wrist
6	16, M.	Tuberculous hip	1898	March, 1907, to January, 1908; tuberculin	In hospital with extension; also as out-patient in splint
7	4, M.	Tuberculous disease of ankles and tarsus	Jan., 1907	July, 1907, up to the present time; still under treatment; tuberculin and staphylococcic vaccine	Splints; three operations
8	22, F.	Tuberculous knee	1901	July, 1907, up to the present time; still under treatment; tuberculin	Plaster and rest in bed; in hospital for a year
9	5, F.	Tuberculous disease of ankle and tarsus	June, 1908	November, 1908, up to present time; still under treatment; tuberculin and staphylococcic vaccine	Plaster
10	7, M.	Tuberculous disease of knee	July, 1907	February, 1909, up to present time; still under treatment; tuberculin	Extension; Thomas's knee splint
11	12, M.	Tuberculous knee	Jan., 1907	September, 1907, to January, 1909; tuberculin	Thomas's knee splint
12	7, M.	Tuberculous knee	July, 1906	October, 1906, to April, 1909	Extension; poroplastic splint
13	10, M.	Tubercle of head of tibia; afterwards tubercle of knee-joint; secondary staphylococcic infection with many abscesses and extensive bone infection	Jan., 1907	April, 1907, up to the present time; tuberculin and staphylococcic vaccine	Operation on head of tibia

ARTHRITIS TREATED BY VACCINES.

Additional treatment during inoculation	Condition at start of inoculation	Condition in July, 1909
Poroplastic shoulder cap	Pain in shoulder; limited mobility, wasting	Shoulders normal, no difference on two sides
Splint	Knee flexed, no movement possible; wasting, pain	Knees normal, no difference on two sides
—	—	No change at present
Plaster case	Ankle swollen, rigid; pain; mother describes child as "quite transparent"	No swelling; about 10 degrees of movement; general condition of child excellent
Carr's splint	Wrist swollen, painful, hot; impaired mobility	No swelling or pain; some deformity of wrist; movement through 20 degrees; uses wrist and hand for light work
Splint	Great pain, wasting, $\frac{3}{4}$ in. shortening; trochanter above Nélaton's line; was getting worse	Walks fairly, occasional pain; head of bone deformed and dislocated; fair movement, very little wasting
Splints	Both ankles swollen, rigid, extended; two sinuses	Slight puffiness inner side of right ankle, otherwise normal; walks well; sinuses healed (healing was complete in July, 1908)
Splint	Knee swollen, painful, fixed, straight	Knee fixed in straight position; much less swelling and pain; walks, but pain and œdema of leg after much exercise
Plaster	Ankle and tarsus swollen, painful, inverted, rigid; sinus	Much improvement; sinus healed, some swelling over tarsus, still inversion and limitation of movement
Thomas's knee splint	Swelling, pain, flexion, limitation of mobility; not improving	No improvement up to present
Thomas's knee splint	Swelling, pain, limitation of movement, no flexion	Knees normal, no difference on two sides
Splint	Swelling, pain; almost fixed in straight position	Flexion possible to 60 degrees; no pain or swelling; still wasting of limb; walks
Fourteen operations, chiefly opening abscesses from secondary infection; splint	Multiple sinuses and abscesses around knee and tibia; great swelling of knee and rigidity; hectic fever, general wasting; amputation considered	All healed; no pain, general condition good, movement free, and walks without pain

TABLE OF CASES OF TUBERCULOUS

No.	Age and sex	Disease	Date of onset	Duration and nature of inoculations	Treatment previous to inoculation
14	21, M.	Tuberculous hip	1904	March, 1907, up to present time; tuberculin	Thomas's splint for three years
15	6, M.	Tuberculous ankle and cervical glands	March, 1906	August, 1906, to February, 1907; tuberculin	Plaster; operation
16	43, M.	Tuberculous knee	March, 1905	March, 1909, up to present time; still under treatment; tuberculin	Splint; operation
17	25, M.	Tuberculous knee (as a child, spinal caries)	1893	June, 1906, up to the present time; tuberculin	Splint
18	30, F.	Tuberculous knee	Aug., 1908	December, 1908, up to present time; tuberculin	Bier's bandage
19	18, M.	Tuberculous disease of head of tibia and knee-joint	Dec., 1905	March, 1906, to July, 1909; tuberculin and staphylococcic vaccine	Operation in February, 1906, head of tibia scraped out; splint
20	16, F.	Tuberculous knee	Dec., 1905	September, 1906, to January, 1907; tuberculin	Thomas's knee splint
21	22, F.	Tuberculous knee	1904	June, 1906, to September, 1907; tuberculin	Splint
22	51, F.	Tuberculous hip	Childhood; symptoms recurred, May, 1906	July, 1906, to July, 1907, and May, 1909, up to present time; still under treatment; tuberculin	Several operations; bone removed (as a child)
23	7, F.	Tuberculous knee, ankle, and hand (dactylitis)	Oct., 1907	February, 1908, to May, 1909; tuberculin	Operations on hand and ankle (excisions of joint and scraping)

¹ Since the above note was made there has been a slight recrudescence of disease, the

ARTHRITIS TREATED BY VACCINES (*continued*).

Additional treatment during inoculation	Condition at start of inoculation	Condition in July, 1909
Thomas's splint	Pain in hip and knee	Can find no evidence of active disease; movements somewhat limited, still complains of pain
Plaster	Two sinuses; ankle swollen, rigid; "cries night and day"	Sinuses healed; runs and walks normally, no pain, "never complains" (condition in February, 1907) ¹
Splint; Bier's bandage	Very swollen, painful; starting pains at night; rigid	Patient says it is "a treat"; some thickening of synovial membrane, movement through 10 degrees, no pain
Splint; aspiration of pus, July, 1908; abscess in thigh opened and scraped, September, 1908	Knee swollen, painful, doughy, rigid; could not walk	No pain, movement through 5 degrees; thickening of synovial membrane has entirely disappeared; can walk without pain
Plaster	"Chronic synovitis of left knee"; much swollen; fainted with pain at night; only slight flexion possible	Knee appears normal to examination, except for some thickening each side of ligamentum papillæ; no fluid; movement free through 60 degrees; still complains of very great pain
Second scraping; splint	Sinus from head of tibia; joint swollen, limitation of movement	Sinus healed, knee movement normal; whilst inoculation was being carried out extensive ulceration of leg developed, which became gradually worse; these ulcers had the appearance of those due to syphilis, and the history of the case was suggestive of congenital syphilis; Wassermann reaction positive
Thomas's knee splint	Right knee much swollen, limitation of mobility, pain on movement	Knee normal, no difference on two sides
Splint and Scott's dressing	Knee much swollen, limitation of mobility, wasting of thigh, flexion, not much pain	Knee normal, no difference on two sides
Splint	Two sinuses; hip rigid and flexed	Sinuses closed and pain gone by July, 1907; then sinuses opened again, May, 1909, with swelling and pain; inoculation recommenced; rapid improvement
Splint	Swelling of synovial membrane, limitation of movement, wasting, no pain	All foci appear cured; movements good

ankle becoming puffy and painful; this is rapidly subsiding with rest and tuberculin.

TABLE OF CASES OF TUBERCULOUS

No.	Age and sex	Disease	Date of onset	Duration and nature of inoculations	Treatment previous to inoculation
24	24 $\frac{9}{12}$, M.	Tuberculous ankle	Jan., 1908(?)	February, 1908, to April, 1909; tuberculin, staphylococcic and streptococcic vaccines	Operation, February, 1908 (erosion and scraping of bone)
25	19, F.	Tuberculous elbow	March, 1904	March, 1906, to June, 1906 (then ceased to attend); tuberculin	Splint for one year
26	5, F.	Tuberculous hip	Dec., 1906	May, 1908, to February, 1909 (then ceased to attend); tuberculin	Two years in Thomas's splint; convalescent homes; during this time improved
27	18, M.	Tuberculous hip	July, 1906	October, 1906, to June, 1907; tuberculin	Rest; Thomas's splint; crutches
28	4 $\frac{3}{4}$, M.	Tuberculous knee	Jan., 1906	April, 1907, up to present time; auto-inoculation test now negative, and treatment will be stopped; tuberculin	Thomas's knee splint; rest
29	40, F.	Tuberculous disease of both wrists and both ankles	1902, left wrist; 1905, other joints	May, 1906, to June, 1909; tuberculin	Operation, 1902, left wrist (erosion of wrist-joint); splints
30	3 $\frac{1}{4}$, F.	Tuberculous disease of left knee (confirmed by auto-inoculation experiment)	Aug., 1907	September, 1907, to January, 1908; tuberculin	Splint (knee became worse)
31	58, M.	"Compound palmar ganglion" and tuberculous disease of carpus	Nov., 1906	July, 1908, to January, 1909 (then ceased to attend); tuberculin	Splint; operation, scraping out palmar synovial sac (melon-seed bodies); disease of carpal bones
32	18, F.	Tuberculous disease of wrist (confirmed by index of 0.64)	Sept., 1906	November, 1906, to March, 1907; tuberculin	Splint for six weeks; no better
33	12, F.	Tuberculous hip	1902, wore Thomas's splint for one year, then ran about normally; 1905, symptoms recommenced; Thomas's splint again	March, 1906, to July, 1907; tuberculin	Thomas's splint; said to have been getting worse all the time
34	5, F.	Tuberculous right knee	May, 1905	August, 1905, to June, 1908; tuberculin	Splint; said to have been getting worse all the time

ARTHRITIS TREATED BY VACCINES (*continued*).

Additional treatment during inoculation	Condition at start of inoculation	Condition in July, 1909.
Plaster	Three sinuses; ankle swollen, painful, stiff	Normal ankle, sound scars; walks with slight limp
Splint	Elbow swollen, painful, rigid	When inoculation discontinued, no change; arm now fixed at right angle, no pain
Thomas's splint	Hip rigid and flexed; no pain except on attempted movement	Improvement continued in same way as before inoculation until abscess developed in February, 1909; patient then admitted to hospital and operated on; since then has not been inoculated; now discharging sinus
Splint and crutches	Pain, could not sleep; hip rigid, limb wasted	Hip normal
Plaster	Swollen, painful, limitation of mobility	Walks well, no pain, flexion possible through 30 degrees
Splints for wrist, bandages for ankles; did not lie up	Ankles swollen and painful; could not walk; wrists swollen and painful, fingers stiff and useless	Walks well, but left ankle weak; slight thickening about right wrist, uses hand and writes easily; no pain
Splint	Knee swollen, limb wasted, limitation of mobility	Knee normal, no difference on two sides
Splint; Bier's bandage	Sinus; wrist stiff, fingers stiff, great pain	Wrist moves well, no pain; sinus; slight limitation of movement of fingers
Splint	Wrist swollen, almost complete rigidity, movements of fingers almost lost	Wrist normal, all movements of wrist and fingers good; general health greatly improved
Splint until January, 1907; then started walking	Pain, rigidity, wasting, progressive shortening (noted as 2 in.)	Shortening $1\frac{1}{2}$ in., rigid; walks fairly well
Leather splint	Knee swollen; wasting, pain, movements of knee good	Knee normal, no difference on two sides; general health improved

they are better than I have myself been able to obtain in the treatment of tuberculous disease of joints by other methods without the aid of vaccine therapy. I do not deny that there may be some surgeons who will be able to prove to you that their own results by the usual methods—splinting, &c.—have been better than those I have detailed to you. An especially expensive form of splint, a special form of operation, a particular brand of iodoform—any of these may have given better results than those I have described. But it is my belief that the cases I have quoted to you, and of which details can be found,¹ show better results than do cases treated solely by the previously accepted surgical methods.

I see that the discussion is, amongst other things, on the limitations of vaccine therapy. That there are limitations no one will, I think, deny. I will speak for a moment of the surgical limitations. Vaccine therapy cannot give rest. Rest is as essential as it ever was in the treatment of tuberculous joints. Failing rest, the patient will be getting inoculations from his own joint, and inoculations given by the vaccine therapist are likely, therefore, to be interfered with, and their effect ill-regulated. Further than that, one may increase the opsonic power of a patient's serum with vaccine, but one cannot make that vaccine penetrate to the middle of a tuberculous abscess. I know tuberculous abscesses may sometimes clear up under vaccine therapy—they sometimes clear up when not treated at all—but, generally speaking, when an abscess is present the surgeon is necessary. The formation of masses of inert material I regard as being a cause of one of the limitations of vaccine therapy, and so masses of carious bone in tuberculous disease are a cause of limitation of vaccine therapy. In other words, precisely those cases which it is difficult for the surgeon to get well, such as discharging sinuses leading down to bare bone, are the cases in which vaccine therapy finds the most difficulty. It is exactly as one would expect—the vaccine therapist is not starting a new means of cure, but only accentuating what is Nature's own cure—one would therefore expect him to meet with the difficulties that the surgeon does. Without discussing the question of the methods of administration, I would take exception to Dr. Latham's experience, that inoculation has had to be discontinued on account of the fear of the needle puncture. With the needles I have seen used there has not been that necessity, and I cannot call to mind that I have seen children cry to the extent necessary to cause even a fond mother to take them away from the vaccine therapist.

¹ *Brit. Med. Journ.*, 1909, ii, p. 1047 (*vide* Tables herewith).

In conclusion, I would say once more that it is a matter of regret to me that I have not heard surgeons speak here whose ideas have been based on their observation of cases which have shown that vaccine therapy is of no service. But so far, Achilles and his friends have remained in their tents, so I have only to tell you what has been my experience of the results of dealing with tuberculous joints by means of vaccine therapy.

DR. ALEXANDER FLEMING: Most of the speakers, up to the present, have treated vaccine therapy in a general way, and have not confined their remarks to any one particular disease or organism. I wish, however, to refer only to one disease—namely, acne vulgaris. I do this because it is an exceedingly common disease, to which I have paid a good deal of attention, and although often ignored and untreated, yet causes very great worry to many individuals. It is a disease, also, where the lesions are very superficial, and one can readily see the effect of treatment without having recourse to any other method of examination than simple observation. It is interesting, also, because of certain diverse views which have been held as to the bacteriology of the condition, and in this respect it instances very well one of the limitations mentioned by Sir Almroth Wright—namely, that of “deficient bacteriological knowledge of the infection.” For some years after vaccines came into more or less general use acne was treated with vaccines of staphylococcus with a fair measure of success. In most of the cases the administration of staphylococcus vaccine diminished the severity of the pustulation or removed it entirely. There were other cases, however, which showed absolutely no improvement with this vaccine, even when it had been administered for a very long time, while a third class of case improved for a time and then relapsed. When we came to inquire more closely into the bacteriology of acne the reason for this seemed fairly clear. The basis of the acne pustule is a comedo which has for many years been associated with a bacillus which has been called the *Bacillus acnes*. This bacillus is very common on the skin of all seborrhœic individuals, and can be seen in myriads if a film of a comedo be made. While authorities are more or less agreed as to the micro-organism of the comedo, there is some difference of opinion as to the causation of the pustule. The large numbers of staphylococci which are present in the pus from some lesions, together with the results of vaccine treatment with staphylococcus vaccine, make it quite clear that

in many of these cases there is a staphylococcic infection, but in some cases the condition is very different. Here staphylococcus vaccine has almost no effect on the pustulation, and on examination of the pus one finds time after time only acne bacillus present in the films, and on cultivation a pure culture of the acne bacillus is obtained repeatedly. Only last Friday I planted out the whole contents of six pustules from one patient on six agar tubes (on which staphylococcus, if present, would flourish). These tubes were incubated until this morning (five days), when, on examination, five were sterile and the sixth showed two colonies of staphylococci. On a previous occasion two pustules had been planted out on a medium suitable for the growth of the acne bacillus. Of these one gave a pure culture of the acne bacillus and the other showed one colony of staphylococcus amongst hundreds of acne bacillus colonies. This seems to me clear proof that the acne bacillus is responsible for the suppuration in some of the cases. Further proof is obtained by the results of administration of vaccines of the acne bacillus, and I propose to illustrate the effect of treatment by reference to one or two cases.

The first case treated with a vaccine of the acne bacillus was a woman who had had very bad pustular acne on the face and shoulders for many years. She had been having staphylococcic inoculations at intervals of ten days for about a year. The condition had improved at first, but for some months had been practically stationary. She then had the same stock staphylococcus vaccine, combined with 20 million acne bacillus vaccine. This was followed by the appearance of fresh pustules. Ten days after she had another inoculation, this time of only 10 million acne bacillus, and she had regularly inoculations of the same dose of staphylococcus that she had previously been having, with 5 to 10 million acne bacilli. In three months almost all trace of acne had disappeared.

Another case was that of a man who suffered from pustular acne for many years. He had been treated off and on for two years with staphylococcus vaccine without any change in his condition, and examination of the pustules showed staphylococcus to be present in only very few, while the acne bacillus was repeatedly isolated in pure culture. In about six weeks under treatment with a vaccine of his own acne bacillus the condition had practically cleared up.

For the most part we have used stock vaccines of staphylococcus and acne bacillus in the routine treatment of our patients, but some cases will be found who do not improve much until a special vaccine of their own acne bacillus is administered. This is illustrated by the following

case: A girl, aged about 26, had had very bad pustular acne on the face for ten years. Her face was covered with large, indolent pustules. For three months she was treated with mixed stock vaccines of staphylococcus and acne bacillus with hardly any improvement. Then for the stock acne bacillus vaccine there was substituted a vaccine made from her own acne bacillus, and in four months the pustulation had almost entirely disappeared from the face.

Dr. Whitfield, at the last meeting of the Society, criticized some of the stock vaccines of the acne bacillus which have been used, on the ground that they were made of bacilli isolated aerobically, whereas he stated that the acne bacillus was an obligatory anaerobe. That the acne bacillus prefers anaerobic conditions is perfectly true, but I think Dr. Whitfield's criticism must break down in view of the fact that he has recognized as a true acne bacillus a culture isolated aerobically and grown through many generations in the presence of air for at least a year.

Dr. T. J. HORDER: If I consider the three points governing this discussion in the order of the increasing difficulty they present to me, I shall speak first of the *value* of vaccine therapy, then of the *administration* of this principle of treatment, and lastly of its *limitations*.

(1) Not that a consideration of even the first of these points is at all simple. The therapeutic argument is always difficult, indeed it is the most difficult in medicine. The difficulty is due almost entirely to the absence of proper controls in the particular experimental treatment that is being undertaken. How can this difficulty be got over in the present instance? In the individual practice of any one of us, however large, probably not at all. In hospital practice it should be possible, provided those in charge of the patients are willing to co-operate. One physician or one surgeon might well treat groups of patients on the principle of vaccine therapy, whilst another treated similar groups by other methods. I fear it is almost too much to propose not only that individual members of a hospital staff should co-operate in this way, but that some arrangement might be made by which all the patients in one hospital, suffering from a disease for which vaccine therapy makes claims, should be allowed to act as controls for all the patients suffering from the same disease in another hospital. And yet until something of this sort is attempted it would seem that the value of vaccine therapy can never be put upon a sound scientific basis. Until now little or no effort has been

made to apply the statistical method to vaccine therapy. The prophylactic use of typhoid vaccine is the only example of the use of vaccines in which scientific proof of their efficacy exists. In this failure to advance the question we are now discussing the clinician is doubtless much to blame. Some smaller matters might be investigated on the lines of comparative analysis: the duration of stay in hospital of patients suffering from such a disease as, say, gonorrhœal rheumatism, when treated by vaccine, might be contrasted with the duration of those not so treated. But, of course, to make conclusions of any value along this line of investigation, the number of cases dealt with must be considerable.

Failing the application of scientific methods in this question to human diseases, one wonders not a little that the chief advocates of the principle of vaccine therapy, if they believe it to be a very great asset in medicine—a belief to which I myself fully subscribe—have never undertaken a series of animal experiments which might prove their contention. This should not be very difficult, and the problem of controls would find easy solution. Not only would it be possible to compare the recovery or otherwise of a series of animals suffering from a local or from a general infection, treated by appropriate vaccines, with a control series similarly infected but receiving no assistance from vaccines; it would also be possible to test that vexed question, the value of the opsonic index as a guide to the choice of dosage. One series of animals might be treated according to the opsonic hypothesis, and another series might be treated without this guide. Two years ago, in conjunction with Dr. Andrewes, I carried out a series of experiments on rabbits with a view to ascertaining the prophylactic value of vaccines in pyogenic infections, and also to determine what was the effective range of dosage for such preventive purposes. But I do not know of any similar experiments on the lines of curative vaccine therapy.

Scientific proof as yet lacking, we are thrown back upon impressions, and these are very largely impressions based upon individual cases. The great triumphs of vaccine therapy are so often seen in atypical cases of disease, where comparisons are impossible. None of us at present, it seems to me, can do more than record his own impressions; to recite long lists of detailed cases really avails little or nothing. I suppose few practitioners exist in England to-day who have not seen many tediously chronic cases of infection, and not a few desperately acute ones, commence a state of speedy recovery after the use of vaccines (At least, I had so supposed, before hearing, in the course of this

discussion, that much doubt still exists on this matter.) My own experience includes so many such cases that my impression of the great value of vaccine therapy is a very deep one—so much so that I should consider I was denying patients suffering from certain infective conditions one of their best hopes of recovery if I did not employ this principle of treatment.

(2) I had thought the question of the *administration* of vaccines would raise such matters as preparation of the vaccine, the choice and time of dose, the route by which the vaccine should be given, and other important points. In this discussion, however, administration seems to have signified matters of medical politics, and to have raised the question of certain difficulties that exist in getting the principles of vaccine therapy properly tested. A note of discord has been sounded by the bacteriologist, who complains that the clinician has not responded with alacrity to the invitation to try the new treatment, that he has put obstacles in the way of the treatment, and that he denies its value. The bacteriologist has piped and the clinician has not danced. I have not myself found the practitioner tardy in availing himself of the benefits of vaccine therapy in the efforts made at curing his patients. But if this be the experience of certain bacteriologists, are there not some reasons for the fact that the clinician has not everywhere come quickly into line? The original claims of the bacteriologist in this matter were too extravagant; they almost attained to the level of an obsession. Here was a panacea at last. No need now for fresh air in the treatment of tuberculosis: London slums would serve, provided tuberculin and the opsonic index were available. The surgeon's art would shortly be defunct. Even cancer promised to yield presently to the "immunizator's" power. But to-day the phthisis sanatoria are full, and some of the inmates are sent by "immunizators" themselves. And I see no sign of diminished activity amongst surgeons. The pseudo-bacteriologist (as Dr. Bulloch aptly calls him) arose, too often bearing the hall-mark of correct training, with his glib and parrot-like repetition of all the master's phrases. This imitation was pardonable; but he spoke of "streps." and "staphs." and "gonos.," and of "coli infections," as though, holding such a sway over life and death, there was now no time for ordinary language, nor need of any grammar; knowing the innermost secrets of disease whilst as yet his contemporaries were perusing a temperature chart or undertaking a blood-count. Here was a spectacle little likely to impress the clinician. I have often been amazed at the tolerance and patience with which experienced practitioners still meet this young man in

consultation, or submit their material to him for expert examination and advice.

Then, again, consider this new departure of substituting the name of an infecting agent for a disease. Can this be an advance? asks the clinician. "What is the matter with Mrs. X.?" "Oh, *Bacillus coli*; she wants a course of vaccine." I was recently asked my advice as to the employment of a very expensive course of inoculation for a febrile patient, and the only answer I could get to my inquiries as to the nature of the disease was "*Bacillus coli*." Even the seat of infection was not known, and no proper clinical examination had been carried out. The cultivation of a specimen of urine and an opsonic index had covered the whole field of diagnosis, and the treatment would doubtless have been embarked upon with confidence but for the fact that abdominal palpation easily discovered a large retroperitoneal sarcoma. The bacteriologist speaks too often only in terms of the infecting agent, and hence his calculations often miss fire. The clinician knows that the disease is greater than the infecting agent, for it is the interaction between the infecting agent and the tissues.

This brings me to the change of front that has occurred in connexion with the opsonic index. Five years ago, and even later, it was taught that opsonic-index estimations were essential to vaccine treatment; indeed, without opsonic-index estimations it was held that he who used vaccine therapy acted dangerously, almost criminally. But to-day what do we find? The facts of vaccine therapy have outgrown the hypothesis of the opsonic index—a big argument in favour of the efficiency of vaccines. Many who originally held that the opsonic index must control the treatment, themselves employ vaccines in large numbers of cases, successfully, with no such mechanical control at all. I think they explain this by saying that the opsonic index has taught them what doses to give in certain cases. The clinician considers himself justified in rejecting this explanation. The cases are never sufficiently alike. If the index was necessary once, it is necessary now. Moreover, experience has led the opsonist to change his doses; yet his curves change not. Wholesale chemists are now supplied by bacteriologists with vaccines which are sold to the profession with an advertisement stating that the use of the remedies is quite safe, and that good results may be obtained without opsonic controls. What is the clinician to make of this? The bacteriologist would seem to have solved that old problem of our boyhood—how to have our cake and eat it too! Altogether, I do not think it is surprising if the clinician is tardy in

handing over his cases of infective diseases to the bacteriologist for treatment.

To the further question, "Who should undertake the treatment of these cases—clinician or bacteriologist?"—surely there is but one answer. However sound a bacteriological training the young clinician has had (and this training must be regarded as an essential part of his education), this does but enable him to appreciate early the cases suitable for vaccine treatment and to collect his materials skilfully. If the clinician cannot collect his materials skilfully the sooner he learns to do so the better. But he needs the help of the expert bacteriologist to proceed past this point and carry out successful treatment. It is only now and again that it is justifiable to impose both clinician and bacteriologist directly upon the patient. Be this so or not, I think (seeing that fleshpots have been mentioned) the bacteriologist deserves, and should receive, his half of the credit, and of whatever else there may be to divide. But if the bacteriologist asks for more than this, I think his claims are unreasonable. When he appeals to the layman in the guise of physician, and describes himself as such in public directories, I regard him as much more dangerous than the clinician who affects a studied interest in the problems of bacteriology in their relation to the treatment of his patients. The sight of a physician unversed in bacteriological methods, faced with a case of obscure fever without physical signs, is no more pathetic than that of a bacteriologist emerging from his laboratory, his clinical medicine hopelessly rusty, attempting to struggle with the same case. The prophecy has gone forth: The physician of the future will be an immunizator. I think that prophecy likely to be fulfilled, but I would fain add: Let not the immunizator cease to be a physician.

(3) On the question of *limitations* I have little to say. Previous speakers have, in this discussion, seemed to deal with somewhat artificial matters rather than with the natural boundaries to the field of useful action of vaccines. Personally, I have found few or no *artificial* limitations imposed either by clinician, bacteriologist, or patient. I regard the doctrine of the opsonic index as the great, almost the sole, artificial limitation to the use of vaccine therapy. I stated this opinion now nearly four years ago, and am more convinced than ever that this doctrine is the greatest incubus to our advance in knowledge of vaccine therapy. Once the bacteriologist opens his windows and realizes that the condition of the patient, and not the state of the opsonic index, is the real test of treatment, we shall see much greater triumphs for this principle of therapeutics than we do to-day. As regards *natural*

limitations, I do not think these can be defined until the principle of vaccine therapy has had a much longer trial than is the case at present. Of some *difficulties* which I had hoped would be discussed, and which have raised questions in my own mind bearing on the natural limitations of the method, I will merely mention three or four.

(i) *The lack of some standard of virulence of the vaccine* is one difficulty: I find it a very great one. Particularly is it a great difficulty in dealing with such micro-organisms as the gonococcus, the pneumococcus, and Pfeiffer's bacillus. The variation in virulence seen in different strains of these and other micro-organisms renders tables of appropriate doses of vaccines prepared from them quite useless in practice.

(ii) *The ideal to be aimed at in the matter of freeing different parts of the body from micro-organisms* is another difficulty. Here, again, we want more statistical knowledge. A few *Bacilli coli* in the urine of a constipated patient, or in a patient suffering from diseases quite independent of colon-bacillus infection, are, I think, too often regarded as enough evidence upon which to base a diagnosis. If some recent work of Conradi's is confirmed, it would appear that not only certain mucous passages but also the solid organs of the body are, in health, constantly being invaded by small numbers of micro-organisms, *Bacillus coli* and *Streptococcus faecalis* especially, and that these are as constantly being killed. A continual hammering away at the tissues by these and other micro-organisms is always proceeding. If this be so, are we right in believing that this occasional presence of micro-organisms necessarily means disease, or that we can hope to chase away all micro-organisms by vaccines?

(iii) A third of my difficulties is *the question of recurrences* in such conditions as boils and pustular acne, after prolonged courses of vaccine treatment. I have seen several such cases. And not staphylococcal cases only; the same thing happens in pyorrhœa alveolaris (*streptococcus*) and pyelo-cystitis (*Bacillus coli*)—and the response to vaccine therapy becomes less and less marked each time. What, then, is the net result of the treatment to our patients? Have we permanently weakened their resistance by the employment of artificially-introduced antigen, or are the recurrences quite independent of our treatment? I only mention this matter as one worthy of consideration.

I will conclude by a statement of my opinion that vaccine therapy is an effective method of combating an important factor—it may be the most important factor—in the struggle between the tissues and many

infecting agents. I believe, however, there are other factors in this struggle which are not touched by the use of the vaccines, and that this natural limitation to the use of vaccines does exist, though at present the limitation is quite undefined.

Dr. D. W. CARMALT-JONES: I am deeply sensible of the honour of being invited to take part in this discussion, and I recall that I was asked to say what little I have to say from the point of view of a clinician. I have heard in this discussion that a clinician is a person who relies on his unaided senses for his diagnosis, and that clinical medicine is an inferential art. The latter statement is true; but if it is an accusation, it comes strangely from a bacteriologist, who mixes bacteria serum and leucocytes together, and on the degree of phagocytosis resulting makes a diagnosis of a particular infection. If that is not inference, I think we have yet to learn what inference is. With regard to the clinician and his unaided senses, that statement is true. A clinician does employ simple methods, but he employs them upon every physiological system of the body, and he claims, and I think justly, to be able to determine by these methods whether each system is performing its functions within the limits of health, and which, in any syndrome, is the system primarily at fault. The essential point is that when he does his work thoroughly he examines every system, and knows enough about each to decide when a specialist's opinion is required. Now the lay public have some such opinion as this about their family physician, and as long as they have that opinion, to their family physician they will go, and it will be for him to decide whether a given disease is an infection and whether a skilled bacteriologist's help is required or no. The only alternative is for the public to go direct to the bacteriologist. Let us consider some of the consequences. A man suffers from attacks of abdominal pain; he consults a bacteriologist, who infers an intestinal infection, and spends a fortnight in separating organisms from fæces, with one of which he ultimately inoculates the patient. When the patient gets tired of the novelty he consults a clinician, who makes use of his unaided senses, and finds that the patient's pupils are inactive to light, and that no knee-jerks can be obtained. On the strength of this he places the lesion not in the gut but in the central nervous system, and introduces appropriate treatment. Now surgeons make mistakes like this sometimes, and surgeons are reputed clinicians: how much more will they be made by those who hold physical examination in contempt?

When a clinician has diagnosed a lesion of an organ, probably bacterial in origin, is there any reason why he should adopt vaccine therapy in preference to other methods of treatment? The reason is this: that he has otherwise no means, medicinal or other, of directly attacking bacteria in the tissues. Take such a condition as chronic bronchitis; this is a bacterial infection, and though you may relieve the frequency of the cough, promote expectoration, and relieve dyspnoea by means of drugs, you thereby do absolutely nothing to get rid of the invading bacteria and so cure the condition. The truth of this will be made abundantly plain by a walk through the out-patient hall of any large hospital between the months of October and March; and it is the cause of the profound lack of conviction with which I, for one, embark on the treatment of such a condition by means of drugs.

It has, however, been discovered in the course of the last few decades that the animal organism has the power of making antibodies to any foreign albuminous substances introduced into it, which neutralize or destroy the foreign substance. Further, these bodies are produced in excess of the amount required to neutralize the stimulus, so that the blood of animals so treated contains antibodies, some of which can be demonstrated by suitable means. Now bacteria are such foreign albuminous substances, and the phenomena of recovery and acquired immunity are thus explained, and it appears that when a disease does not end in recovery, but becomes chronic, the mechanism of immunity has broken down; but that if the infecting bacteria, killed to prevent spread of infection, that is in the form of a vaccine, are introduced into a part of body which has not been exhausted, new antibodies will be formed in excess of those required to neutralize the vaccine, and these will pass into the blood stream and be available against the chronic infection. The value of the method is that it can be counted upon to produce a certain effect, and is not an empirical remedy. Fibrolysin, for instance, is a drug much employed of late, and its friends claim great results from it, doubtless with justice; but we are quite ignorant of how it acts. As far as we are concerned, it is merely a fortunate accident that it produces the results that it does; whereas by means of vaccine therapy we are stimulating a physiological property without which life would be insupportable in a bacteria-infested world. This is the great difficulty in the way of accurately gauging the results of a treatment which consists in stimulation of the natural powers of recovery, so that much heart-burning arises over the question of whether a given improvement was spontaneous or induced.

These, then, are the reasons which have weight with clinicians with regard to the value of vaccine therapy.

The next question for the clinician is, how this method, so obviously satisfactory in theory, works in practice. In the course of this discussion some eminent clinicians have reported their results, which are sufficiently brilliant. We have, I think, heard at this conference what may be called the extreme case for vaccine therapy. We have heard of case after case snatched from the jaws of death; we have heard of striking benefits conferred on sufferers from diseases not primarily bacterial, such as cancer; even such an unpromising field as miscarriage has not proved sterile. I think nothing that I could say would add anything to this weight of evidence of what is attainable by vaccine therapy. In fact, I think it is high time for quite a different note to be struck. It is very likely that practitioners who are unacquainted with the method have attended these meetings, in order to learn what they may achieve thereby. I can imagine such persons leaving this conference under the impression that immediate success in the most desperate cases is assured if they can only obtain appropriate vaccines; they might even doubt if there was such a thing as failure. I do not suppose for one moment that that is the impression which the speakers intended to convey, but I do think that it is one likely to be left on the minds of an inexperienced audience. Well, I have been associated with St. Mary's Hospital Inoculation Department for nearly four years, and I have seen some remarkably fine results; but no impression of such unvarying success is left upon my recollection, and I fear that anyone who embarks upon vaccine therapy in that hope is laying up for himself considerable disappointment.

Last year I published in the *British Medical Journal* the results obtained in 367 consecutive cases of chronic tuberculosis treated at St. Mary's Hospital. I found that in tuberculous glands, 1 case in 3 was cured, and 5 in 8 much improved; of tuberculous ulcers, 1 in 5 was cured, and 3 in 5 much improved; of tubercle of the genito-urinary tract, 1 in 5 was cured, and 3 in 7 much improved; of lupus, 1 in 8 was cured, and 1 in 2 much improved. Considering what tubercle is, I think these results are extremely good and most encouraging. In the glands, for instance, there were 79 cases; 27 were cured, and 22 were much better. And these were bad cases: more than half had been operated on, some as many as ten times. Now the treatment of these cases lasted from six months to about two years, and sometimes longer, so a good deal of patience and perseverance is required to attain these results; but I think

they are such as anyone might hope to attain by taking sufficient trouble.

I think some very obvious limits are set to the usefulness of purely antibacterial treatment in disease, particularly in such a disease as tuberculosis, in which large areas of necrotic or caseous tissue occur. No blood-vessels pass through such tissue, and blood-serum containing fifty times the normal amount of immune bodies would produce no effect upon it; and, whenever practicable, it should be removed. Sir Almroth Wright did not lay stress on this point in his opening address, but he has done so on many previous occasions, and has demonstrated that pus from an abscess is poorer in protective substances than the circulating blood. I think it may be laid down as an axiom that all sources of irritation should be removed at the outset of treatment. Vaccines have no power whatever to remove them, and they must be removed by surgical methods. In cases of glands in the neck, carious teeth or pediculi must be removed, sequestra must be removed from ulcers, stones from bladders; the presence of these foreign bodies damages the tissues and lets in the infecting organisms, and unless these are removed it is quite unreasonable to expect a cure. Bacteriologists, I venture to think, are apt to overlook these points; it remains for a clinician given over to inspection and palpation, and such-like pharisaical observances, to make reasonable suggestions with regard to other methods of treatment. Dr. Bulloch told us with immense pride of a case of breaking-down glands in which he had suggested letting out the pus. To a clinician it appears merely common-place; the first piece of clinical work which the trembling fingers of the casualty dresser are allowed to perform is to stick a knife into an abscess to evacuate the pus. The reproach is raised that this is surgery. Of course it is surgery, and surgery is essential to the success of many cases under inoculation treatment. The same applies to some remarks of Dr. StClair Thomson at the opening meeting. If a nasal sinus is full of pus, no amount of inoculation will remove that pus—the case requires, as he puts it, not a gardener, but a plumber—but the removal of the organisms embedded in the mucous membrane within reach of the tissue fluids depends on the development of protective substances, either spontaneous or induced. At a recent meeting of the Odontological Section of this Society the use of vaccines in pyorrhœa alveolaris was under discussion, and several gentlemen regretted that no cases were recorded in which inoculation had been the only method employed. To ask for good results under such conditions is to ask

for the impossible. The mouth is a septic cavity, and teeth coated with tartar and impregnated with organisms must reinfect the gum. Inoculation will only touch the deep-seated organisms, the superficial ones must be treated by local antiseptic remedies.

The days of miracles have gone by; we no longer pour water over our sacrifices and expect fire to come down from heaven to consume them. Inoculation cannot be expected to succeed in the presence of dead tissues; surgery and medicine cannot deal successfully with chronic infections in which natural immunity has broken down. Leaving entirely out of account the value of proper clinical treatment of symptoms, we may feel fairly convinced that the best results will be attained by an intelligent collaboration of the clinician and bacteriologist, each having a wholesome respect for the province of the other.

DR. F. RUFENACHT WALTERS: My experience of vaccine therapy is almost entirely confined to the treatment of cases of pulmonary tuberculosis or phthisis in a sanatorium. Many of these recover promptly and satisfactorily under the ordinary sanatorium methods, but there are many others that do not do so. In many cases the fever persists or recurs, and the treatment is therefore exceedingly tedious and apt to lead to much destruction of lung tissue. These I now believe to be chiefly, perhaps entirely, cases of mixed infection. Here one requires something more than the ordinary hygienic methods adopted in sanatoria. Treatment by antipyretics is apt to be disappointing, and I think it is especially in this class of case that vaccine treatment is likely to be of considerable service. Until comparatively recently, owing to considerations of expense, it was only exceptionally that I employed vaccine treatment other than tuberculin; but lately I have been treating all the obstinate cases, and all those with high fever in which the existence of mixed infection was proved, with corresponding vaccines. My results are, to a very large extent, too recent to deal with now; I shall have to leave many to a future occasion. Tuberculin, however, I have been using for longer, chiefly in small fractional doses ($\frac{1}{100000}$ mg. to $\frac{1}{10000}$ mg. of T.R.). As far as my experience goes, one is likely to get satisfactory results in the vaccine treatment of cases infected with *Staphylococcus pyogenes aureus* or pneumococcus. My experience with *Staphylococcus albus* vaccine has been disappointing.

I may mention a rather striking instance of vaccine treatment for *Staphylococcus aureus* infection dating from 1906. A medical man,

aged 42, came under my care in April, 1906, with extensive lesions in the left lung and slight damage to the right upper lobe. Pulmonary tuberculosis had been present for fifteen months, and he had had during the year before admission two attacks of hæmoptysis, two of influenza, diphtheria, right pneumonia, and finally whooping-cough, which caused his final breakdown. The pneumonia does not appear to have damaged the right lung to a noticeable extent, and in spite of his repeated illnesses he kept at work most of the time until Christmas, 1905. On admission there were many râles after cough from the second rib anteriorly nearly to the base, marked friction above and inside the cardiac area, slight dullness in the left supra-spinous and upper inter-scapular regions with deficient air-entry, but no adventitious sounds there even on cough. Both bases were resonant. The temperature on admission ranged between 100° F. and 102° F. *per rectum*, and, in spite of complete rest in bed, rose more and more, until it rushed up on June 3 to 106.4° F. At this time the consolidation of the left lung extended downwards to the eighth rib behind and the cardiac area in front, with diminished breath sounds and a few râles, while at the side there was a basal patch with dullness, diminished vocal fremitus, but no tubular breathing or cardiac displacement—i.e., the signs were those of tuberculous rather than of pneumonic consolidation. There were also a few râles at the right base, front and back. A culture was made of the sputum, revealing pneumococcus and *Staphylococcus aureus* as well as tubercle bacilli. The opsonic index was nearly normal against pneumococcus, fluctuating against tubercle, low against the staphylococcus. A vaccine was prepared of the latter, and in the meantime a dose of tuberculin ($\frac{1}{20000}$ mg. T.R.) was injected *sub cute*. The temperature rose in six days to 105.2° F., after which it began to subside. Two doses of the staphylococcus vaccine (20 millions each) were given at intervals of about a week; and within three weeks the temperature was almost normal, with a corresponding improvement in the physical signs in the lungs. There were therefore eleven weeks of high fever, brought down within three weeks by one dose of tuberculin and two of staphylococcus vaccine.

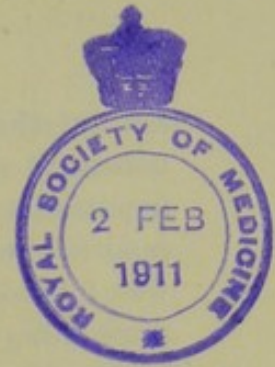
I am not now in the habit of giving so large an initial dose of tuberculin as $\frac{1}{20000}$ mg. T.R.—at all events, where marked fever is present—although it did no harm in this case. Some people are of opinion that highly febrile cases of tuberculosis should not be treated with tuberculin, believing it to be a dangerous practice; but such is not my experience. I think it is very largely a question of dose. Dr. Latham has pointed out that the appropriate minute doses of tuberculin will bring down

temperatures in febrile tuberculosis, and I can confirm this. I think, if you start with a tiny dose, and feel your way—I am in the habit of relying partly on the opsonic index and partly on other considerations—you will find a dose which will reduce the temperature. It is a familiar fact to those who have used tuberculin that a certain dose of tuberculin will raise temperatures; but it is not sufficiently recognized that an appropriate dose will reduce temperature. Personally I have found that a tiny dose of $\frac{1}{120000}$ mg. T.R. to $\frac{1}{80000}$ mg. will cause a lowering of temperature next day, and, according to the dose, this lowering of temperature will persist for one day or more. The same may be said of auto-inoculation by exercise. We know the effect of railway journeys and over-exertion in precipitating an attack of high fever in a tuberculous patient. We do not realize enough that a judicious increase of exercise may have an opposite effect—namely, in reducing the temperature. I have had cases in which a patient has gone up to see a consultant in London, and the effect of the journey has been to bring down the temperature to some lower level. I have kept the patient at rest next day, and presently he had better temperatures and could take more exercise than he had been able to take before the visit. I do not think it can be attributed to the cheering effect of the consultation, but that the railway journey had something to with it, through auto-inoculation; and I can point to other cases in which an extra long walk has had a similar effect. We all know that an injudicious increase in exercise in tuberculosis may very easily raise the temperature for some weeks to an undesirable extent; and therein lies the value of strict rest in bed where a phthisical patient is suffering from high fever; but I have had cases under my care in which the fever has persisted for months, and only subsided when the patient has been allowed to be out of bed for a short time—at first every few days, later on every day. This is exactly comparable with the effect of doses of tuberculin. There are, I believe, two classes of cases in which tuberculin is likely to be of service—those in which even the slightest exertion causes an overdose of auto-inoculation, and those in which a large amount of exercise has but little immunizing effect.

Another point is the administration of tuberculin by the mouth. I have seen several cases in which the method has been most successful, and many in which it has done some good without any ill effects. But there are two drawbacks which are sometimes met with. There are cases in which it causes digestive disturbances, such as pain in the abdomen and nausea; another drawback is the uncertain effect of a

given dose. I had a patient to whom doses were given by the mouth gradually raised from $\frac{1}{40000}$ mg. to $\frac{1}{5000}$ mg. of T.R. They did not seem to have any effect, and I was doubtful whether they were large enough; they caused no febrile reaction or constitutional disturbance. I decided to give a few doses subcutaneously; and, relying on previous experience and the counsels of others (such as Dr. Latham) who have had a larger experience of mouth administration than I had, I gave $\frac{1}{10000}$ mg. *sub cute*. There was, however, a violent reaction, the temperature rising to 103.6° F., and for three weeks there was much more fever than was desirable. Then I gave $\frac{1}{120000}$ mg. *sub cute*, and even this caused a reaction to over 103° F. In this case a large proportion of the tuberculin was probably not absorbed from the alimentary canal, so that the effect was almost nothing, while the dose by the mouth was no guide to the required dose *sub cute*.

In conclusion, my own impression is that it is a mistake to regard phthisical cases as merely cases of pulmonary tuberculosis. For some reasons it is a pity that the old term "phthisis" is discountenanced. In some ways it gives a truer impression than the modern name. In many cases the infection is a mixed one, when it seems to me that the best treatment is a combination of all the appropriate recognized remedies, hygienic and medicinal, together with vaccine treatment, directed both against the tuberculosis and the associated organisms.



Royal Society of Medicine

June 15, 1910.

Dr. J. MITCHELL BRUCE, Vice-President, in the Chair.

Discussion on Vaccine Therapy: its Treatment, Value, and Limitations.¹

MR. W. DEANE BUTCHER: The subject which I wish to bring to your notice is the "Production of Auto-vaccination by Electrical Methods." I do so with some diffidence, since it is outside the lines of the previous discussion, and I fear, in the time at my disposal, I may not be able to throw much light on this somewhat obscure subject, which is, however, of the deepest interest to one of your Sections, and, I believe, of growing importance to all.

The hypothesis of electro-vaccination, or radio-vaccination, has gradually grown up to account for a number of phenomena otherwise inexplicable. The evidence in any one direction is not very abundant or very conclusive, but the cumulative evidence along various converging lines is, I think, considerable. The first thing that led to the suspicion of the possible vaccinal action of the Röntgen rays was the fact that a number of skin diseases of totally different origin and nature seemed to improve under exceedingly small doses of the irradiation. Psoriasis, lupus, eczema—all were apparently benefited. An acne that had resisted treatment for years would disappear under the rays, just as if the case had been treated by the injection of a vaccine. What more

¹ Fifth meeting (adjourned from June 8).

natural than to suppose that the patient himself had furnished the necessary vaccine, under the stimulus of the Röntgen irradiation? The hypothesis received still further confirmation when cases of lupus were reported in which an irradiation of one region—the leg, for example—was followed by improvement in another region, such as the face. The same thing was observed in other diseases. Acne of the face was cured by X-ray and high-frequency treatment applied to similar lesions on the back and shoulders; high-frequency effluves applied to a crop of boils would apparently render the patient immune to further inoculation; lupus erythematosus of one region was influenced by X-ray treatment of an adjacent part, and even widespread carcinoma of the breast was influenced by irradiation of only a portion of the affected area. The hypothesis received further corroboration from the observation that in certain cases of lupus, and even of cancer, irradiation of the affected glands was followed by an improvement in the lesion itself.

Let me give you a few instances to show the sort of evidence on which we base our case. They are but impressionist sketches, but perhaps may give as accurate an idea of the facts as a more formal picture, duly authenticated by initials, dates, and curves:—

A young soldier—turned out of the Army as incurable—deeply pitted with variolar acne—face, neck, shoulders, and back covered with indurated nodules and suppurating abscesses. He is cured in a few weeks by X-rays and high-frequency effluves. No other treatment is given, either external or internal, and the abscesses are not even opened; they gradually shrink, the adjacent skin becomes dry and brawny; the fluid contents of the abscesses dry up, with the final evacuation of a tiny plug of inspissated pus. There is no further formation of pustules. The man is immune to staphylococcic infection.

A poor governess comes in much the same condition—pale, anæmic, half starved, with pustular acne of many years' standing. She is treated with high-frequency effluves—a mixture of sparks, X-rays, and ultra-violet light. The back and neck are chiefly treated, but the face also rapidly improves. The nodules disappear, the abscesses dry up, there is no further development of pustules: the case has been cured by electrical vaccination.

A young naval officer has been plagued all his life with slight acne. He is treated with two very slight irradiations by X-rays. The treatment is unexpectedly interrupted by his return to his ship. Nevertheless he is cured, and has no return of his life-long complaint. He has been rendered immune by radio-vaccination.

A nurse has lupus in the posterior nares, and begs for X-ray treatment, although she is told it will be absolutely useless. Only two small doses of X-rays are given, such as one would expect could hardly reach the affected region. Nevertheless the case is greatly benefited, perhaps cured.

A married woman is treated for psoriasis by X-rays, with the result that there is a premature menopause, and a menorrhagia of many years duration is cured.

One could easily add to these cases many others, to prove the profound influence of electric and radio-active treatment on the general organism. Even the ordinary process of Röntgen epilation appears to be a biological rather than a merely destructive phenomenon. It is, at least in part, a vital reaction—a phagocytosis, since it has been found that the process of epilation is more rapid in the diseased areas, and is delayed by the application of disinfectants, and the consequent depression of the processes of vital reaction.

But the strongest evidence of the vaccinal action of electrical treatment is derived from a consideration of the various modes of attack on rodent ulcer. In the whole purview of medicine there is nothing more impressive or more certain than the cure of a small rodent ulcer by electrical methods. But the cure may be effected in many ways—by Röntgen rays, by radium, by ultra-violet light, by the high-frequency effluve, or by zinc ions. What is the common factor in all these cures?—cure, I say, for the process is not one of destruction but of repair. It is not merely a bactericidal action, nor is it merely a selective destruction of tissue. It is a biological recoil—the resentment of the cells of the organism to the insult of the ethereal vibration. The habitual defence of living cells to such an insult is exactly the same as that to a bacterial invasion—namely, the production of an antitoxin or other antibody. It is a true vaccination.

I believe that Sir Almroth Wright is of opinion that the therapeutic effect of Finsen light and X-rays is in fact vaccinal in its nature, but that they act only by their congestive action, bringing a larger supply of lymph into contact with the diseased tissues. This is manifestly not the whole truth, as anyone may convince himself by contrasting the effects of Finsen light, of radium, and of X-rays on a lupus nodule. The supporters of our hypothesis maintain that the X-rays themselves assist in the elaboration of antibodies or the like, at the site of the irradiated lesion, or more probably in the adjacent glands.

Our hypothesis then supposes that the ethereal waves contribute to the process of auto-vaccination by the production of opsonins, by the detachment of the side chains of Ehrlich, by facilitating the reaction of toxin and anti-toxin, or by setting free the vaccine from its laboratory in the glands. This is rendered the more probable when we reflect that the toxin and anti-toxin carry opposite electrical charges, one flowing down and the other flowing up the electrical stream. Not only so, but we have recently had evidence that the micro-organisms themselves may be carried along an electrical current.

All this gives rise to more than a presumption that the therapeutic effects both of electro-therapeutic and radio-therapeutic treatment may be due to the production or liberation of vaccines. We knew that a glandular tumour of the neck would melt like snow before the Röntgen rays, but we did not know why. We knew that the X-rays could produce both *in vitro* and *in vivo* a cytolytic serum, or even a spermolytic serum, but we did not know why. We now begin to suspect that the common factor in all these phenomena is akin to that with which we are familiar in ordinary vaccination.

One of the greatest arguments in favour of the vaccinal hypothesis is the latent period which follows Röntgen or radium irradiation, and which precedes the reaction. This ominous pause is, to my mind, eloquent, and indicates that all the resources of the organism are being called upon to resent the insult. The reaction is not merely a physical or chemical one, but a biological reaction, in which the energy of the recoil may exceed the energy of attack.

Let me explain. If I strike this table, it returns the blow immediately, and strikes my knuckles with the exact force expended; whereas if I were to strike my neighbour he would probably return the blow with interest, an interest that would be rather increased than diminished by a brief period of latency. Similarly the pause after Röntgen or radium irradiation is proportional to the degree of the insult, and is a participation of all the complicated mechanism of organic resistance called out to oppose the electrical or ethereal invasion.

It is not the place here to advocate the practical uses of electrical treatment, but I do urge the use of radio-active and electrical methods as instruments of research in the study of vaccination. For this purpose I would most strongly urge the collaboration of at least three of our Sections—the Dermatological, the Pathological, and the Electro-Therapeutical. Such a collaboration is the special note, the very *raison d'être* of the Royal Society of Medicine. It is useless for a pathologist

to assert that X-ray or radium irradiation has no influence on the opsonic index, unless he is familiar with the practical methods of giving accurate and measured doses of the irradiation; just as it is useless for an X-ray specialist to report cases of cure which are not verified by the pathologist and the clinician.

I can only briefly allude to two recent developments of electrical treatment which may have a practical bearing on the production and control of auto-vaccination. These are the methods of "thermo-penetration," and that of "muscular exercise electrically produced." By the former method, that of thermo-penetration, we are able to produce a considerable, a definite, and an easily regulated rise of temperature in a deep-seated tissue, such as a diseased joint, a gland, or an internal organ. It is easy to imagine how potent a means of control this method may give us for the production and regulation of auto-vaccination, or the supply of lymph to a diseased organ. Still more important results may be obtained by the second method—viz., "muscular exercise electrically produced." This method, which has been largely used in the cure of obesity and the like, gives all the good results of muscular exercise without its attendant nervous and mental fatigue. I would venture to suggest that it should find its place in the treatment of phthisis by auto-inoculation, as it can be better regulated and is not so exhausting to the invalid as exercise produced by an effort of the will.

Time alone will tell if our surmises are correct. Much time must elapse before we can hope for a practical means of producing or controlling auto-vaccination by electrical means. If the vaccine theory itself is correct—if the production of antitoxins and antibodies is our only means of resisting bacterial invasion—then you will allow that the electrical method of exciting the resistance of the cells, of calling out the home-levies, the militia of the organism as it were, is a great advance on the cruder methods of vaccinal treatment by the injection of foreign-bred vaccines.

In one of his most eloquent passages the "Autocrat of the Breakfast Table" compares the organism to a seventy-year clock, locked and enclosed in its case, and laments the impossibility of influencing its machinery from without. "If anyone would only contrive some kind of lever that one could thrust among the works of this horrid automaton and check them, or alter their rate of going, what would the world give for the discovery?" Hitherto we have striven chiefly by chemical means to influence the cell life which swarms within the closed case of

the automaton. I venture to predict that in the future much more use will be made of the various ethereal undulations which so readily penetrate the case, in order to stimulate, by a sort of wireless telegraphy, that resentment of the cell community which we associate with the phenomena of vaccination.

Dr. H. LEWIS JONES: I have only to endorse Mr. Deane Butcher's very interesting and suggestive remarks. He has submitted ideas and experiences from the clinical side, but the phenomena clearly demand the study of the clinical pathologist. The technical difficulties of serum therapy and vaccines are considerable, and indeed the terminology of the subject is so difficult as to put these investigations out of the reach of the electro-therapeutic specialist. The observations which have been made by more than one observer on the healing of lupus in one part of the body after irradiation of a different part of the body have been received in the past with profound disbelief. These facts, if facts they were, demand an explanation. I have believed them, although unable to explain them, and Dr. Butcher has put forward an explanation which may prove the right one. That blood changes do occur after X-ray exposures is well shown by the action of X-rays in leucocythæmia, and experiments have also shown that leucocytes react to serum from an X-rayed animal in a way which differs from their response to normal serum. Even the irradiation of an isolated part, such as the ear of a rabbit, will suffice to set up general changes in the leucocytes of the general blood.

Dr. CRACE-CALVERT: I have only a few remarks to make this afternoon, and they are chiefly from the clinical aspect, and mostly in regard to cases of tuberculosis. I have now been working in connexion with vaccines almost from the beginning, in a sanatorium, and most of my experience is in regard to tuberculosis of the lungs. But I have had a few cases of other conditions, which I will mention later. I may, however, say that so far as I have gone, I have been very much impressed by the results of vaccination, using more especially the tuberculin emulsion (T. E.) in preference to T. R., which is often employed. Most of my cases I have selected because they were not doing well on ordinary sanatorium methods, and I have not therefore chosen many early cases; in fact most of the cases have been fairly

advanced, and cases which were largely stationary. They had improved to a certain extent under sanatorium treatment, and then they wanted, as it were, a fresh stimulus to enable them to complete the cure, using the word "cure" in the proper sense of arrest. In most of those cases I have found that the addition of tuberculin to sanatorium treatment has resulted in a stimulus to the case, so that the signs which previously had remained more or less stationary have tended to clear up and finally to disappear. I have noticed, I think, most of the signs which Dr. Latham and Dr. Inman mentioned in their papers—flattening of the temperature curve, decrease of the cough, lessening of the sputum, &c. I have had rather odd results at times, such as increase of sputum in one case and decrease in another, and I do not know exactly why, because it does not seem to depend quite on the dose. But the variation in the symptoms does not seem to have made any difference to the progress of the case, and I do not think it has depended altogether on the dose, but rather upon the patient. I have also inoculated a few of the early cases, and they have all done well. I do not think early cases of tuberculosis of the lungs are fair tests of the value of the vaccination, because with appropriate sanatorium treatment they nearly always do well without vaccination, and it is not fair to ascribe their improvement to the effects of tuberculin.

Just lately I have been doing what I think one is often told not to do, and that is, giving tuberculin in acute cases. I have had two or three patients with whom I was at my wits' end to know what to do; they were going downhill, the temperature rising and the physical signs increasing. In my first case every time I gave an exceedingly small dose there was at first a rise of temperature, but the result was extremely good, because that patient lost the whole of his physical signs; the temperature dropped to normal, he put on weight, and left the sanatorium with his disease arrested. He came back again four months later with typhoid fever and a serious relapse of his tuberculosis of the lung, the condition being mistaken for acute tuberculosis. The typhoid cleared off and his temperature dropped, but tuberculosis was left, and his temperature was rising again. I started him again on a very small dose of tuberculin, and he began to respond, and now the temperature is nearly normal. The physical signs have lessened and the cough and expectoration have almost disappeared, and he is apparently going to get well, though a larger area of lung was affected the second time. I have tried it in two other acute cases; one was a success, and in the other it made no difference. The point of that small experience

seems to be to show that a great deal depends on the dose. Tuberculin is very powerful, and if it is worked with in minute doses and given properly it will flatten the temperature chart and help to arrest the disease.

Lately I have not worked very much with the opsonic index, as I have given tuberculin and other vaccines by the mouth. That is not altogether because I do not believe in the opsonic index, but I have not time to work it out as I should like to. Much has been said against the opsonic index by those who have not been able to work at it properly. It means you have to stick at it, not only daily, but hourly, before you can be sure of accurate results. The first few cases which I worked at by the opsonic index gave very good results, and if I could I would do the same now; but my circumstances are rather altered, and I cannot give as much time to working it out as I should like. I have used vaccines with mixed infections, in tuberculosis and so forth, with very good results. There was one case in particular where a patient with slight tuberculous disease of one lung had a sudden rise of temperature to about 103° F., which took a week to subside, only to be followed a week later by another rise. This occurred three times, and then I obtained a pure culture of streptococci from his sputum and made a vaccine, which I gave by mouth, and he had no further attacks. But here, again, the number of cases treated has not been sufficient to warrant my speaking absolutely definitely, though in most of the cases I have achieved the result which I wanted—namely, to get rid of all the other organisms from the sputum, leaving the tubercle bacillus only. And where there has been an erratic temperature I have usually succeeded in bringing it down to normal. I have used a vaccine also for middle-ear disease, where the sole organism was the *Bacillus pyocyaneus*, and met with success up to a certain point. But just as the mischief was quieting down, the lady developed hay fever, and the trouble flared up again; the case is still under treatment. The vaccine has been stopped by the advice of the surgeon, but the ear is now discharging as freely as ever, and the organism is still limited to the *Bacillus pyocyaneus*. I had one case of cystitis where the infecting organism was the *Bacillus proteus*, and that has improved immensely by vaccinations with that organism. I had one case of tuberculous peritonitis which I treated with T. R. with good results, but in the one or two tuberculous-gland cases that I have vaccinated I have not met with much success.

To sum up, I am certain that in the case of tuberculosis of the lungs especially there is scope for a great deal of work to be done with vaccines, and I am sure that that work will repay the time and labour if the doses are used with care and not pushed unduly. Tuberculin is a powerful remedy, and so the doses must be very minute, but if it is used with judgment, especially in conjunction with sanatorium treatment to build up the patient's general condition and resistance, I feel sure that the results will repay us.

Mr. LEONARD NOON: I want to ask you to consider what is an ideal vaccine—what should be its constitution and what properties it should possess. As has been pointed out already in the course of this debate, a diseased animal receives into its system, from the site of infection, products which may be grouped under three headings: (1) The first of these corresponds roughly to the protoplasm of the bacterial body, and gives rise, in the animal, to the production of opsonins, of amboceptors, and of agglutinins; (2) The second includes toxins and endotoxins, a series of bodies which cannot be defined very easily, but which we may roughly describe as soluble products of bacterial growth, which exert a toxic action when injected into animals; (3) Lastly, there are the substances set free by the disintegration of the animal tissues at the site of infection. In the course of disease, and in response to this auto-inoculation, the body elaborates antibodies corresponding to all these different products, and in many cases recovery is the result. But in many others, on the contrary, the immunity is not sufficient, and the natural process fails. This is the place where medicine steps in, and claims to improve on the processes of Nature; for I think that the moment we begin to practise therapeutics we are assuming a kind of authority over Nature's workings, and that we should recognize this fact and not try to shirk the responsibility which it carries with it. The masters of our profession who have claimed, in the past, to follow with humility Nature's lead were insisting on what was at the time the more important point of view, but a point of view which cannot be considered to embrace the whole truth.

Now in vaccine therapy we try to make use of a natural reaction, but we try also to increase this reaction beyond the limits it would attain without our interference. This we can do because we have learnt that in every disease some tissues are left at least comparatively healthy, and that these tissues may be stimulated to activity for the

benefit of more gravely injured parts of the body. We have also learnt that the auto-inoculations of disease may be either deficient or excessive, whilst our therapeutic inoculations can be regulated at will. Thus far most of those who have taken part in this debate will be agreed, but beyond this point there seems to be a wide divergence of opinion. There are those who consider the labour and uncertainty of further investigation, and would rather devote their time to reaping the harvest of our present knowledge. On the other hand, there are those more hopeful beings who are convinced that a more detailed analysis of the processes of immunization will be rewarded by the discovery of wider fields of practical utility in the future.

One line of inquiry deals with the constitution of the vaccine itself. The heated bacterial emulsion generally used is obviously a very different thing from the living bacteria themselves, and from the bacterial matter which escapes from an infected focus into the surrounding tissues. These differences can only be investigated, at present, indirectly, the chief method being that of inoculation into man or animals and measurement of the reaction set up. Investigation by this method will answer the questions as to whether our heated vaccine will give rise to increased production of opsonins, amboceptors, agglutinins, antitoxins, antitrypsin, and the like. Let us review the present state of our knowledge on these heads.

Opsonin.—Abundant proof is forthcoming that the opsonic power of the serum is increased by inoculation of heated vaccines. In the case of one organism I was able to compare the opsonic response to inoculations of living cultures and emulsions sterilized by heat. The organism was the *Bacillus pseudo-tuberculosis rodentium*. The experimental animals were rabbits; these animals are easily killed by the inoculation of living cultures, so that partially immunized rabbits had to be used. This had the further advantage that the reaction was more rapid than in the case of untreated rabbits, and the fallacy introduced by the multiplication of the living microbes after their introduction was thus minimized. A batch of rabbits was rendered partially immune, and then one lot were inoculated intraperitoneally with living, the other lot with killed emulsions. It was found that the emulsion sterilized by heat was competent to produce a rise of the opsonic index in doses smaller by many times than the living emulsion. The minimal dose of the latter was ten or fifteen times greater than that of the heated emulsion. It seems probable, therefore, that the active substance is held locked up

within the living bacilli, and set free in available form by the process of sterilization by heat.

Amboceptor.—If we accept Ehrlich's views, and the work of Bordet and Gengou on complement deviation, then we can measure the bacterial antigen in any emulsion by mixing it with a known immune serum containing the corresponding amboceptor and determining the complement-deviating power of this combination. The *antigen* thus measured is supposed to be the substance which stimulates the formation of amboceptor in the tissues. The available antigen in living and heated emulsions of the *Bacillus pseudo-tuberculosis* was compared by this method, and again the advantage was on the side of the heated emulsion.

Antitoxin.—Most of the toxins which can be obtained in workable quantities are destroyed by heat, so that our heated vaccines are, generally speaking, free of these toxins, and probably, therefore, do not give rise to antitoxin production in the body. The heated vaccine is not, however, to be condemned on this score, for the presence of a notable quantity of toxin would limit the dose which could be employed with safety. With such a vaccine the toxin would be the predominant factor in determining the dose, and we should, of necessity, aim at producing antitoxic immunity, whilst other forms of resistance would be lost sight of. But these latter are the more important, because they are directed to the removal of the infecting agent. It is therefore an advantage to use an atoxic vaccine in what is essentially an antibacterial treatment. At the same time, one may admit that there is room for an antitoxic treatment in some cases, either by the use of antitoxin as in the case of diphtheria, or by the inoculation of small doses of toxin, regulated to excite an active immunity. I would only insist that this latter scheme of treatment is one of which we have as yet no accurate knowledge, and which will probably present difficulties of its own. Its rules need to be worked out separately almost from the beginning. The attempt to induce antitoxic and antibacterial immunity by one and the same inoculation seems to me only likely to lead to confusion and failure.

Antitrypsin.—The products of disintegration of the animal tissues, which flow into the system from the site of infection, no doubt give rise to antibodies of various kinds, but at present we are ignorant of all these except one—antitrypsin. The inoculation of bacterial vaccines, as a general rule, increases the antitryptic power of the blood serum, this reaction being explained by the breakdown of some of the leucocytes which crowd the tissues at the site of inoculation.

From the above it is clear that the reaction to inoculation is a complicated one, corresponding to the complex constitution of the vaccine. We cannot expect to obtain a reaction which is the best possible in every respect. Where the conditions are such that ordinary clinical examination enables us to judge between success and failure in the case of each successive inoculation, we are watching a summation effect, and we say the balance is on the side of improvement or the reverse. But where the case is more difficult and we cannot thus sum up the results of an inoculation, we are driven back on blood examinations, and we have to select one or more of the components of the total immunizing reaction for measurement. The opsonic reaction derives its pre-eminent importance from the fact it is almost universally applicable. All animals use the phagocytic method of defence against bacterial invasion, and, among mammals at least, phagocytic activity is dependent on the opsonic power of the blood. This holds true for all bacteria yet investigated, and the opsonic power may be measured by one and the same method in nearly every case.

There is one point of practical detail which has been raised in this discussion to which I should like to refer—namely, that of stock vaccines. Dr. Whitfield treated this subject rather shortly at the end of his speech. He has found, and I think most of us will agree with him, that staphylococcal vaccines, prepared from recently isolated cultures, are more active than those made from old laboratory strains. The vaccine once prepared will keep for a long time. But these observations on staphylococci must not be taken to apply generally to vaccines prepared from other groups of bacteria. One need only mention the typhoid bacillus, which gives efficient vaccines after going through frequently-repeated subcultures for months or years; whilst, on the other hand, the vaccine prepared to-day will be useless in six months' time, and will have deteriorated in a shorter time still. In the case of pneumococci we are faced with another difficulty, for the pneumococcus isolated from one case of pneumonia may have little effect when inoculated into another patient. But it is very necessary to have a stock vaccine for the treatment of a disease so rapid as pneumonia, where every day is of importance. A stock vaccine prepared from several well-attested strains of the pneumococcus, isolated from cases of acute pneumonia, is found to give good results in nearly every case, and a first dose of this may be followed by the autogenous vaccine after a day or two.

Dr. W. PARRY MORGAN : I propose to confine my remarks to one acute disease, pneumonia. During the last two years, chiefly in conjunction with Dr. Willcox and Dr. Luff, to whom I am indebted for much help and kindness, I have treated many cases by vaccine therapy. In advocating any new form of treatment one is open to the charge of being biased, and this attitude is the more likely in pneumonia when Nature frequently does so brilliantly on her own account. Still she fails in so many cases that it remains the most fatal of acute diseases. This justifies us in looking for new methods of treatment.

Up to the present good nursing, symptomatic treatment, and surgery when necessary, constitute the recognized measures of treatment. These can in no way be called specific, and only help to maintain the patient in a condition in which he himself can deal with his disease. Specific treatment has been tried only in recent years. We have the two principles of passive and active immunity. The former first held the field, but it certainly has not been satisfactory. The latter has been responsible for brilliant results in other diseases, and the few records of its application in pneumonia are those of success. However, it has had but an imperfect trial, and I submit that my experience shows that, although we may expect some failures, further trial is more than justified. There is no doubt that lobar pneumonia may be caused by different strains of pneumococci; hence we cannot expect one vaccine to be efficient in all cases, and the method must not be condemned, as it is by some people, because certain cases do not react when treated with stock preparations.

Again, dosage is difficult and will depend very much on the individual applying the method. There is no doubt that idiosyncrasy is a most important factor in vaccine therapy; thus it is impossible to say that one dose will suit the same body-weight in all cases. This is what we should expect when we consider the variation in susceptibility to infection. In many other diseases the opsonic index has been our guide to the resistance and to the dose, but in pneumonia I have been unable to use it for this purpose. This has been given as an argument against the general use of the index for determining doses. It is quite unjustifiable to quote my failure with the pneumococcus as a reason against the use of the index in infections where its value has been proved. My difficulties have been as follows: Most pneumococci—at any rate, those obtained directly from the lung or pleural cavity—are not phagocytosed except when acted on by immune serum. So striking is this phenomenon that the field of an opsonic

film prepared with normal serum may be crowded with organisms, whilst the phagocytes are empty. Again, the opsonic power of serum of apparently normal people differs very considerably—a fact which is not surprising when we consider the frequency of pneumococcal infections, and the fact that infection leads to variation in immunity. Agglutination of the organism often takes place with immune serum, but the phenomenon is very irregular. Notwithstanding these difficulties I have made many observations, and find that early in the disease the opsonic power is never high, whilst nothing is more striking than the opsonizing power of some immune serum to an organism not acted on by normal serum. It is obvious, therefore, that the determination of the dose is a matter of extreme difficulty, and it will certainly happen that good results will be recorded with large doses which in other cases would cause failure. We must therefore commence with minimal doses and look for minimal effects. Soon perhaps, when we overcome the difficulties of using the opsonic index in pneumococcal infections, we may be able to use vaccine with the feeling that we know precisely what is taking place in the immunizing process.

In the treatment of acute disease there is one obvious limitation—time. What is to be done must be done quickly. Therefore I think that a suitable stock vaccine should be given at once. Subsequent procedure depends on circumstances, the ideal being to obtain the autogenous vaccine. Three methods of doing this are available, and are as follows:—

(1) *Cultivation of the Organism from the Sputum.*—I must emphasize that this method is open to the very grave objection that we might get an organism other than the one infecting the lung. Diplococci are so common in the upper respiratory passages that one may obtain an apparently pure culture, and that not of the pathogenic organism. I have seen this done in a case in which the pneumonia was due to an organism belonging to the coliform group, the diplococcus being obtained from profuse expectoration. Again, my observations point very definitely to the sputum organisms having different reactions from those obtained from the lung, notably as regards phagocytosis. I consider therefore that this method is by no means reliable.

(2) *Blood Culture.*—I have tried this method in several cases. As a rule, I have been unable to obtain any growth from 10 c.c. of blood, whilst sometimes I have not had a growth early enough to prepare the vaccine. I have no doubt that the frequency of extensive blood infection is as variable as the virulence, and although some observers find

the organism frequently, others will fail. Again, the time at which a blood culture is made is an important factor, for no doubt bacteræmia is more frequent early in the disease. A point in favour of this method is the relief it often gives the patient, and the confidence it gives him in the vaccine therapist.

(3) The third method, that of *lung puncture*, was described, not as something new, by Dr. Willcox and myself, and subsequently by Dr. Horder, as a method of diagnosis of thoracic conditions. This was afterwards severely criticised on account of certain dangers, but Dr. Willcox and I maintain that the comparatively fine needle (only a little larger than a hypodermic) which we recommended reduces these dangers to a minimum. I have never failed to obtain blood-stained fluid from a consolidated lung by this method, but I have often been unable to obtain a culture. Therefore, this method, the most rapid, of obtaining a reliable vaccine often fails, and so in many cases we are compelled to use stock vaccines throughout.

Regarding doses, I feel confident that no harm has followed the larger doses I have used, although I have repeated doses of 50 million of the autogenous vaccine. Still, I think my best results have been with doses of from 15 to 30 million for an average adult. If a dose is small, it can be repeated with impunity; whilst if larger, one hesitates because it has been possibly too large. The temperature may be a guide, but often it is not. One of the most noticeable features is the improvement in the general condition, without much change in the temperature. The anxiety which one often feels for a patient is relieved. Sleep comes readily, the appetite improves, and even if the pulse-rate does not fall, its strength is well maintained. At other times there is a fall in the temperature soon after the dose, sometimes even in a couple of hours. If this is the case, another dose is indicated when the temperature rises again. If there is no change in twenty-four hours, I repeat the dose, sometimes increasing, more often decreasing, it. Between subsequent doses I may leave longer intervals. One does feel, however, that this method of determining and giving doses is not satisfactory, and that some measure of the immunity is wanted. We look for some one to suggest an indication which is not dependent on so many functions of the patient as is the case, say, with the temperature which would often lead us to give a dose of vaccine instead of a pill.

Of the cases that I have treated, 24, with two deaths—one from nephritis after the pneumonia had subsided—were reported in the *British Medical Journal*, October 9, 1909. I have directly treated 19 more

since that time, all of which have recovered. Thus, 1 case out of 43 has died of the disease—a result which is not altogether unsatisfactory. Of the 19 cases, only 2 were treated as early as the third day, 4 were treated on the fourth day, 5 on the fifth, and the rest later. Thus it will be seen that my opportunities have not been of the best. Most of the cases have been treated with stock vaccine, but some have had autogenous. Of the 2 cases treated early, one proved to be a streptococcal infection. The other had his crisis on the sixth day and made a good recovery. In a child, aged 7, it was difficult to ascribe any effect to the vaccine. She had a somewhat protracted crisis, after which recovery was rapid. In 4 other cases there was a distinct crisis, one occurring immediately after an inoculation on the eighth day, the others on the sixth or seventh day. In several cases the temperature fell by lysis with marked improvement in the symptoms. These cannot impress any but those actually observing them. My judgment may be biased, but I certainly think that most of these cases were benefited by the vaccine, and this judgment was corroborated by others. If we shall be unable to produce an artificial crisis at will by using a vaccine, I maintain that if we can induce lysis with improvement from the beginning of treatment, we shall have made a great advance in the therapeutics of pneumonia. Some cases were complicated, and these are the more instructive and the most convincing. I will therefore give a brief account of some of them:—

W. H., aged 40, a typical alcoholic, who acknowledged his habit, was taken ill on October 13. He was admitted to hospital on October 15 with well-marked signs in the left lower lobe. The first night in hospital he was very restless, and the next day he was obviously much worse. Towards night delirium tremens threatened, and he was given 30 million stock vaccine. He had a very good night, the restlessness passing off, and was much improved in the morning, when the temperature fell to 99·8° F. Later in the day it rose to 101·6° F. He had another good night, and the temperature in the morning dropped to 98·2° F. On its rising later he was given a further dose (sixth day), after which the temperature only once rose above 99·4° F. It became continuously sub-normal on the ninth day. Recovery was very rapid. All signs and symptoms disappeared within a fortnight.

S., a girl, aged 15, who had previously attended a dispensary for consumption, on November 15 was seized with shivering and pain in the left side. On November 20 she was admitted to the hospital very seriously ill. There was consolidation of the whole of the left lower

lobe and part of the upper left and lower right; pulse 144, respiration 68. The next day patient was no better, so 15 million stock vaccine was given. At the same time a blood culture was made, from which I obtained a profuse growth of pneumococci. A comfortable night was passed, and, although the patient was most seriously ill, the whole aspect of the case had changed by the next day, the temperature falling to 99.5° F. It rose again towards night, so a further dose was given. I had prepared the autogenous vaccine, but the stock had such a marked effect that I repeated it rather than give the new. The temperature did not come down, although the patient was obviously improved, sleeping better and coughing less. I gave 10 million of the new vaccine on November 23, and 15 million on November 24. The temperature fell to 99.2° F. on November 25, and to 97.8° on November 26. However, it did not remain normal, and ranged several days below 100° F.; after that it became intermittent, and I began to look on the case as a failure. The lung was twice explored with no result, no cultures being obtained. I therefore estimated the tuberculo-opsonic index on four occasions, one being before, the others after, forcible deep breathing. There was such a variation that the presence of pulmonary tuberculosis was made certain. Tuberculin was given in very small doses until the patient left hospital for a convalescent home. Some signs still remained, but no cough nor sputum. The last report, for which I am indebted to Dr. Willcox, is that she had quite recovered.

My next case is that of an old man, aged 61, with very hard tortuous arteries. He had been ill for a week when admitted to the hospital on November 28. The whole of the upper two right lobes were consolidated, whilst both lower lobes were full of crepitations. The pulse was very irregular and feeble, and the patient's mental condition confused. The prognosis appeared most grave, and Dr. Luff gave no hope. Sixteen million stock vaccine was given. Next day the old man was better, the temperature and pulse lower. That evening a further dose was given. Two days later the temperature was normal. However, it began to rise again after that, and became intermittent for nearly a fortnight. Notwithstanding, the old man appeared very well and cheerful, eating and sleeping well. The pulse was much improved. The consolidated lung cleared up, and the crepitations disappeared after a time, and on January 6 he went to a convalescent home quite recovered.

G. H., a girl, aged 1 year and 9 months, was admitted on March 2 with signs at the right base. The temperature fell slowly until

March 5, when it rose steadily until March 8, when I was asked to inoculate. I gave three injections of 3 million stock vaccine, but with no result, the patient getting gradually worse. On March 15 the prognosis seemed hopeless; nevertheless, I did a lung puncture, and within eighteen hours inoculated her with 4 million autogenous pneumococcal vaccine. The effect was most striking, the temperature falling immediately. Further doses were given, and three days later the temperature had fallen by a steady lysis to normal. It began to rise again on March 25, but fell immediately on giving a further injection of 4 million. She steadily improved, but some dullness remained in the right chest when she left hospital. This has since completely cleared up.

E. H., a woman, aged 31, who had been treated for pulmonary tuberculosis at several sanatoria, was admitted to hospital for treatment with tuberculin, under which she improved, the temperature which she had on admission becoming normal after several weeks. However, the cough remained bad and expectoration profuse, with large numbers of tubercle bacilli, whilst the appetite was very indifferent. About the beginning of the third week in February she developed a temperature again, with pain in her right side. Dyspnoea became marked, and the general aspect of the case serious. The sputum was examined, and a few pneumococci and many tubercle bacilli found. A dose of 15 million pneumococcal vaccine was given. A few days later the pleural cavity was aspirated, and a considerable quantity of fluid obtained. This clotted very quickly, and in the clot were found tubercle bacilli and many pneumococci. I was unable to obtain a culture of the latter, but it was obvious that the patient was suffering from pneumococcal pneumonia complicating the phthisis. I gave stock vaccine, after which the patient rapidly improved. The whole result of the attack was a well-marked change for the better in the tuberculous condition, for the cough and sputum almost entirely disappeared, so that she could sleep through the night, a thing she had not done for two years. The physical signs, too, showed a corresponding improvement in the lungs. A point of extreme interest in this case was the behaviour of the opsonic index. It was above 1.10 on twelve consecutive occasions. On account of these very high readings tuberculin was withheld. Subsequently it was again given, the dose being regulated by the index. The patient continued to improve, and the last reports from the sanatorium, where she is undergoing graduated exercise treatment, promise complete cure.

S. B., a child, aged 10 months, had been ill for three weeks. On May 31 she became rapidly worse, and was admitted to hospital the next day with very obvious dyspnoea and cough. There were well-marked dullness and bronchial breathing at the right base, with crepitations. She was given 4 million vaccine at 6.30 p.m. on June 2; the temperature fell steadily to 100.4° F. at six the next evening. At ten it was 102° F., so I gave 15 million; the temperature again fell steadily to 99.6° F. next evening. When it rose I gave a further 4 million. It again fell, this time to 90.2° F. The general condition of the child meanwhile improved in a most remarkable way, and, except when coughing, she had a healthy appearance. However, it became obvious that she had pertussis as well. Although so severely ill when she was admitted to hospital, it was thought quite safe to send her away rather than isolate her. I saw her yesterday, when her condition was quite satisfactory.

A. T., a man, aged 44, with typical signs in the right lower lobe, was inoculated with stock vaccine on the third and fourth days. There was no apparent effect, the patient being very restless and getting worse, so a lung puncture was made, and from the cloudy fluid aspirated from the pleural cavity a pure culture of *Streptococcus mucosus* obtained, and a vaccine prepared. Fifteen million of this was given on the fifth day. The patient afterwards passed a good night, and the next day the temperature fell to 98.8° F. On its rising again a further dose was given, the temperature falling on the morrow to 98.4° F. Further injections were given, the temperature never rising as high as before the injections. The temperature did not settle to a normal course before the tenth day, after which convalescence was well maintained. This case is of special interest on account of the failures of stock vaccine and the success of the autogenous. The former could not be expected to succeed, seeing that it was a streptococcal infection, and not a pneumococcal.

My cases have not been selected. I have treated all those I have had the opportunity of doing. Several have come into hospital late, and recovered before I could treat them. These, if I had chosen, would have improved the statistics had I inoculated with a falling temperature. I have described some of the worst, and I think I can claim to have done them good. If vaccine were calculated to do harm, one would hardly expect such excellent results when the prognosis is of the worst. I think, therefore, that with care and judgment pneumococcal vaccine can be used with the conviction that only good can result.

MR. J. COURTENAY MACWATTERS: During the past three years I have applied the principles of therapeutic immunization to all cases in my practice that have seemed suitable to me, and am in every way satisfied with the results taken as a whole. I have carefully considered this line of treatment, and compared the results with those obtained by other methods, and, being a general practitioner, I think I may claim exceptional opportunities, as I have access to a large variety of cases for comparative observation. I have notes on some 300 cases, and in no instance have I had any reason to regret its application, and in the large majority I have obtained better results than by older methods.

In my hands vaccine therapy has yielded such uniformly good results that I have formed the opinion that, in cases of localized bacterial invasion treated by this method, cure is bound to result in almost every case, if one can succeed in three things—viz., the isolation of the offending organism, the preparation and administration in suitable doses of a vaccine made from it, and in promoting the flow of the resulting highly opsonized lymph through the infected tissues. Where failure has occurred, it has been my experience that the fault lay with the would-be immunizator, and not with the method.

Of the ordinary localized infections I need say nothing, nor need I weary you with a recital of successful cases of staphylococcic skin infections, catarrhal mucous membranes, &c. I would, however, direct your attention to the results I have obtained in a few cases of pyorrhœa alveolaris, pneumonia, rheumatism, and glycosuria.

Pyorrhœa alveolaris is of such frequent occurrence, and so far-reaching in its results, that it deserves far greater attention than it till recently has received; and now that vaccine therapy has afforded a means of successfully treating this hitherto intractable disease, its early recognition and treatment by bacterial vaccines are imperative. I have now treated over 50 cases, either sent to me by members of the dental profession or occurring in my own practice. I have considered as pyorrhœa those cases where there is an exudation of pus from recesses round the necks of the teeth, usually associated with the deposition of a greenish-brown tartar in a variable degree at the alveolar margins; the teeth as a rule are sound, but often loose from destruction of the alveoli. I have noted the presence of pyorrhœa from the age of 12 up to advanced years. In these cases I have considered as cured only those in which I failed to obtain pus on several occasions after the lapse of some weeks from the cessation of treatment. In addition to the obvious local symptoms, such as bleeding from the gums,

a bad taste in the mouth and foul breath, I have frequently noted morning vomiting, gastric ulcer, profound anæmia, constipation with irregular attacks of diarrhoea, vague rheumatic pains, susceptibility to sore throats and colds, irregularity of the heart, depression or even melancholia—all these symptoms disappear with treatment. I have frequently found that a patient suffering from an intractable dyspepsia, with anæmia and loss of weight—cases that have been a recurring testimony to the inefficacy of other treatment—have pyorrhœa as the underlying cause. Treat the pyorrhœa with vaccines, and the case clears up after years of futile treatment by older methods.

Bacteriology.—In all cases I have treated I have found a streptococcus in the pus, a streptococcus occurring singly and in chains of up to five or six members; other organisms present in order of frequency were: *Staphylococcus aureus*, *Micrococcus catarrhalis*, pneumococcus and leptothrix. In cases in which I have estimated the opsonic index, I have found a lowered resistance to this streptococcus, and this has risen to, or above, normal after vaccine treatment. It may be argued that streptococci are present in most normal mouths, and are frequently non-pathogenic; I believe that many so-called non-pathogenic organisms only require a local reduction in immunity to render them pathogenic, and the fact that improvement and cure result after the administration of these streptococci as vaccines is sufficient proof of their pathogenicity.

Additional Treatment.—It is of prime importance that the mouth should be rendered as clean as possible by the removal of hopelessly decayed teeth, and of accumulations of tartar, which afford beneath them a hiding place for the invading organisms, and, what is more important still, pen in the discharge of the affected alveoli, and prevent lymphagogue lotions from reaching the ulcerated surfaces. It is my practice to leave loose teeth which are otherwise sound, and with half or more of their roots still embedded in the alveoli, and almost invariably I have found that they become firmly fixed, as soon as the discharge is much reduced; and many teeth that seem at first sight beyond hope are thus saved. With a view of putting an end to any digestive disturbances as soon as possible, I usually advise the patient to disinfect the mouth thoroughly, immediately before each meal, by the free use of carbolic tooth-powder, but for local help I place greater faith in a mouth wash of sodium chloride 4 per cent. with sodium citrate 0·5 per cent. flavoured to taste; this by osmosis increases the flow of the highly opsonized lymph through the diseased tissues. Beyond this I have purposely avoided the use of local applications. Frequent

saline purgatives, I believe, are helpful in the early days of treatment, possibly by carrying off any swallowed pus. With regard to the application of vaccines, when possible I give the patient a vaccine prepared from his own streptococci, but I find that quite a large number of cases do well when given a stock vaccine prepared from half a dozen mixed strains obtained from similar cases. As a rule, I find a dose of 5 million is sufficient, repeated every eight days. In two instances, however, I have found this excessive, producing great aggravation of symptoms for some days, and therefore should the constitutional symptoms be very marked, I usually begin with a dose of 3 to 4 million; as soon as a dose is well borne, I endeavour to increase it to 10 million.

The duration of treatment I have found to vary greatly, and the duration does not seem to have any bearing on the apparent severity of the case, but depends rather on the immunizatory response at the patient's disposal. In one case cure resulted after four inoculations, but the majority require systematic treatment for six months or more. I invariably found improvement after a few inoculations, but the final clearing up and total absence of pus on repeated observations is always much longer deferred, and I now prefer to give fortnightly doses of vaccine for some months after the disappearance of pus. As to the permanency of the cure, it is too early for me to speak from my own cases, as I do not feel it is justifiable to claim a cure until a year or more has elapsed after the cessation of treatment; yet the results in about 75 per cent. of my cases have been so successful, and the improvement in constitutional conditions so marked, that I feel confident in advising the adoption of the method in all cases of pyorrhœa alveolaris.

I have frequently noted the presence of pyorrhœa in cases of melancholia and other mental aberrations, and have noted these symptoms disappear when the pyorrhœa improves while under treatment, so that I would suggest the possibility of pyorrhœa being at least a contributory factor in these cases, and will quote one case bearing on this point. The frequency with which this disease manifests itself in two or more members of a family, particularly in a husband and wife, suggests the possibility of infectivity; and the fact that several cases have been noted in which the tendency to sore throats and colds in the head, &c., have disappeared after treatment by vaccines is worth remembering. The following cases are typical of others:—

A thin, sallow-complexioned, haggard-looking man, aged 38, and a chauffeur by occupation, had for two years previous to treatment by vaccines been treated by myself and another doctor for progressive loss

of weight, and a dyspepsia associated with morning vomiting and a sinking pain in the epigastrium two or three hours after food, which was usually relieved by a meal. He had a persistent foul tongue and bad taste in the mouth, his gums bled easily, and pus was present in quantities round the lower front teeth. He frequently found blood and pus on his pillow in the morning, and suffered from colds in the head and sore throat, and was subject to vague rheumatic pains in the shoulders and arms. He had lost nearly 2 st. in weight, and could with difficulty follow his occupation, and consequently had become very depressed. Treatment on usual lines did him but little good, and he continued to lose weight. All this time he had cleansed his teeth regularly with carbolic tooth-powder. I carefully overhauled him on several occasions, but could find no trace of organic disease other than pyorrhœa. On September 4, 1909, his weight was 6 st. 10 lb. The pus obtained from the alveoli, after wiping away the first drop exuded, yielded a culture of streptococci. On September 7 his opsonic index to these organisms was 0·6, and I gave him five million of his own streptococci. This was followed by increase in the tenderness and in the discharge of pus from his gums for two days, after which improvement took place. A week later he expressed himself as being much improved in health and able to work, and enjoy it, and but little pus could be expressed from his gums. Three weeks from the commencement of treatment he had gained 4 lb. in weight, his opsonic index had risen to 0·9, and no pus was found in the alveoli. In eight weeks I had given him six doses of five million each; no pus could be obtained, his dyspepsia was a thing of the past, and he expressed himself as being quite well. After eleven weeks of treatment he had gained 10 lb. in weight, and at the expiration of fourteen weeks he had gained 21 lb. He had now received his eleventh inoculation, and was quite well. He had gained 1½ st. in weight, and his dyspepsia was quite cured. No pus was found, and his skin had regained a healthy colour. At the end of five months, after the cessation of treatment, he had maintained his weight and his freedom from dyspepsia, and no trace of pus could be found in his gums. He expressed surprise that during the past winter he had been free from colds and sore throats.

Another case: A thin, pale woman, aged 62, in November, 1909, was suffering from melancholia, with symptoms of religious mania for the previous four or five weeks; and this condition had become so serious that her family begged for her removal to the county asylum, where she had been on three occasions during the previous four years. She had

been detained for six to eight weeks each time. Her breath was most offensive, the fangs of her lower teeth were exposed to the extent of about half their length, and there was a large accumulation of greenish-brown tartar and pus round them. The disease was so obvious that I thought it might have some bearing on the causation of her condition, as it was associated with severe dyspepsia, pains in the abdomen, morning vomiting, and emaciation. Pus obtained from the alveoli yielded a copious growth of a short streptococcus, and I therefore gave her an initial dose of 5 million of a stock vaccine of mixed strains of streptococci, obtained from other cases of pyorrhœa. This was followed for two days by an aggravation of the local symptoms. She was instructed to thoroughly clean her teeth and mouth with a carbolic tooth-powder, followed by the use of a mouth wash of citrate of soda and salt, four times a day. I removed enormous accumulations of tartar from her molars as well as from her front teeth. At the end of a week she was decidedly better, and her friends were only too glad to let her remain at home. After four weekly inoculations she was almost free from depression, her dyspepsia had ceased, and she had gained $\frac{1}{2}$ st. in weight, and but little pus could be expressed from the gums. After three months' treatment by weekly inoculations, she was fatter and in better health than I had known her during the previous six years; she was in good spirits and all her delusions had gone; she had long resumed her household duties, and was quite free from dyspepsia, expressing herself as feeling better and brighter than for many years. I continued inoculations at fortnightly intervals till April last, and I still find her improvement maintained.

To summarize, the cases I have treated number 48; of these, 4 discontinued treatment after one or two inoculations, 30 have completed treatment. These, I find, have received an average of ten inoculations each, 21 showed no return of pus two months after cessation of treatment; the remaining 9 have greatly improved.

With reference to *pneumonia*, my experience in treating cases of this disease is limited to 6 cases; in 3 of these the results were most encouraging. The cases were of ordinary lobar pneumonia, in which the pneumococcus was found in the sputum, or was obtained by puncture of the affected lung after the method advocated by Dr. Parry Morgan. In each case inoculation was begun with doses of a stock vaccine of pneumococcus obtained from other cases of lobar pneumonia, and in 2 it was noteworthy that no response occurred till the patient received a vaccine prepared from his own organism. Yet it would

appear that good results may follow from a stock vaccine in some cases. In 1 case, an alcoholic, aged 50, with a dilated heart and hyperpyrexia with delirium, death resulted on the seventh day, but this appeared to be a hopeless case from the first. It appeared to me that the other cases were much more comfortable during the course of the disease, the cough looser and less distressing, the expectoration was more copious and less tenacious; and, lastly, the pulse, respiration, and temperature were less disturbed than one sees in cases treated on the usual expectant lines. In 2 cases the temperature fell to normal by the fourth day; in 1 case lysis began on the third day, and the temperature was normal by the fifth day. The remaining cases appeared unaffected by the vaccine as regards duration of the disease, crisis occurring on the seventh day.

Rheumatism.—The following case of sub-acute rheumatism is of interest from the apparent bacterial cause of the disease, and from the ray of light that it may possibly throw on the pathogenesis of many cases of rheumatism: J. R., a labourer, aged 26, has several times in each of the past five years attended me for attacks of pain and swelling in the joints of his hands and feet, and occasionally in his knees. These attacks have lasted from two to four weeks, and of late have been more severe. In October of 1909 a more severe attack than usual led me to admit him to hospital. His condition was then such that he could not undress himself, the joints of his hands, wrists, and fingers being swollen and painful; his right knee, both ankles and feet were similarly involved; his temperature was between 99° F. and 100° F., and he appeared to be a typical case of sub-acute rheumatism. After treatment for eight days by salicylates and a milk diet he had improved, and so long as he was kept under the influence of salicylates—20 gr. every two hours—he was without pain, and most of the swelling disappeared. On reducing the salicylate to half the quantity the pains and swelling reappeared, relief being again afforded by return to the larger doses. This sequence of events occurred four times. Iodides, arsenic, alkalies, and milk diet, all failed to maintain definite improvement, or to procure results as good as the salicylates, which were then continued till December 20, and after eight weeks in hospital he was but little better than when he was admitted. During this time I had repeatedly examined his urine bacteriologically, and invariably found Friedländer's bacillus present. I also found that he had a reduced opsonic index to this organism. On December 20 I withheld all medicines, and his joints became more troublesome by the next day. I then gave him 10 million of his own

bacilli as a vaccine. This was followed by improvement, the patient expressing himself as feeling better than he had felt for months, and his joint troubles remained in abeyance for five days, in spite of the fact that salicylates had been withheld. On the sixth day I repeated his inoculations, as there was some return of pain and swelling, and this was again followed by improvement. After the expiration of another week a dose of 20 million was administered; this was followed by a slight exacerbation of symptoms lasting three days, after which improvement took place, and a few days later the patient was discharged. He was instructed to report himself in a fortnight, when he received a dose of 15 million; after this he returned to work and remained away for four weeks, then he presented himself with a slight return of symptoms, which yielded to a further dose of 15 million. Since February he has followed his work regularly, and has been more free from rheumatism than for many months. Considering how frequently reduction in the dose of salicylate was followed by a return of swelling and pain, and how any other treatment had failed to give relief, I think one is justified in crediting the vaccine with producing the amelioration of the patient's symptoms and ultimate cure, and in considering that the rheumatism was an exhibition of a toxæmia produced by the presence of the bacillus of Friedländer. In connexion with this I would direct your attention to the frequency of so-called rheumatic pains in cases of influenza, tonsillitis, pyorrhœa alveolaris, &c. I can recall a case of what I considered to be muscular rheumatism, which yielded *Bacillus pyocyaneus* from the urine; another, of rheumatoid arthritis, which yielded a streptococcus from the urine, sputum, and fæces; and both of these cases were markedly relieved by the corresponding vaccine.

I therefore contend that many of the cases of so-called rheumatism may be simply an expression of a toxæmia due to bacterial invasion of some remote tissue, by one of a variety of organisms, not necessarily the streptococcus described by Poynton and Payne, Beattie, and others, as the specific cause of acute rheumatism. I do not deny that in the case of typical acute polyarthritic rheumatism it is probable that there may be some specific organism to which the disease is due.

Glycosuria.—Inasmuch as it is well known that cases of glycosuria are liable to invasion by staphylococci, as evidenced by manifestation of carbuncles, boils, eczema, &c., it has occurred to me that the glycosuria may be the result of, and not the cause of, the lowered resistance to this organism, and with this point in view I would draw your attention to the following cases which I have had under observation:—

A large well-nourished man, aged 56, had had attacks of carbuncles and boils for the past three or four years. These ran a protracted course till 1908, when he came to me to be treated by vaccines for a carbuncle. It was at this time sugar was first noticed in his urine, and was present on every observation up to August, 1909, in spite of codeia and careful dieting. On August 2, 1909, he received a wasp sting on the forearm, which was followed by invasion of *Staphylococcus aureus*, which in two days caused an extensive cellulitis of the arm and a temperature of 103° F., although the focus of invasion was extremely minute. His urine contained 6 per cent. of sugar, and his staphylo-opsonic index was 0·6. I accordingly gave him 200 million of an auto-staphylococcic vaccine. Three days later the arm was much better, his urine contained 2 per cent. of sugar, his staphylo-opsonic index was 0·91, and I gave him 200 million of his vaccine. At the end of a week from his first dose of vaccine his urine was free from sugar and his index had reached 1·1. A week later his index had fallen to 0·82, and a trace of sugar was found. I therefore gave him another 200 million of his vaccine, and ten days later his index was 1·2 and sugar was absent from his urine. Three weeks from the commencement of treatment the patient was feeling much better, no sugar was present in his urine, and he was allowed ordinary diet, including sugars and beer. At eight weeks no sugar was present, and his index 1·2; at twelve weeks his index had dropped to 0·87, and sugar was present in his urine; he therefore received a dose of 200 million, which raised his index to 1·1 and freed his urine from sugar in two days. From November to March he kept in excellent health, and once in every two or three weeks received a dose of his vaccine, his urine all this time showing no return of sugar on periodic examination, and a normal opsonic index to staphylococcus was maintained. He then was away for some weeks, and I saw nothing of him till May this year, when I obtained a sample of his blood; this, I found, showed an index of 0·86, and on examining his urine found sugar present to the extent of 3 per cent. I gave him 250 million of his vaccine, and a week later the sugar was 1 per cent., and thirst and increase of urine that had been present had almost disappeared. Since this he has had one more dose of vaccine, and on my last examination of his urine a few days ago sugar had decreased to 0·5 per cent. In this case it is noteworthy that sugar had been present on every examination for over a year previous to systematic treatment by vaccines, in spite of administration of codeia and a restricted diet. Yet from November, 1909, till May, 1910, his urine was free from sugar, although he was

taking ordinary diet, and receiving no other treatment than vaccine, also on many occasions the appearance of sugar in his urine was synchronous with the falling of his staphylo-opsonic index.

Case II.—The patient, a builder by trade, was an emaciated man, aged 60, who three years ago suffered with boils; he appeared acutely ill and had a haggard and cyanotic appearance. Two years later he had a large carbuncle on his neck, and for a year previous to his commencing treatment he was known by my partner to be passing sugar in his urine. Three years ago his weight was 12 st., and in February last, when we started treating him by vaccines, his weight was only 9 st. 3 lb. He complained of great thirst, to relieve which he was in the habit of taking a quart jug of water to his room every night, and this he finished by the morning. He had to get out of bed six or seven times each night to pass urine, voiding every night one or sometimes more chambers full; he complained of absolute loss of appetite, and of a most disagreeable sweet taste in the mouth. The man had at this time ceased to work, as he felt too weak to continue. His urine contained 9 per cent. of sugar, and was of a specific gravity of 1042. Treatment: On February 3 he was given 300 million of an autogenous vaccine of staphylococcus; this was followed by marked improvement, the amount of sugar excreted was diminished, as was also the quantity of urine voided, and all the above-mentioned symptoms were distinctly relieved. A week later he was given 500 million of the vaccine, and this was followed by a marked negative phase, and during the three days that this lasted there was an augmentation in the amount of both total sugar and of urine excreted, and, of course, a temporary return of thirst, &c. By the expiration of a week, however, he improved and was given a smaller dose, which was followed by marked improvement. I need scarcely say that he has received no other treatment while being treated by vaccines, and has not had any restriction placed on his diet. Now, after three months, his urine contains a mere trace of sugar, he does not have to get out of bed at night, the sweet taste and disgust of food have gone, and he eats well and expresses himself as better than for many months, and has gained 2 st. in weight, having, of course, lost the haggard, acutely ill, and cyanotic look that was noted at the commencement of treatment. Although this patient was a man of advanced years, yet he was not one of the obese type that resist the disease so well and are prone to periods of marked improvement; on the contrary, at the outset of treatment he appeared to be running down-hill rapidly, and he at least thought his days were numbered.

Case III.—My third case is not so satisfactory, as far as final results go, yet there are points of definite interest in the case. The patient was aged 38 when sugar was first discovered in his urine, and it was three years later that he came under my observation, and, as he seemed absolutely doomed, I was particularly anxious to apply this line of treatment. He was exceedingly emaciated, and smelt strongly of acetone; he had marked peripheral neuritis; his vision was $\frac{1}{60}$, owing to diabetic cataract; one of his great toes had become gangrenous after a burn. He was passing over 100 oz. of urine, and his daily output of sugar was over $\frac{1}{2}$ lb. He suffered from intolerable thirst and prostration after the least exertion, which, added to this train of severe symptoms, rendered it more than probable that his drowsy condition was the forerunner of coma. The administration of 250 million of a vaccine prepared from a staphylococcus isolated from his gangrenous toe was followed by a reduction in the daily output of sugar to one-half, and the volume of urine by one-third within three days, and after five days a similar dose was followed by a further reduction of the sugar to $3\frac{1}{2}$ oz. and the volume of urine to 50; up to this time the patient had gained 5 lb. in weight. Subsequently a dose of 500 million was followed by a great increase in the output of both sugar and urine, these reaching 11 oz. and 144 oz. respectively; this increase was followed by a corresponding fall, and after four days the quantities had fallen to 38 oz. of urine, with 2 oz. of sugar. A fluctuating improvement followed for a week, after which the patient became more drowsy, the output of sugar increased, and he lapsed into persistent coma, which terminated the case.

Let it be understood that, in reporting these results in glycosuria, I do not claim to have established an incontrovertible theory as to the pathogenesis of the disease in question. I trust, however, to have provided food for thought, and a suggestion for further investigation in this direction, in the hope that a method of successful treatment may be established.

Speaking from the point of view of the general practitioner, I would strongly urge all those who have sufficient patience and perseverance, combined with a desire to do the best possible for their patients, to render themselves not only *au fait* with the principles underlying the application of vaccine therapy, but to devote sufficient time in a good *clinical* bacteriological laboratory to enable them to carry out the necessary manipulations in preparing vaccines. To those whose chief aim in life is the reduction of personal effort to a minimum, and who will grudge the many hours spent and the inevitable disappointing failures in

laboratory technique during their apprenticeship, I would say leave vaccines alone, for in my experience, as I have already stated, when failure results it is far more frequently due to fault on the part of the would-be immunizator than on the part of the method.

In bringing these remarks to a close, I would like to take this opportunity of recording my great indebtedness to Sir Almroth Wright and his staff at St. Mary's Hospital Inoculation Department for the great kindness they have shown me during the all too short a time I have been able to spend there.

Dr. F. ASHTON WARNER: What has struck me at these meetings more than anything else has been the regular chorus of consent as to the value of vaccine therapy, and in that I beg to join. My experience of the use of vaccines is purely clinical, and I am dependent on the trained bacteriologist for the estimation of the opsonic index, culture of the particular micro-organism in each case, and the supply of the necessary vaccine. I find it is practically out of the question to make use of the opsonic index as a matter of routine owing to the necessary expense which the work entails and the disinclination of patients to pay the fees, so that in the majority of cases I have to depend on the clinical signs as a guide to the amount and frequency of the doses. But in dealing with tuberculin in cases of infected cervical glands, I make it a rule to rely on the opsonic index as a guide, and not on the conditions of the glands as judged by appearance and palpation. For it is impossible to judge of the condition of the deeper glands in the chest, and consequently the superficial ones do not afford a reliable guide.

Now, as to the administration of the various vaccines, I have made use of them by the mouth and hypodermically, and, so far as my experience goes, most satisfactory results are to be obtained by either method. Patients certainly prefer oral administration to the hypodermic, and especially children, so that in their case, at any rate, it is of great advantage to be able to dose them by the mouth. Another advantage is that in cases of acne the dose of vaccine may be taken at intervals with only occasional visits to the medical man, the dose being regulated in accordance with the local reaction, which can be noted by the patient—a distinct advantage to the patient when the treatment is lengthy. The simplest way to give vaccines by the mouth is to direct the dose to be taken in a sherry wineglassful of milk, the first thing in the morning, on an empty stomach. The milk must be first boiled.

The following short notes are of cases treated with the vaccine, and have not been selected, but taken in the order in which they were dealt with :—

(1) W. H., a young officer in the Army, contracted a gonorrhœa in July, 1907, which was followed by arthritis of the left knee, right hip-joint, and, in a lesser degree, the left ankle. He was confined to his bed for nine weeks, and was then sent to Bath, where he went through a regular course of baths and was put on a very restricted diet. He was seen by me for the first time in January, 1908, and his condition was pitiable. He was depressed, pale, wasted, and hobbling about the house with the aid of a stick. The left knee-joint was swollen, painful, and movement was restricted. He also complained of pain in the right hip-joint. I first put the patient to bed and gave him a dose of stock gonococcal vaccine hypodermically. On my visit to him the next day he complained of pain in the knee and the right wrist and a slight headache. There was no apparent change in the knee, nor could I detect anything amiss with the wrist. The second dose was given nine days after the first, and in the course of the treatment, which extended over four weeks, he had five injections altogether. By the end of six weeks from the commencement of the treatment he was able to drive his motor-car and was fit to join his regiment. No medicine was given, but the patient was put on a very full diet.

(2) W. B., a fine, healthy lad, suffered from eczema of the right ear, from which there was a copious discharge of serum and pus. This condition had lasted off and on for several months, and was a source of worry and annoyance to the patient as well as to me. No treatment that I adopted had any but the most temporary effect. A swab of the discharge was sent for examination, and gave a culture of the *Bacillus coli communis*. A special vaccine was prepared, and two doses given by the mouth at an interval of a week. After the first dose my patient told me that the irritation was decidedly less, but the amount of discharge appeared unaltered. After the second dose, towards the end of the third week, the irritation had ceased, and the discharge was very much less than it had been all along. By the end of the fourth week there was no discharge, and the ear, though slightly red, caused no discomfort. I have seen the patient frequently since, and there has been no recurrence of the eczema. But for a plug of sterilized cotton wool in the ear to prevent the discharge trickling over the lobe, there was no local treatment after the first dose of vaccine.

(3) These two cases were patients, both young ladies, who had suffered from acne for years. Miss C.: Severe facial acne, which debarred her from going into society, and necessitated her wearing a thick veil to hide the disfigurement. A special vaccine made from the contents of a pustule was prepared, and the doses given by the mouth. For the first three or four months there was marked improvement, but after this progress was very slow, until a mixed vaccine of staphylococci and acne bacilli was given; then almost immediate improvement began, and at the end of ten months there was not a pustule to be seen. Miss L.: Acne of the back, which prevented her wearing a low-neck dress. In this case, by way of contrast, I used *stock* vaccine. The doses were given by the mouth, and at the end of eight months' treatment the result was as satisfactory as in the case above. In both the vaccines were given by the mouth, and I saw the patients at intervals of three weeks. The interval between most of the doses at the commencement was a week.

(4) Miss S., aged 18, complained of great pain in her throat and both ears, and she was particularly careful to impress upon me that the throat was not sore, but painful. The pharynx, soft palate, and fauces were intensely injected and of a bluish-red colour—very like a piece of underdone beefsteak. The glands at the angles of the jaw were enlarged and tender. The tonsils were inflamed, but there was no follicular secretion. Temperature varied between 101° F. and 102° F. There was intense headache, no cough, and nothing to note in the chest. Local treatment gave no relief, and the pain was severe enough to necessitate an opiate on three nights. A swab of the throat was taken from which "an almost pure culture of pneumococci" was obtained. After the first dose of specially-prepared vaccine, given hypodermically, there was marked relief. The vaccine was given in the early afternoon, and the patient was able to obtain sleep the same night without the aid of drugs. A second dose was given four days after the first, and the temperature, which was above 100° F., fell and remained below normal, and all the throat symptoms improved, pain ceased, and the patient gradually got well. She looked much more ill than was to be expected from the local conditions, and assured me more than once that she felt very ill. This case of painful throat was one of many that came under my observation about the same time, but was by far the most severe, which was my reason for having a bacteriological examination made.

(5) A. M., aged 55, sent for me one evening, and I found him suffering from an attack of acute cystitis, passing small quantities of bloody urine, with a temperature of 103° F. to 104° F. The acute stage

passed over, and then pus appeared in the urine, which persisted for three weeks with no improvement. The patient during this time was much bothered with frequent micturition, which interfered with his rest at night. Treatment had very little effect on the amount of pus, which measured about 1 in. at the bottom of the specimen glass. A catheter specimen was examined for me and the *Bacillus coli communis* found in quantities. Treatment was commenced with a specially-prepared vaccine, and, after the first dose, given hypodermically, the patient expressed himself as feeling much better, and there was less frequent micturition. The amount of pus and mucus rapidly diminished, the urine cleared up, and at the end of a month the patient began long bicycle rides. The first dose of vaccine was given on July 19, and the last on August 21, 1909; and the patient, whom I saw at the beginning of this month (June, 1910), remains perfectly well. The rapid improvement and complete recovery were in marked contrast with cases of cystitis before the vaccine treatment was introduced, when washing out the bladder night and morning with solutions of boroglyceride was the routine practice.

(6) Miss L., aged 47, was advised by me to have her appendix removed, as she had suffered from several attacks of appendicitis, none of them severe. She was of a nasty clay colour, languid, and complained of frequent attacks of headache, which she did not connect with the attack of appendicitis. A well-known surgeon operated and had no difficulty in amputating the appendix, which was found inflamed with some old, and more recent adhesions. The wound broke down, and there was a discharge of most foul-smelling pus. A stock vaccine was used until one prepared from the patient's own pus could be obtained; but, notwithstanding this, the patient went from bad to worse, and died of general septicaemia in the third week. The use of the vaccine had absolutely no effect on the temperature, the discharges, or the general condition of the patient. I think in this case the time to use the vaccine would have been before the operation, and not after. The patient was evidently, I think, suffering from a toxæmia long before the date of operation, which would explain the headaches, the colour of the skin, and the depression.

(7) Mrs. T., a lady whose child had been seriously ill with pneumonia and empyema following upon influenza, also suffered from a comparatively mild influenzal attack. She recovered up to a certain point, but for weeks subsequently complained of headaches, and the fact that her temperature was never below 100° F. Treatment with drugs

and change to the seaside had little or no effect, and I decided to see what effect the use of a vaccine would have. Captain Douglas was kind enough to supply me with the necessary vaccine, and I gave it hypodermically. After the third dose, at the end of two weeks, the temperature fell below normal and never rose again; the headaches ceased, and the patient assured me she felt better than she had done for weeks past.

From the comparatively small experience gained in the course of treatment of the above and other cases, my feeling is that—

(1) Brilliant results are to be obtained from the timely use of vaccines.

(2) They may with advantage be given by the mouth.

(3) Whenever possible, the opsonic index is to be used, along with the temperature and clinical conditions, as a guide to dosage.

Royal Society of Medicine

June 22, 1910.

Sir WILLIAM S. CHURCH, K.C.B., President, in the Chair.

Discussion on Vaccine Therapy: its Treatment, Value, and Limitations.¹

Dr. W. D'ESTE EMERY: The discussion which is now drawing to a close has been of a somewhat desultory nature, touching on many subjects, and amongst others on one of extreme importance at the present day—namely, the relation which exists and that which should exist between the clinician and the pathologist. That this is not at present all that it should be is, I think, apparent to all, and I have no doubt in my own mind what the solution of the problem will be in the future. Sir Almroth Wright, in his opening speech, said the time would come when every physician would be his own bacteriologist. I agree with this most heartily. It is an ideal which I have always used my best endeavours to bring about. But it does not follow that every bacteriologist will be a physician. There will always be those who have studied the subject more deeply and have spent more time in acquiring technique than the physician in the active practice of his profession can afford to do. Their duties will be to carry out the more delicate and laborious researches, such as exist now, and such as will become more and more important in the future. But when the all-important subjects of clinical pathology and bacteriology have taken their proper place in the medical curriculum, when as much time is devoted to them as to subjects of not greater importance, such as anatomy or physiology, and when the student is encouraged to study what takes place in the body in disease as well as in health, then

¹ Sixth meeting (adjourned from June 15).

I think the difficulty will right itself, and the pathologist, called in to make a difficult research in a difficult case by a physician who is himself a competent pathologist up to a certain point, will be regarded not as a drudge but as a colleague. Signs are not wanting that this process is commencing, and the clinician of high attainments in pathology is already with us. But there is a real danger that the pathologist may be devoid of clinical experience. This I regard with profound apprehension, and should forbid any one to specialize as a pathologist until he had had a good clinical training. Without this the clinical pathologist is as great a danger as the physician without a practical knowledge of pathology and bacteriology in their modern developments.

In discussing the more immediate object of these debates I shall not attempt to produce lists of cases, but to record my general impressions of the results obtained. I have had both successes and failures in many branches of vaccine treatment, but I think it only fair to say that many of the failures and some of the successes have been in patients in whom ordinary clinical methods had been given a full trial and had also failed. A few marked successes of this kind—that is, rapid and complete cures in cases in which no good at all can be effected by the means formerly employed—make a deep impression, and it was one such case that convinced me of the value of vaccine treatment. It was a very severe case of gonorrhoeal arthritis of more than two years' duration, which had had most thorough and careful treatment both in England and abroad, but without benefit. When I saw him both knees, both ankles, one shoulder and many small joints of the hand were affected. He made a complete cure under vaccine treatment in less than three months, and the improvement was most obvious within a week of the first dose.

To summarize the results I have seen and obtained, in *staphylococcic* lesions of the skin the method is most successful, and I suppose no one would attempt nowadays to treat such cases without vaccines. In general, boils are more amenable to treatment than is acne, but in the latter case the addition of vaccines of the acne bacillus leads to much better results, though of this I have had but little experience. Next to staphylococcic lesions I should place infections of the urinary tract by *Bacillus coli*. Here, as a rule, the effects are marked and immediate, only a small proportion of cases failing to show improvement within a few days. I must, however, admit that if the bacteriological test of cure be adopted, in most cases the cure is incomplete. All symptoms are

removed, and from a clinician's point of view the patient is well: but as a rule some bacilli, though in comparatively small numbers, persist in the urine. *Gonococcic* infections, such as arthritis and iritis, are uniformly benefited, and are often completely cured in a rapid and striking manner. I have had little experience of the treatment of urethritis, whether acute or chronic. *Pneumococcic* lesions are sometimes cured quickly and completely, whereas at other times they are most resistant. As an example of the former I may quote a case of suppuration of the frontal sinus of some years' duration, twice operated on (to secure drainage) and showing not the slightest tendency to spontaneous cure. The discharge ceased after two injections; the patient received three more, and there has been no recurrence of the disease after three years. I have also had a very striking case of cure of a case of frontal sinusitis due to Friedländer's bacillus. I must also mention a very interesting case of failure after the use of pneumococcic vaccines. A patient under the care of Dr. Murray Leslie had suffered from a chronic pneumococcic abscess of the lung for more than two years. I gave him four courses of vaccine treatment during the course of the next two years, and left him neither better nor worse. I mention this case because the patient gave the method a most careful trial, and every possible form of modification of the treatment was tried. He had the most careful opsonic control, and small, large, and colossal doses were tried at short and long intervals. In all probability the abscess was shut in by a thick wall of fibrous tissue, and this constituted the great obstacle to the cure. With regard to *tubercle*, my experience (which has mostly been in cases of surgical tubercle, since in them the value of the treatment is more easily watched than in phthisis) is this: the use of tuberculin on Wright's principles is of some value, but it rarely if ever effects a cure of large lesions—that is, those in which active tubercles are protected from the blood by masses of fibrous tissue or by caseous or necrotic material. In such cases there is often a decided benefit, especially to the general health; but the direct effect on the lesion is usually inappreciable or at most very slight. In cases where there is a thin layer of tubercles in contact with healthy vascular tissues much better results can be obtained. Thus I shall describe in fuller detail subsequently two cases of tubercles of the iris quickly and completely cured by tuberculin. I have also seen a few chronic sinuses heal rapidly, and one large and severe tuberculous ulcer get better up to a certain point in a very extraordinary manner. It then hung fire, and, though a complete and lasting cure was obtained ultimately, it took several months.

I am perfectly aware that many vaccinists claim much better results than I am able to bring forward. I wish therefore to state that most of the results quoted were obtained whilst I made use of the opsonic control, and that since I have abandoned the method my results have been neither better nor worse. In concluding this brief account of success and failure I ought to add that, even allowing for all the disappointments, vaccine therapy has established itself as a permanent addition of great value to our methods of cure, and its discovery is a triumph for English medicine and for Sir Almroth Wright.

I pass on now to discuss a question apparently highly theoretical, but really of great practical importance—that is, the meaning of the opsonic index, and the importance to be attached to it as a guide to the exhibition of vaccines. I may say at once that I disagree absolutely with those who hold that it is impossible to estimate the opsonic index with accuracy. I have never studied the question in its mathematical aspects, but have made numerous practical tests, such, for instance, as working out the indices of a series of sera collected by someone else, and containing duplicates; I have found the figures for these duplicate specimens always corresponded very closely. I have also prepared various dilutions of the same sera, and prepared curves indicating the indices, which, from their regularity and constancy in different cases, afford in themselves a proof of the accuracy of the method. Lastly, the curves of the indices obtainable after inoculation of a vaccine are also a sufficient demonstration of the same fact. Given careful technique, it is quite easy to show the absolute accuracy of Sir Almroth Wright's account of the series of changes following the injection of a vaccine into an infected patient. I might, however, be allowed to state that the method is laborious in the extreme, and that if correct results are required, the most careful attention to every detail is necessary, any attempt to cut short the process rendering the results absolutely useless.

We are not dealing here with the diagnostic value of the opsonic index. I may just remark, however, that I am quite in agreement on this point with the opsonic school, more especially in regard to the value of determinations of the index before and after an injection of a vaccine of the organism with which the patient is supposed to be injected. I believe this method to be one of great value; the only objection to it being the technical difficulty arising from the necessity of making several determinations, each demanding the greatest accuracy.

When, however, we turn to the meaning of the opsonic index in its bearing on the question of immunity and the exhibition of vaccines, we

encounter great difficulties. The point that I wish to discuss more especially is this: Is the opsonic index to be regarded as being in any sense an indication of the patient's resisting power against the disease in question? That it is such an index is the assumption, as Sir Almroth Wright has told us in his opening address, that underlies the use of the opsonic index as an indicator for the dosage and spacing of vaccines. The arguments in favour of this view are: *First*, that, the activities of the leucocytes being equal in the two cases, the blood of a patient having a high opsonic index will deal more easily with an infection than will the blood of a patient in whom the index is low. This is, of course, both true and self-evident; but its value in treatment depends on a demonstration of the fact that the phagocytic value of the blood of the patient with the low index is too feeble to protect him against the disease under discussion. This, however, is not self-evident, nor do I believe it to be true. I may quote one case: a patient under Dr. Whitfield, suffering from a slight tuberculous lesion of the skin. His opsonic index was determined on many occasions, both by Dr. Whitfield and myself, and always found to be low. Sometimes it was extremely low, less than 0.1, but it was usually about 0.3 or 0.4; only on one occasion did it reach 1, and then as the result of tuberculin treatment. Yet this patient showed no evidence whatever of increased susceptibility to tubercle; his disease underwent gradual cure, and he did not develop any fresh lesions, although, like the rest of us, he must have been frequently exposed to infection during the eighteen months he was under observation. *Secondly*, the evidence that a raised opsonic index implies increased immunity depends on the fact that clinical improvement is often coincident with the elevation of the index, as brought about by an injection of a vaccine. This, of course, is also admitted, but the elevation of the index is only one of a complex series of phenomena which follow the injection. Nor is it always the case: Allen has noted that after the use of gonococcic vaccine continued improvement may accompany a prolonged negative phase, and I can corroborate the fact. I have also seen it in tuberculosis, and in one of the few cases of this disease in which I have noticed a very marked and rapid beneficial effect from tuberculin the improvement took place almost entirely during a negative phase lasting three weeks.

The evidence in favour of the opposite view may be stated as follows: *First*, a high index is not necessarily accompanied by a recovery or by a mild form of the disease. Every opsonist must have met with cases of lupus with a very high index, which nevertheless showed no sign of

improvement. I had under my care a case of lupus of the face of fifty-six years' duration associated with an index of nearly 2; it was practically stationary, and certainly showed no tendency to heal. The result of vaccine treatment was to lower the index, and there was some slight improvement in the lesions. It is the same with acute diseases. As a rule, undoubtedly, a severe attack is accompanied by a low index; but even here exceptions may be found, as, for instance, in generalized tubercle or tuberculous meningitis, in which normal or high indices are not infrequent, and the preagonal rise in other infections is well known. Sir Almroth Wright has pointed out and emphasized the fact that, admitting the rise in the opsonic index to be an indication of the immunizing response, we must not expect it to be necessarily coincident with clinical improvement. Many other factors, and notably the free access of the blood to the lesion, have to be taken into account. I have not lost sight of this, but it appears to me not to account for the development of fresh lesions in patients with a high index; for example, patients suffering from furunculosis have frequently high indices at the time fresh crops of boils are forming. Here it is difficult to see how the staphylococci can be in such a position that the blood and leucocytes have not easy access to them, and other examples might be quoted. *Secondly*, as I have pointed out already, a low index does not necessarily imply that the disease will make rapid progress. A low index may accompany a severe, a mild but progressive, or a healing lesion. We are led to believe, therefore, that the defensive powers present in blood of feeble opsonic power is adequate to the destruction of the bacteria in the body, and that, although the raising of the index may be, and probably is, an increased safeguard (especially, perhaps, against hæmic infections), this is not the mechanism by which vaccines produce their effects.

This mechanism I believe to be threefold. First, and of greatest importance, there is the local reaction; secondly, a general alterative or metabolic effect; and, thirdly, an immunizing effect. By the term "local reaction" we mean the series of changes which take place in the immediate vicinity of the lesion, and which we may describe briefly as an aseptic inflammatory process. Given a suitable dose of the vaccine, these changes are practically limited to hyperæmia of the vessels immediately surrounding the lesion, with probably a slightly increased exudation of fresh plasma and diapedesis of functionally active leucocytes. This sequence of events, of course, constitutes (in the case of tubercle) Koch's phenomenon in its slightest form. Given larger doses, more acute inflammatory processes, accompanied by obvious swelling, by stasis in the

vessels, and perhaps by necrobiosis of the lesions, will be brought about, as well as a general reaction in the form of sudden rise in temperature. These severe reactions are what we wish to avoid, and we may do so by one of two methods: we may give very small doses at long intervals, so that the immunizing effect is little or absent; or we may give larger and increasing doses at short intervals, so that the patient is immunized to tuberculin, and the effect of each dose is diminished by that which has gone before. The so-called opsonic method I believe to act in the first manner almost entirely; the doses given are those which cause a slight and beneficent local reaction, but which do not exert any appreciable immunizing influence, so that by the time the second injection is given the patient has returned to his original condition of susceptibility. In most cases these reactions are so slight as to be inappreciable clinically; they cause no rise of temperature, and are unassociated with obvious swelling of the affected region. In some cases, however, this may be seen, as, for example, in tubercle of the iris. This disease is, of course, especially favourable for observation, the actual tubercles being visible throughout the course of treatment. I have treated two cases, each being an absolute cure within two months. The doses given were $\frac{1}{5000}$ mg. of T.R., at intervals of ten to fourteen days. In each case the injections were followed by the production of a narrow, pink zone round the lesions, which developed within twenty-four hours, and lasted two or three days, and it was obvious that when the reaction had passed off that the lesions had diminished in size. I believe Mr. Mayou has made similar observations. I regret that I did not make systematic estimations of the opsonic index in these cases, and am therefore unable to say whether the reaction coincided with any of the events following the injections. Another effect of the local reaction may sometimes be seen in cases of slight phthisis, in which there is ordinarily no cough or sputum. An injection of a minute dose of tuberculin may be followed with great regularity by the expectoration of a small amount of mucopurulent sputum.

The points which I wish to emphasize in connexion with these cases of tubercle of the iris are: (1) That the reaction took place after a very small dose of T.R. (I am unable to say whether a smaller dose would have had any effect, but the fact that $\frac{1}{5000}$ mg. was definitely efficacious appears to be worthy of notice). (2) That exactly the same sequence of events followed the second injection, given ten days later, as was produced by the first; in other words, if any immunity was produced it did not last for this length of time. (3) That the reaction was mild in

the extreme, and not associated with any obvious necrobiosis, or breaking up of the nidus or dissemination of the bacilli. I mention this because in one of Sir Almroth Wright's papers, in which he discussed this local reaction in the case of staphylococci and tubercle, he remarks that the inflammatory reaction leads to a breaking-up of the nidus in which the bacteria are lodged, and a "fluttering" of the bacteria themselves. The spread and dissemination of the disease which followed large doses of tuberculin he attributed to a diminution of the patient's power of resisting the organisms thus let loose; and leads us to infer that this unfortunate occurrence might have been avoided had the patient's resisting power, as measured by the opsonic index, been raised. But the reaction after doses like this is extremely slight, and unattended by any rise of temperature, or in ordinary cases by any obvious tumefaction of the lesion. Either of these phenomena I regard as proof of an overdose, and I believe the optimum dose of tuberculin to be the largest that can be given without the occurrence of either.

How the local reaction is caused is not yet known, and this is not the occasion on which to study the numerous theories as to its causation which have been advanced. It is, however, more profitable to consider for a moment the manner in which a frequently occurring reaction may result in the cure of a lesion. The usual suggestion is that the cure is brought about in virtue of the flooding of the diseased tissue with lymph rich in bacteriotropic substances, and in particular in opsonins. But the evidence in favour of the view that a high opsonic index does facilitate the cure is not strong, and rests mainly on some observations by Dr. Bulloch on patients suffering from lupus, and treated with the Finsen light. Now this method of treatment causes a local reaction similar in all respects, as far as we can tell, to that caused by inoculation with vaccine; and Dr. Bulloch found that as a general rule those patients did best in whom there was a high index. We find, however, on looking at his tables that, although his deductions were perfectly correct, there were, as a matter of fact, numerous exceptions: thus the patient with the lowest index (0.25) of the whole series is recorded as doing well under light treatment. Here, therefore, this patient's blood was, if we accept this theory of the action, sufficient to kill the organisms if brought into contact with them by means of a reaction induced by the Finsen light. I wish to make it clear that I am not denying the value of the flushing of the tissues with healthy blood or lymph. I am trying to show that even with a low, opsonic index there is a sufficiency of defensive substances in the blood. In this connexion please notice: (1) That the

number of bacilli in the lupus lesion is very small in comparison with the number of tubercle bacilli that are taken up in an opsonic test, even with a serum of low index; (2) that the time which the plasma and leucocytes may act in the body is indefinite, in place of the fifteen minutes of an opsonin experiment; and (3) that if we accept certain recent researches there is a constant shower of bacilli from the local lesions in phthisis, yet without the development of distant tubercles, showing that, contrary to former ideas, the blood must have a very considerable bactericidal action on the tubercle bacillus. May I suggest that it is probable that apart from, and perhaps more important than, the bactericidal action of the blood thus induced to stream through the lesion, there is also a stimulating action on the tissue cells of the lesion, so that the same substance which, when present in excess, causes necrobiosis, causes, when present in extremely minute amount, an increased vitality and increased resisting power in the cells in the neighbourhood of the bacteria? I believe that this is the primary effect in a reaction, and that the hyperæmia is a consecutive effect due to the heightened functional activity of the cells in the lesion or in its immediate vicinity.

The second effect, which I have termed the "alterative action," does not always occur, but is occasionally very well marked. It consists in a general improvement in nutrition, often accompanied by a marked sense of well-being and stimulation of all the bodily faculties. It is not entirely an effect of suggestion, for it may be seen in very young children. This improvement in the general health may take place when there is no obvious improvement in the local lesion, especially in some cases of pyorrhœa alveolaris, in which a decided improvement in nutrition and the general health has occurred without being accompanied by any apparent local benefit. Of course, the general tonic effect may, and probably will, have a beneficial effect on the lesion if continued long enough. Another result frequently seen during a course of vaccine treatment, which I include under this heading, is diminution of anæmia, should this be present. Thus I have on two or three occasions seen marked temporary improvement in the anæmia of malignant cachexia treated with neoformans vaccine, an improvement which I need hardly say I do not attribute to any direct curative effect on the malignant growth. In one case of severe frontal sinusitis, due to the pneumococcus, the percentage of hæmoglobin when I started vaccine treatment was 20, and it rose to 40 in three weeks. This was practically at the rate of 1 per cent. per diem, which is about the rate at which

hæmoglobin is regenerated in a healthy person after a severe hæmorrhage. In this case there was decided local benefit, but hardly sufficient to account for the dramatic improvement in the patient's general condition. I have some reason for thinking that this tonic or alterative effect may be non-specific, and may be induced by vaccines other than that of the organism with which the patient is infected, but I do not regard this as certain. This alterative effect has been carefully studied by Campbell Bruce,¹ who found a very marked increase in the weight in patients suffering from chronic mania when treated with streptococcic vaccine; he also holds that the effect is a non-specific one, and offers a plausible and interesting suggestion, based on Ehrlich's side-chain theory, as to its causation. It is also alluded to by Dr. Courtenay McWatters,² who refers to the "pale, fretful, easily-tired children, with no appetite, who are never well and who are 'bad doers.' These cases often do remarkably well, gaining in colour, appetite, weight and vigour after a few doses of tuberculin." I can quite corroborate this.

The third effect of vaccine treatment is, or may be, the production of immunity. This is, of course, best seen in the use of prophylactic injections of typhoid, cholera, and plague vaccines. I believe this immunizing effect is not one to be striven for in the therapeutic uses of vaccines in ordinary diseases. Take, for instance, the organism against which vaccine therapy has won its most conspicuous triumphs—the staphylococcus. Here the curative effect is most conspicuous, but it is extremely doubtful whether it is possible to raise appreciably the resistance of the body to the organism, and certainly it is very difficult to induce the massive immunity that can be produced to typhoid or cholera in animals, whatever the size or the spacing of the injections. In the staphylo-mycoses a further demonstration of the fact that the cure of the lesion is not due to any immune substance circulating in the blood is seen in the fact that the cure of one lesion, whether natural or due to a vaccine, may coincide with the spread of another and the appearance of a third. I may remind you of the remarkable paradox that a horse with an abundant supply of antitoxin in the blood may die from a small dose of toxin, and that a patient whose blood is powerfully bactericidal to typhoid bacilli may nevertheless suffer from a relapse after typhoid fever. It appears to me that the production of a high degree of immunity may even be prejudicial to success in the treatment of an existing lesion, by raising

¹ *Brit. Med. Journ.*, 1910, i, p. 430.

² *Practitioner*, 1909, lxxxiii, p. 327.

the dose of vaccine necessary to cause a reaction, and that the real advantage of the small doses that have now come into use is that they avoid any cumulative immunizing effect and allow the patient to revert to his previous state of susceptibility before a second injection is made.

The conclusion I wish to draw from these theoretical considerations is that the curative action of a vaccine is due mainly to its reactive action, and to a much less extent, if at all, to an elevation of the opsonic index. As a practical result of this I do not believe it to be necessary or even advantageous to control the injections by means of the opsonic index. In giving a vaccine I am desirous of causing a local reaction, and of thereby benefiting the patient, not of raising the opsonic index. The danger of the negative phase I believe to be a fictitious one; of course it is undesirable to give too large a dose of a potent vaccine, just as it is undesirable to give too large a dose of a potent alkaloid, but I believe that by this time the doses of the two substances have been fairly ascertained, and, given accurate counting of the bacteria in the vaccine itself, the danger of an overdose is little or none. I have only seen one case in which I felt tolerably certain that an overdose had been given, and in this case I was working with an unknown organism, and one that it was impossible to count in the ordinary way. I had intended at this point to discuss the alleged dangers of the negative phase, but will content myself by referring to Major Russell's article,¹ in which the subject is dealt with at some length. Sir Almroth Wright, in his opening speech, said that the bacteriologist who abandoned the use of the opsonic index was the real foe to vaccine therapy. I must deny this in my own case most strongly. In ordinary clinical work we often meet with cases of great susceptibility to the use of certain drugs, but we do not on that account decline to use those drugs. We proceed with caution, basing our doses on previous experience; and this, I think, is the only practicable method.

Dr. DAVID LAWSON (Banchory): Presumably it is due to the not unimportant part which I took in the discussion held in 1904 under the auspices of the Medico-Chirurgical Society, a discussion which ushered in the great wave of popularity which of late has attended the employment of opsonic methods in medicine, that I have been invited to place upon record my impression of the value and limitation of serum therapy in relation to lung disease.

¹ *Bull. Johns Hopkins Hosp.*, Balt., 1910, xxi, p. 83.

The impressions which I propose to submit are, for the most part, drawn from experience gained in the continuous use of opsonic methods in association with my clinical work during the five years which have elapsed since that time. The vast majority of the cases dealt with have been cases of pulmonary phthisis, mostly at an early stage of the disease. In addition, however, I have had to deal with one case of pure streptococcal abscess of the lung; four staphylococcal infections of the same organ, an uncertain number of mixed infections of pulmonary phthisis, together with a small number of bladder, renal, and gland forms of tuberculosis, and one case of adult tuberculous meningitis. I have also come across a large number of cases of acne amongst my phthisical patients, and these have been invariably treated by vaccine methods, generally with success.

If it be objected that this experience has been gained in a somewhat narrow field of observation, it should be borne in mind that within these limits the experience has been an extensive one, not less than 600 cases having been dealt with during that time. It has been an advantage, arising out of the circumstance that I have been living under the same roof day in and day out with my patients, that I have enjoyed exceptionally favourable facilities for watching the course of the disease in these cases closely and minutely. Moreover, most careful and complete clinical records have been kept of every case throughout that time. It is convenient to submit the observations under four headings, namely:—

- (1) Oral administration of vaccines.
- (2) The use of T.R. tuberculin in diagnosis.
- (3) The use of T.R. tuberculin in prognosis.
- (4) The use of T.R. tuberculin and vaccines in the treatment of pulmonary tuberculosis.

FIRST—ORAL ADMINISTRATION OF VACCINES.

In Copeman's work it is recorded that so far back as 1810 the administration of the contents of vesicles to a girl by the mouth was followed by the appearance of a typical variola eruption, thereby demonstrating the fact that it is possible to obtain a reaction by orally administering a vaccine. When Koch produced his tuberculin he definitely stated that administered orally it was inert, and so great was the influence wielded by that great pathologist that for many years no one appears to have questioned his assertion. In 1908 Dr. Arthur

Latham published in the *Proceedings of the Royal Society of Medicine*¹ a preliminary communication dealing with work done on the oral administration of horse serum. Again, at a later date we find in the *Proceedings*² of the same Society a paper by Dr. Latham, in association with Dr. Spitta and Dr. Inman, dealing with the same subject. The latter paper in particular is one of extreme value and importance, not only on account of the extensive nature of the research, but also because of the conclusions at which the observers have arrived. Amongst other conclusions arrived at by those workers is this one: "T.R. tuberculin administered orally exerts a definite influence on tuberculous disease."

With the object of testing the validity of this conclusion, along with Dr. H. S. Gettings I carried out an independent inquiry on the lines followed by those observers. We selected six cases of pulmonary tuberculosis; four of these were apyrexial, and two were pyrexial. All were cases of somewhat extensive disease, and all were more or less old-standing. Full clinical records were kept embodying observations of the pulse, respiration, temperature, weight, and urine. We were not able to base any conclusions upon some of those records, and so far as they seemed to have no bearing on our ultimate conclusions they have been omitted. Only those parts of the record essential for our purpose have been retained in the charts prepared. The blood of each patient was taken every morning before breakfast and subjected to the ordinary opsonic test. The doses of tuberculin were given at 10 p.m., when presumably the patient's stomach was empty. Certain precautions were taken to eliminate the more apparent sources of error. To obviate the personal factor, measures were adopted to prevent the observer from being aware whose blood he was dealing with until the close of the experiment. To effect this the blood capsules, both of control and of the patient, were handed to him merely bearing numbers, and it was not until the completion of the counting had taken place that he was made aware of the identity of each blood.

Secondly, in regard to technique, the earlier practice of counting twenty-five or even fifty polynuclear cells is now recognized as not sufficiently reliable, and therefore throughout the inquiry a minimum of 100 cells was dealt with. In this way over 28,000 cells were examined in the course of the research. Further, it had been previously recognized that when the bloods were incubated in batches, withdrawn at the same time, filmed and stained seriatim, the cells of those last prepared showed

¹ *Proceedings*, 1908, i (Clin. Sect.), p. 100.

² *Proceedings*, 1908, i (Med. Sect.), p. 195.

a uniformly larger proportion of bacilli than those done first. This is due to the phagocytosis that evidently still goes on at room temperature during the interval of waiting. It occurred to one of us that probably if the leucocytes were chilled such phagocytosis might be stopped. Accordingly, on withdrawing the pipettes from the incubator, they were at once placed in a vessel of cold water and taken out one by one as required. We think that this method gave us increased accuracy in our results, and we desire to draw the attention of our fellow workers to this point.

A study of Chart I reveals the ground upon which the conclusion arrived at rests. The charts have been drawn out in such a way as to show: (1) An opsonic curve indicated by a single line; (2) the doses of tuberculin and the dates on which they were administered by mouth indicated by vertical lines. The question we set ourselves to answer was this: Can tuberculin, when given by the mouth, exert an action on the blood content as indicated in the variation of the opsonic index in a person suffering from tuberculous disease?

Out of thirty-six instances in which doses of tuberculin, varying in amount from $\frac{1}{4000}$ mg. to $\frac{1}{1000}$ mg., were administered, in twenty-three instances (or 64 per cent. of the whole number) a negative phase immediately appeared. The fact that in 64 per cent. of the occasions referred to a definite negative phase was recorded seems to support the claim made by Dr. Latham and his colleagues that tuberculin administered by the mouth in cases of tuberculosis is absorbed and modifies the blood content. Following upon this inquiry, we have gradually substituted for hypodermic medication the practice of administering tuberculin by mouth. Only on rare occasions and for special reasons is the needle employed. So far as we can see, by this change of procedure one has not in any way sacrificed or diminished the benefit which in suitable cases the administration of tuberculin undoubtedly confers.

PROGNOSIS.

There is a practice which obtains in certain quarters amongst pathologists in this country—not confined to the lesser lights, but favoured by some in high places—of predicting to the patients or friends from the slender data which one, two, or at most three tuberculo-opsonic estimations afford, the subsequent course which the disease is likely to follow in cases of pulmonary phthisis. It seems to amount to this: that when these readings are within two points of 1, then the patient is assured that the prognosis is favourable. The patient leaves the room

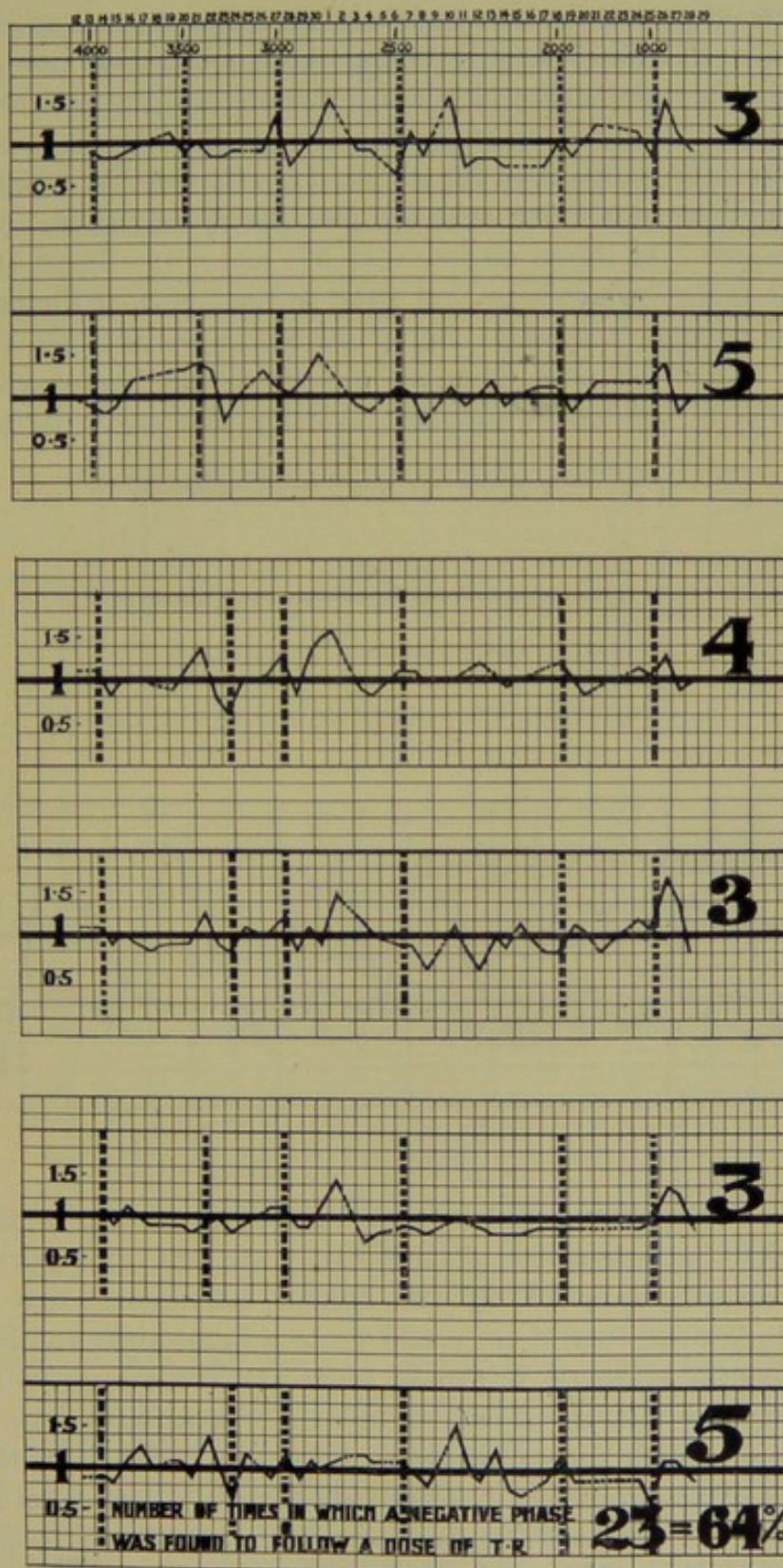


CHART I.

greatly marvelling at the wonderful advance the science of pathology has made. The burden of fulfilling these predictions passes to the shoulders of the unfortunate physician to whose care the patient returns. How utterly unreliable the indication furnished by opsonic indices in relationship to prognosis may be, Charts II, III, and IV, selected from a large number of similar ones in our possession, show. Chart II is a simple one. It shows an index of 0.8 and 1.1. Chart III shows a range of indices which pass but little beyond normal limits. If we except the single fact that the physician, who referred this case (Chart II) to him for blood examination, stated that he believed it was a case of early pulmonary phthisis involving one apex, the top chart

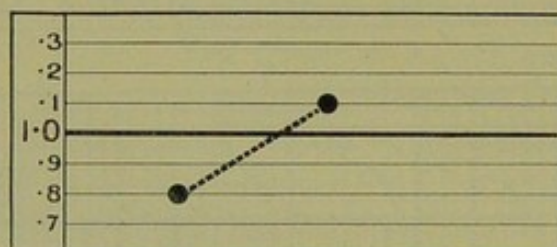


CHART II.

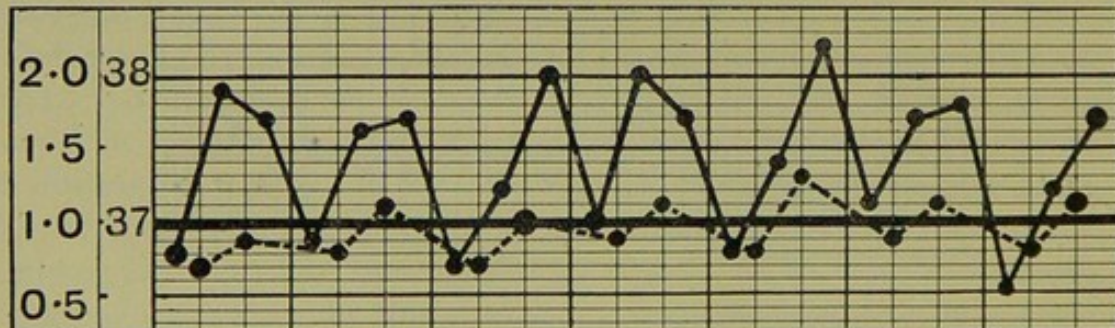


CHART III.

indicates all the facts which were available to one of the most distinguished bacteriologists of the day. On the strength of that limited knowledge supplied, by two opsonic estimations, this observer assured the patient that if he would go to a sanatorium and live there for three months he would return to town a sound man. In the case represented on Chart III a similar opinion was expressed by another pathologist on much the same data. Case No. 1 (Chart II) happened to be one of diabetic phthisis, and the patient died in four months. The urine of Case No. 2 (Chart III) was soon afterwards found to contain a large amount of albumin, and Ehrlich's diazo reaction was very well

marked indeed. Of course, here again an unfavourable termination ensued in the course of a few months. Opsonic indices entirely failed to yield any indication in either of those cases of the presence of urinary conditions so vital to the patient and so necessary to him who would prognose.

Chart IV shows opsonic curves taken from two patients suffering from terminal miliary disease. Neither furnishes any striking departure

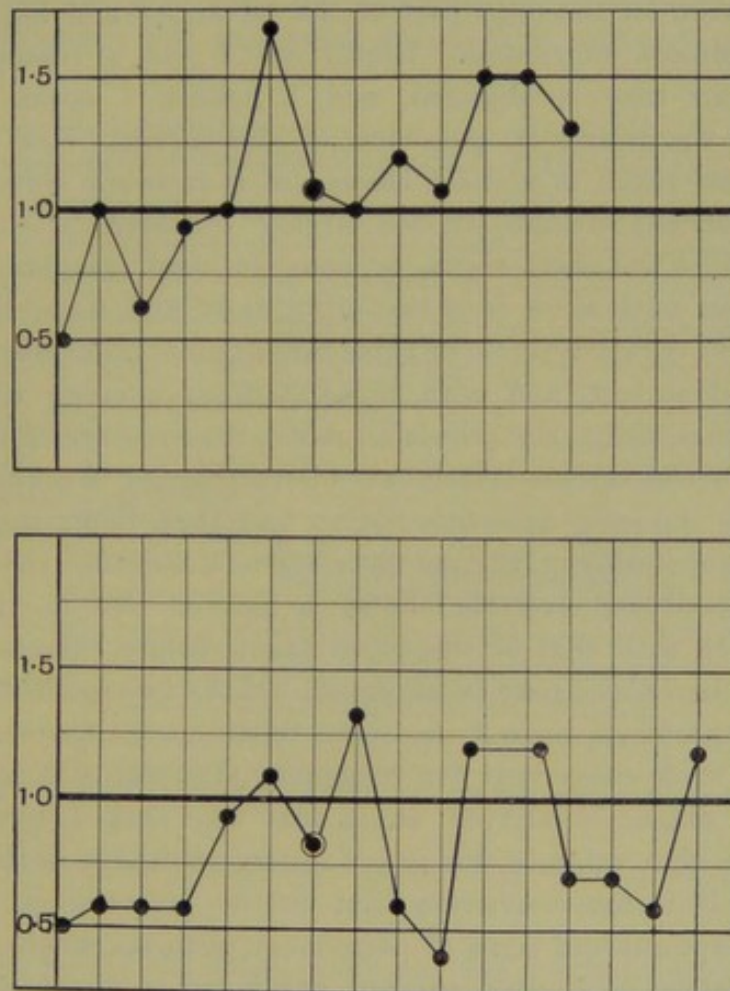


CHART IV.
Terminal opsonic index curves.

from normal. Yet one died in twenty-four hours and the other in seventy-two hours. Instances such as these can be multiplied out of our experience, but they suffice to illustrate this point. In pulmonary phthisis the tuberculo-opsonic index is quite valueless as a guide to prognosis, and such investigators would do well to discontinue a practice which in the end can only lead to disillusionment and disappointment on the part of patients and friends alike.

VACCINE THERAPY AND DIAGNOSIS.

One point stands out in striking clearness in this connexion. A marked change has in recent years come over the clinical type of case which is presenting itself for treatment at the better-class sanatoria. I recall my experience in the earlier years of my work with feelings of pain. The recollection of that time is a nightmare. Cases which came were for the most part of the advanced and hopeless type. Many were almost moribund. Rarely did I see a reasonably early case. Now all that is changed, and I believe I speak for others when I state that quite 80 per cent. of the patients now arrive in a condition when there is a good chance of a recovery being achieved. For this beneficent change we are largely indebted to Sir Almroth Wright. Whilst the chest signs, or constitutional symptoms, are still little more than suggestive, it is becoming more and more the practice of physicians to obtain a series of tuberculo-opsonic observations of such patient's blood at rest, and with those showing a range which varies outside of normal limits, the physician infers the presence of tuberculosis and at once advises serious treatment. Others prefer to employ exercise with a view to inducing auto-inoculation and then observing the effect of that auto-inoculation on the patient's tuberculo-opsonic index. If the index after moderate exercise shows a marked rise in the altitude when compared with that of the blood taken before exercise, then the presence of tuberculosis may be assumed. Of the two methods, the latter has, in our experience, proved the more reliable. So frequently have I been able in such cases sent for treatment afterwards to confirm with certainty the diagnosis arrived at in this way that I have come to attach a very high value to this use of opsonic methods in the diagnosis of phthisis. It is my conviction that in the presence of indefinitely suggestive symptoms and signs of pulmonary phthisis, where the microscopic examination of sputum present has failed on repeated examination to reveal tubercle bacilli, the physician has not done his duty to his patient if he gives it as his opinion, and bases advice upon that opinion, that the case is not one of phthisis, if before doing so he has not first employed one of the methods of serum diagnosis associated with the names of Wright, Calmette, or von Pirquet.

TREATMENT.

Whilst my experience has been chiefly confined to simple cases of tuberculous infection—by that I mean cases in which only tubercle

bacilli have been found in the sputa, or apyrexial cases with other signs of pulmonary tuberculosis but yielding no sputum suitable for examination—I have met with a number of other interesting conditions and treated them by serum methods which may be worthy of mention.

(1) *Streptococcal Infection of the Lung* (Chart V).—Two cases have been met with where the pus yielded a pure culture of streptococci. In one case complete recovery followed evacuation by the surgeon. The other was also operated upon and subsequently treated by streptococcal serum injections. The injections appeared in no way to modify the

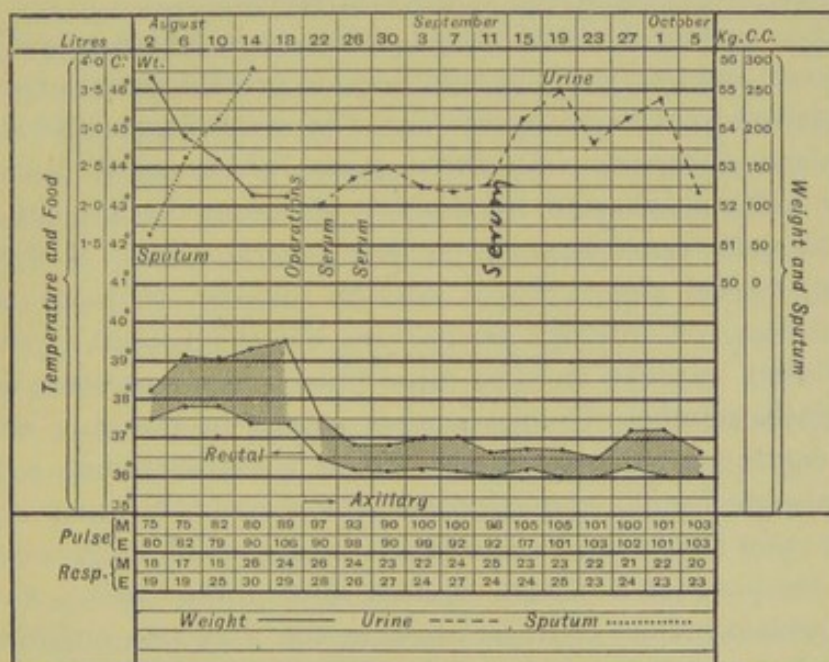


CHART V.

Chart of case of streptococcal abscess of lung (four daily records).

unfavourable course of the disease, and the patient died of exhaustion eight weeks after the operation had taken place.

(2) *Staphylococcal Infection of the Lung*.—Four cases of lung disease, at first believed to be cases of pulmonary tuberculosis but subsequently found not to be so, all yielded pure cultures of staphylococci. The tuberculo-opsonic indices of those cases taken repeatedly were always found to be within normal limits; but it was not so with the opsonic indices to staphylococci. When the initial fever had subsided these were all treated by injections of staphylococcal vaccine obtained from the patient's own brand of organism. In each instance a favourable

result was obtained and complete recovery ensued. I have recently heard, however, that one of the cases had again broken down after two years of office work.

(3) *Pneumococcal Infection of the Lung*.—My experience of treatment by serum therapy of this form is extremely limited. It is confined to three cases in which pneumonia set in in extensive cases of phthisis with mixed infection, and where, at that stage, enormous numbers of pneumococci were found present in the sputum. In one instance we recovered pneumococci from the blood. Each was treated by pneumococcal vaccine without avail. They all terminated fatally within three weeks of the onset of the pneumonic symptoms.

(4) The common form of mixed infection in which tubercle bacilli, staphylococci, and frequently streptococci are present in the expectoration will be referred to at two stages:—(a) *The marked pyrexial stage with "hectic" manifestations*: In those cases I have never been able to trace any influence exerted by the use of serum therapy either on the more prominent symptoms, or on the general course of the disease. (b) *The apyrexial stage*: In a certain number of cases one finds following a term of ordinary sanatorium life the patient's general and local condition improve and the rapid pulse and temperature disappear. A considerable number of moist sounds persist in the lung and expectoration continues to be produced, which when examined is found to contain tubercle bacilli, staphylococci, and sometimes other organisms. Two such cases after they had reached the apyrexial stage were treated by mixed vaccines for a period of close upon three years. For over a year the opsonic indices of those cases to the first two organisms were estimated daily, and the information derived from this source utilized in the administration of the vaccines. The first organism to disappear from the sputum was the tubercle bacillus, and next to that the streptococcus. The staphylococci have proved in both cases most persistent, and are still present. When I last had an opportunity of examining those patients I found slight physical signs still present at the apices. The patients are very well. One, an army officer, efficiently discharges the full duties of his profession. The other, a lady, leads a careful life in good surroundings, and is also very well. The persistence of staphylococci in those cases is at variance with the view held by some observers (amongst others by Habershon) that the transference of a case of mixed infection from town to pure country atmospheric surroundings invariably promptly changes the case from being one of mixed infection to one of simple tuberculous infection.

Tuberculous Cases.—Contrary to the experience of some, I have never found the exhibition of tuberculin in cases of pulmonary phthisis accompanied by pyrexia followed by the reduction of the fever or activity of the disease. I have seen it act in this way in gland cases, but not where the lungs were known to be involved. On the contrary, I have in more than one instance had occasion to believe that the pyrexia was unfavourably influenced by the vaccine. As a matter of practical procedure I have now abandoned the practice of administering tuberculin in lung cases where fever is present.

In treating early cases of phthisis from the commencement by a combination of tuberculin administration and sanatorium treatment, and watching recovery take place, it has been found difficult, if not impossible, to allocate to the action of tuberculin its just share in promoting recovery. The difficulty is increased when we recall the fact that for several years before we were using T.R. as a routine procedure a very large proportion of cases got quite well under sanatorium treatment alone. There remained a certain number, however, drawn from this class, and also from a class of more serious type, where the recovery advanced to a certain point and then all progress appeared to cease. Many of these cases ultimately went wrong. It is in such cases that we now recognize how great a service may be rendered by the careful, systematic, and persevering use of tuberculin. By adopting tuberculin treatment at this juncture, and continuing its use for a prolonged period—from six to twelve months—I am convinced that a large proportion of those cases, where our ultimate successes in our pre-tuberculin days were few in number or modified in completeness, may now be guided into a state of complete recovery. Moreover, I have the impression, although not in a position to submit that convincing proof which figures may yield, that the proportion of relapses is smaller in those cases than in the cases which have not been treated by tuberculin. In this connexion it is appropriate to recall the experience of so careful and laborious a worker as Trudeau, who quotes figures to show that by the employment of tuberculin in all stages of the disease he found not only that a larger proportion of recoveries was obtained, but that a smaller number of relapses occurred than took place amongst those cases in which tuberculin had not been employed. From other sources, and from what we have heard at this debate, I gather that another view is held in certain quarters upon this subject. We have heard the opinion quoted with approval by pathologists that the use of tuberculin or vaccines in pulmonary phthisis is practically worthless. After making

due allowance for the great service bacteriologists have done and are doing in medicine, we must remember there are branches of the work upon which, before accepting their opinion, it is well to examine the basis upon which that opinion rests. This is a case in point. The average pathologist's experience of the treatment of phthisis is drawn from two sources. Firstly, from the ordinary advanced and usually hopeless case which is to be found in the wards of a general hospital; secondly, from private patients, for the most part old-standing chronic cases who have placed themselves in the hands of the pathologist for vaccine treatment. Many such have eventually come under our notice who had previously undergone more or less prolonged courses of treatment under pathologists who had judged of their cases purely from information derived from systematic opsonic estimations, had never examined their chests, and who did not see their patients for weeks at a time. It is a welcome feature of the situation that this practice one understands is tending to become less common, for neither by training nor by experience is the pathologist who is not working in association with a physician qualified to advise in the best interests of the patient. The patient ultimately becomes dissatisfied, expresses his views freely on all sides on a variety of subjects in language in which such expressions as "charlatanism" is to be found, and the pathologist lays himself open to be misunderstood. An opinion on the value of vaccine therapy in pulmonary phthisis which rests upon so slender a basis as this should not be allowed to pass unchallenged by others, whose wider and more varied experience of the disease has led them to arrive at a conclusion of quite a different nature. Vaccine therapy is a valuable weapon in the physician's armamentarium in treating lung conditions, and where it is possible to employ it in association with systematic opsonic estimations, better results can be obtained than where the guide employed is of a purely clinical nature. In this branch, at least, the bacteriologist's claim to rank equally with the physician cannot be admitted. The information he supplies can be utilized by the physician in the treatment of the patient, but the part he plays must always be subordinate to that of the clinician, who should have full charge of the case.

Dr. A. C. INMAN: I must thank the Council of the Society for the honour done me by asking me to take part in this most important discussion.

Those who have preceded me have not always confined their remarks to the various points of the discussion, but have merely given a series of cases treated with vaccines. These have been of value if only because of the number of branches of the medical profession represented by the speakers. I do not intend to add to the list of cases treated with vaccines, but rather to confine myself to the discussions which have arisen around the various points at issue. Firstly, I would venture, with all due deference, to criticize the attitude of the medical profession as a whole to the work of Sir Almroth Wright. If we inspect closely and seriatim the contributions of Sir Almroth Wright to the study of immunization, and to a host of other subjects, we find that they are all attempts at finding a guide or guides to medical treatment which shall make treatment more accurate, rational, and individual. When he was brought into daily contact with numbers of soldiers suffering from and dying of typhoid fever, he sought to find means of gauging the extent of the production of protective substances of the blood. He gave us a method for the quantitative estimation of the agglutinins and of the bactericidal substances. As a result of these laborious investigations he proposed the prophylactic typhoid inoculations which have been attended with such gratifying results. Now Sir William Leishman holds out the hopes to us that the inoculation of typhoid vaccines may be of value in the treatment of this grave disease.

An appointment at a large general hospital in London stimulated Sir Almroth Wright to study a larger class of bacterial infections, and, ever seeking for some guide to help him, he devised the opsonic technique which has led to the adoption of active immunization in the treatment of a large number of bacterial infections. In a few months these labours had shown that the inoculation of infinitesimal doses of tuberculin is able to call forth an immunizing response in the infected individual. This alone would have been a great triumph. A study of the elaboration of protective substances in the blood in other chronic diseases led to the exploitation of the corresponding vaccine in the treatment of such diseases. The results claimed for this method of treatment have been amply confirmed by subsequent workers: witness the parade of successfully treated cases at this meeting. Sir Almroth Wright, and the small band of workers who stood by him, continued in this way to study the various problems of immunity in a laborious, scientific, and accurate manner. One of the most momentous outcomes of these studies has been the enunciation of the principles of auto-inoculation, spontaneously occurring or artificially inducible. These

principles are so important in the study and treatment of bacterial diseases that no physician can afford to neglect them. Gentlemen, to my mind, we ought to emulate these methods of research. We, too, must study disease in this methodical way, and seek for scientific explanations of pathological phenomena, of failures and successes in the treatment of disease.

There has been a good deal of discussion as to who should and who should not administer vaccines to patients. Unhesitatingly I say that the physician must be the selector of cases for this as for any other method of treatment; he must guide the treatment and must be the judge of the results obtained. Equally unhesitatingly I affirm that the trained laboratory worker must be appealed to for help, for help in the more accurate preparation of the vaccine, for help as to the results of the inoculations—whether for good, bad, or indifferent—in the establishing and spacing of doses when necessary, and for evidence of cure or arrest of disease where such is lacking. In this connexion I would emphasize that the laboratory worker is not necessarily a laboratory hermit who experiments with small animals and then seeks to apply his knowledge thus gained to the treatment of human beings, with laughable, nay, even disastrous results. We have now at most of our hospitals clinical pathologists, men who have perforce to spend a considerable amount of time daily in the wards, at the bedside, where they are confronted with the many difficult pathological problems which are constantly before the physician. Many of these men have served a long apprenticeship in the wards, and have, in addition, undergone a long training in laboratory methods. Now, I doubt whether the ideal time will ever come when the clinical pathologist and the physician shall become one and the same person. As our knowledge steadily advances technical methods become more and more difficult and complicated, and for the sake of accuracy a man has to devote a great deal of time to perfecting his technique and keeping his fingers deft. Again, who would doubt that the making of a great physician is the study of a lifetime? I am one of those who believe that the physician, the man who, as Dr. Fowler said, always has to deal with human nature, the practitioner of that medicine to which there is no royal road, is as essential to the study of medicine as the researcher in the laboratory. There is plenty of work for the two of them, and, for the sake of advancement, these two must work together—the *chef de clinique* and the *chef de laboratoire*.

As regards the value of vaccine therapy, I associate myself with those who recognize that it is of value in certain classes of bacterial infections, whilst in others it is as yet impossible to form an opinion on the matter. But surely even the most ardent supporters of this method of treatment recognize that it is still in an experimental stage. At all events, the opinions expressed at these meetings should stimulate a wide and systematic trial of the method in the acute as well as in the chronic bacterial infections. Vaccine therapy is not, and never will be, an empirical form of treatment; it is based on scientific facts and is essentially an individual treatment. Every case approached needs investigation. In the diagnosis of the case I would insist on supplementing the clinical methods with the direct and indirect evidence derived from laboratory tests. Then, as regards treatment, we have of necessity to consider the effect of the bacterial invasion on the body, and the attitude of the body towards the infection. To help us in this respect we have three guides:—

(1) A consideration of the general condition of the patient, symptoms, and physical signs.

(2) The temperature curve, for evidence of intoxication and activity of disease.

(3) The investigation of the serum as regards its content in protective substances—evidence of response or failure of response to the infection on the part of the infected organism.

Each of these is valuable by itself, but the three together are much more valuable. All three must be considered individually and collectively; none must be ignored.

A discussion has centred round the question as to whether vaccines can be administered by the mouth. I invariably prefer the hypodermic method to the oral, and, when possible, I always employ it. But, from a consideration of the clinical results obtained by the oral administration of vaccines, from a study of the blood changes and modifications in the temperature curve which ensue, I am convinced that vaccines can be satisfactorily absorbed from the stomach; and if boils and acne pustules disappear, as I have seen them do, after doses of staphylococcus vaccine given by the mouth, the result may be considered satisfactory from the point of view of the patient. As regards ill effects following the oral administration, I have once seen vomiting and twice a generalized urticaria, but never serious complications.

The relationship between the opsonic curve and the temperature curve is a more important question. In previous communications I have

published a series of observations which show that there is a very definite relationship between the two. These results were all obtained by working with unknown samples of blood, and the two curves were superimposed some time after the experiments had been done. A number of similar experiments made since only go to confirm the results. To obtain these curves the blood and temperature must be recorded synchronously, and over a certain period. I, too, have found no relationship between tuberculo-opsonic curve and the temperature curve in several cases of pulmonary tuberculosis, but further investigation of these cases showed a very definite relationship between the opsonic curve of one or more other organisms recovered from the sputum and the temperature curve. I do not hold that the temperature can give the whole information as to dosage and spacing of vaccines, but I do think that it gives us a very good mirror of what is happening in the blood, and should in no case be neglected. Similarly, it would scarcely be upheld that the opsonic curve given is the whole story of the immunizing response on the part of the body, but it gives very valuable information, and, when practicable, should not be neglected. It is, I think, certain that in a case of active febrile tuberculosis daily, even hourly, variations occur in the blood curve just as in the temperature curve. Now we should get very erroneous information from a single temperature observation taken at, say, eleven o'clock in the morning; similarly, it is no good seeking information from single daily opsonic indices in such cases. It is scarcely practicable to institute four-hourly indices on any number of cases, and so I believe that in these cases the imperfect guide of the temperature curve must suffice, with occasional reference to the opsonic index when necessary. In this connexion it may not be out of place to emphasize the fact that it is a fallacy to presume that all cases of "tuberculous glands in the neck" are afebrile. It is only too often the case that palpable or visible glands in the neck are associated with others equally infected with tuberculosis in other parts of the body; and, on investigation, many such cases turn out to be not localized, but generalized, infections.

The last clause of the discussion is on the limitations of vaccine treatment. It is obviously a very difficult question to discuss at the present stage of our knowledge. Of first importance is the recognition of the fact that we are dealing with active immunity. By appropriate inoculations we try to stimulate the body to respond, and, aided or unaided, to bathe the infected tissues with serum rich in the necessary protective substances. If the body is already responding to its fullest

extent, or cannot be made to respond at all, and under both circumstances the lesion does not heal, we are powerless to do any more by this method of treatment. We are to a large extent at the mercy of the body.

Again, to a large extent, we are at the mercy of the patient, for whereas many of the diseases yield to treatment in the early stages of the disease, later on we are unable to permanently, or even temporarily, arrest the disease. It must be remembered in this connexion that the immunizing mechanism of the body is the last to give out both in naturally and artificially acquired infections. Even passive immunity—e.g., diphtheria antitoxin—cannot protect the body from the evil effects of bacterial toxins when actual damage has already been done to body-tissues. This is a fundamental principle of immunity which needs to be borne in mind by many who still think that a high opsonic index or a high agglutination titre of a serum means that a patient is doing all that is required of him to overcome his infection. It is also further evidence of the necessity of taking everything into account when a case of infective disease is under consideration. Therapeutic active immunization tries to aid the natural processes of healing. It must be borne in mind that the body sometimes manages to arrest and cure disease of itself without help from without. At other times the body does not respond to the infection; the stimulus does not seem to be sufficiently great. In such cases one or two appropriate inoculations are sufficient to rouse the body to rid itself of the infection. The chart (p. 214) refers to a generalized infection with the *Bacillus coli communis*, the organism having been recovered from the urine three weeks after parturition, during which instruments had to be used. It will be seen that after two doses the temperature came down, and this was concomitant with marked improvement, both local and general, which resulted in a cure. Similarly, in a case of acute staphylococcal infection following the use of a dirty needle for the self-administration of morphia in a morphomaniac, the boils which covered the face, trunk, arms, and legs entirely disappeared after two doses of an autogenous vaccine.

In the more chronic infections, such as tuberculous glands in the neck, acne, &c., a longer or even very long time is necessary before the desired result is obtained. I have seen disappearance of extensive glands of the neck after five, seven, and twelve inoculations; others, apparently very similar in extent and character, took eighteen months, and in one case two years, to disappear. In other cases the inoculations had either no effect or only produced slight diminution in size.

I agree that one of the first and most marked results of the inoculation of vaccines is the tonic effect; the circulation improves, the patient gains weight, subjective symptoms disappear, before any noticeable effect is produced on the local condition. In a certain number of cases the next stage is amelioration of the local condition, which may be complete or incomplete. As an instance may be quoted the disappearance of fever and all symptoms in cases of acute or chronic cystitis due to the tubercle bacillus, or the *Bacillus coli communis*. In some cases all the

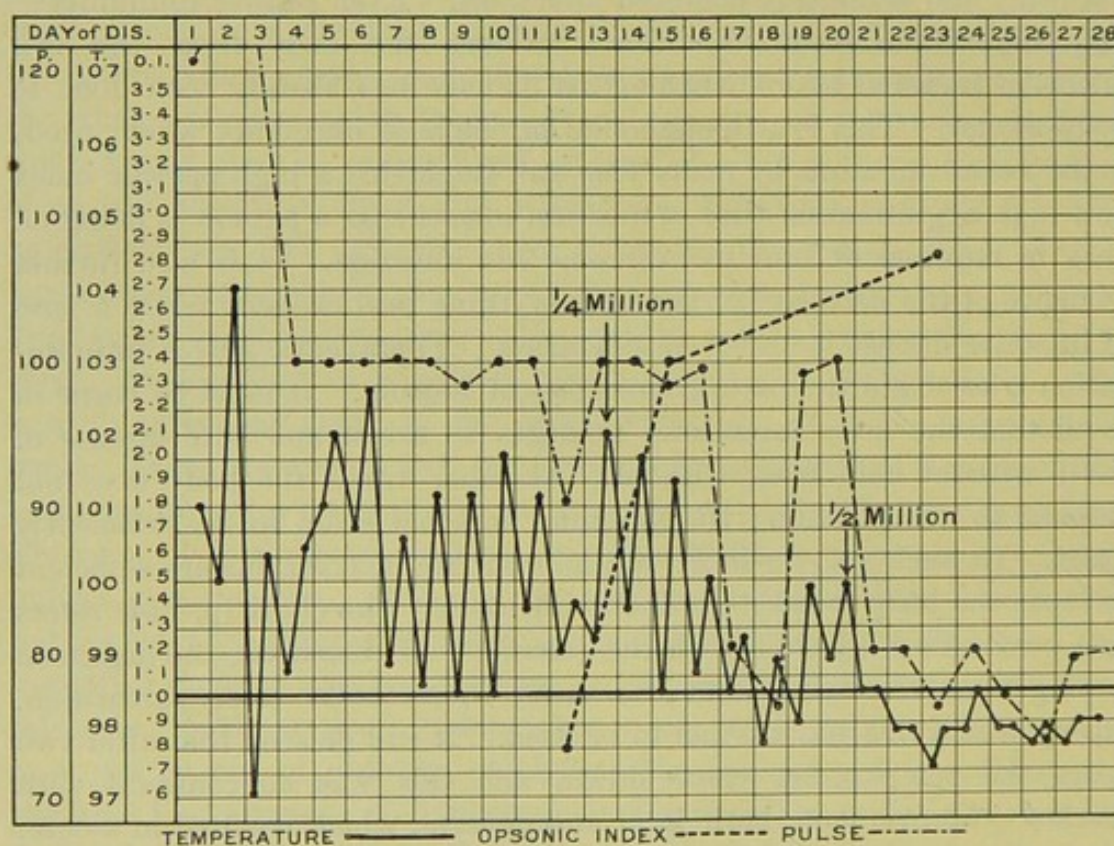


Chart (selected) to show the effect on temperature, pulse and opsonic index of two doses of *Bacillus coli communis* vaccine. The culture was obtained from the urine and vaccine prepared on the eleventh day of the disease.

bacilli disappear from the urine, but in the majority of cases which have come under my observation repeated cultures of the urine have revealed the persistence of bacilli long after all symptoms have disappeared. This must be counted one of the limitations of vaccine therapy.

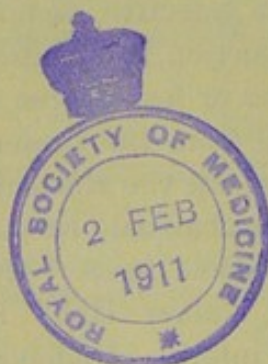
I have purposely refrained from dealing minutely with the value of tuberculin, its administration and limitations in the treatment of pulmonary tuberculosis. In this discussion we have been inquiring into

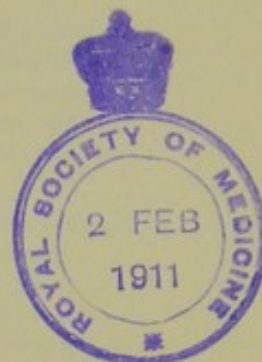
the value of vaccine therapy as a whole. The discussion which centres round the tuberculin treatment of pulmonary tuberculosis is as large a subject as is the present one; for this reason I have not touched on it. I trust that this discussion will have the effect of encouraging a wider study and application of vaccine therapy, of putting an end to a useless conflict between physician and clinical pathologist, and of doing away with the prejudice which exists in some quarters for this rational and, above all, individual method of treatment.

DR. P. WATSON WILLIAMS: My experiences with the administration of vaccines in infective diseases of the nasal accessory sinuses, by which term I include non-suppurative as well as purulent sinusitis, leave me in no doubt as to the value of vaccine therapy in suitable cases. But there is another field for the useful employment of vaccines to which I desire especially to invite attention—viz., the treatment of incipient adenoid growths. Only a fuller experience than I have had up to the present time would enable me to indicate how far operative measures can usefully be replaced by vaccines, and I certainly do not suggest that, with rare exceptions, definitely established adenoid growths should not be removed by operation. But I have long held the view that¹ “adenoids are simply a lymphoid overgrowth directly resulting from the invasion of infective organisms. In some patients such invasion is productive of marked hypertrophy; these were formerly described as ‘of the strumous diathesis’; in others the same measure of infection calls forth less marked hypertrophy. If the infective organisms continue to exist in the tissues and escape destruction, the patient suffers from repeated attacks of catarrh, with greater or less degree of systemic disturbance.” So, too, the deafness resulting from the presence of adenoids is due to an infective catarrh spreading up the Eustachian tubes, and practically never is the deafness due to mechanical pressure on, or occlusion of, the Eustachian orifices by the adenoid mass. My colleague at the Bristol Royal Infirmary (Professor Walker Hall) has isolated for me the following organisms from the interior of adenoid growths: *Streptococcus longus* and *brevis*, *pneumo-bacillus*, *strepto-bacillus*, giving group reactions, and *Staphylococcus*, chiefly *albus*, and has prepared vaccines made up in the proportions of the organisms obtained by growing in + 10 veal broth. Children suffering from adenoids have been treated in my clinic with these vaccines, and have always improved in general health, the

¹ Williams (P. Watson), “Rhinology,” 1910, p. 75.

associated nasal and nasopharyngeal catarrh has been lessened, and in some instances marked diminution in deafness has resulted without any other treatment. One of the patients now undergoing treatment was referred to me at the Royal Infirmary by Mr. MacWatters, and he writes: "June 4: I saw the child, R., yesterday, and I understand from the parents that she has far less snoring at night, and, from my own observations, I certainly think that there is less post-nasal obstruction than was present before treatment." The cases so treated could not conveniently be operated on, owing to the distance from which they came, and beds at the time were unavailable. I usually begin with doses of 125 million of the mixed vaccine, gradually increasing the dose to 500 million. I am not aware that vaccine therapy has hitherto been tried for this class of affection by other observers, but I am convinced that in suitable cases it is a method of treatment worthy of careful investigation, more especially with a view to preventing the development of incipient "adenoids," and in clearing up the catarrhal symptoms that sometimes persist after their removal, and particularly in those rare cases of adenoid growths where operative measures would probably be attended with special dangers.





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