Pathology and treatment of war wounds / by Sir Almroth E. Wright.

RESEARCHES FROM

THE INOCULATION DEPT., ST. MARY'S HOSPITAL, LONDON W.2

I

RESEARCHES FROM
THE INOCULATION DEPARTMENT, ST. MARY'S HOSPITAL
LONDON, W. 2

PATHOLOGY AND TREATMENT OF WAR WOUNDS

PATHOLOGY
AND
TREATMENT OF WAR WOUNDS

BY

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

DIRECTOR OF THE INOCULATION DEPARTMENT AND PRINCIPAL OF THE INSTITUTE OF PATHOLOGY AND RESEARCH, ST. MARY'S HOSPITAL, LONDON

CONSULTANT PHYSICIAN TO THE ARMY IN FRANCE 1914-1918

1942

WILLIAM HEINEMANN · MEDICAL BOOKS · LTD

99 GREAT RUSSELL STREET

LONDON, W.C. 1

D.6.

CONTENTS

PAGE

ACKNOWLEDGMENTS - - - - - - - - - - - - - - vi

PREFACE BY THE CHAIRMAN AND HON. TREASURER OF THE INOCULATION DEPARTMENT OF ST. MARY'S HOSPITAL, LONDON, W. 2 - - - - - - - - vii

AN ADDRESS ON WOUND INFECTIONS; AND ON SOME NEW METHODS FOR THE STUDY OF THE VARIOUS FACTORS WHICH COME INTO CONSIDERATION IN THEIR TREATMENT (Royal Society of Medicine, March, 1915) - - - - - - 1

A LECTURE ON WOUND INFECTIONS AND THEIR TREATMENT (Royal Society of Medicine, October, 1915) - - - - - - - - - - - - - 30

A LECTURE ON THE CONDITIONS WHICH GOVERN THE GROWTH OF THE BACILLUS OF 'GAS GANGRENE' IN ARTIFICIAL CULTURE MEDIA IN THE BLOOD-FLUIDS *IN VITRO*, AND IN THE DEAD AND LIVING ORGANISM (Royal Society of Medicine, December, 1916) - - - - - - - - - - - - - - - 43

FURTHER OBSERVATIONS ON ACIDAEMIA IN GAS GANGRENE AND ON THE CONDITIONS WHICH FAVOUR THE GROWTH OF ITS INFECTIVE AGENT IN THE BLOOD-FLUIDS (*Lancet*, February, 1918) - - - - - - - - - - - 70

ON THE ACIDOSIS OF SHOCK AND SUSPENDED CIRCULATION (*Lancet*, June, 1918) 85

THE CONDITIONS UNDER WHICH THE STERILISATION OF WOUNDS BY PHYSIOLOGICAL AGENCY CAN BE OBTAINED (*Lancet*, June, 1918) - - - - - - - 93

A LECTURE ON THE LESSONS OF THE WAR AND ON SOME NEW PROSPECTS IN THE FIELD OF THERAPEUTIC IMMUNISATION (Royal Society of Medicine, February, 1919) - - - - - - - - - - - - - - - - 113

THE PHYSIOLOGY OF WOUNDS (from the *Official Medical History of the War*) - - 129

ON 'INTERTRACTION' BETWEEN ALBUMINOUS SUBSTANCES AND SALINE SOLUTIONS (from the *Proceedings of the Royal Society*, 1925 and 1926; with an ADDENDUM, 1942) - - - - - - - - - - - - - - - - 163

APPENDIX

THE QUESTION AS TO HOW SEPTIC WAR WOUNDS SHOULD BE TREATED (being a Reply to a Criticism by Sir W. Watson Cheyne, *Brit. Jour. of Surgery*, 1916) 175

INDEX - - - - - - - - - - - - - - - - - 206

ACKNOWLEDGMENTS

The Author's grateful acknowledgments for permission to reprint the papers which are collected into this volume are made here to the following :

The Honorary Editors of the *Proceedings of the Royal Society of Medicine.*

The Editor of the *Lancet.*

The Controller of H.M. Stationery Office and The Director General Army Medical Services.

The President and Council of The Royal Society.

PREFACE

The Committee of the Inoculation Department of St. Mary's Hospital wish to associate themselves with this volume, which it is hoped may be followed by the publication of further work done by Sir Almroth Wright and some of his principal colleagues. As Founder Members of the Department, we take great pride in the happy co-operation between the scientific workers and the lay members of the Committee.

From its earliest beginning in 1906 as a department of St. Mary's Hospital, a more separate entity was established in 1909 at a meeting at the House of Commons under the chairmanship of the then Mr. Arthur Balfour, who continued to act as chairman until his death, when he was succeeded by the late Lord Fletcher Moulton, and he in his turn by the present chairman. The funds for the provision and the upkeep of the Research laboratories were originally provided by grateful patients and personal friends of Sir Almroth Wright. Rather over £4,000 was given by way of donations to permit of the preparation and equipment of the Department to take over a portion of the newly built Clarence Wing of the Hospital as laboratories and wards. The minimum annual requirements were covered by seven-year promises which it was hoped to supplement, as the work became more widely known, by general support from the public.

The fundamental purpose was to link, in the closest possible way, laboratory research work with the treatment of patients. The association of research laboratories with out-patient clinics and in-patient wards, as it exists in the Inoculation Department of St. Mary's Hospital, furnishes probably the first example of such a combination.

A further development occurred when vaccines prepared in the laboratories were made available to the general medical public through the agency of one of the best-known pharmaceutical firms, and this source of income, somewhat augmented by donations from appreciative patients, took the place of the annual guarantee.

During the war of 1914–18 great service was rendered to the Allied cause. A very large amount of vaccine was issued to the Army and Navy free of charge, and the Belgian Government relied for practically all its supplies on the help given by the Department.

In the year 1933, synchronising with the rebuilding scheme of the Medical School of the Hospital, the Department was rehoused in its present quarters adjoining the Medical School. The cost of this excellent accommodation was defrayed in large part by the present Chairman. Other friends also assisted, and the balance of the cost, amounting to some £46,000, was met out of the accumulated reserves which had been built up by the Department as a general development fund.

We thus continue, under ever-changing conditions, to adhere to our fundamental conception of combining service to those actually suffering, with scientific research.

Throughout these years, the author of the present volume has been the pivotal figure. Whilst we are not competent to speak of his attainments and his exceptional position in the scientific world, we are happy to pay a tribute to a lifelong friend and the head of so distinguished a team of research workers. We laymen have derived great interest from the association, and trust that we have in some measure furthered the common purpose.

IVEAGH
Chairman

MAX. J. BONN
Treasurer

INOCULATION DEPARTMENT
ST. MARY'S HOSPITAL, W.2
11*th February*, 1942

AN ADDRESS ON WOUND INFECTIONS; AND ON SOME NEW METHODS FOR THE STUDY OF THE VARIOUS FACTORS WHICH COME INTO CONSIDERATION IN THEIR TREATMENT

(*Delivered before the Royal Society of Medicine, 30th March*, 1915) [1]

There are a number of quite elementary problems which must be solved before we can arrive at any really effective treatment of wound infections. A very brief consideration of the facts will bring us face to face with the questions to which we have to find an answer.

Evolution of Wound Infections.

In this war practically every wound is heavily infected. The chain of cause and consequence seems to be as follows: The clothes and skin of the soldier on war service become contaminated with all manner of filth containing pathogenic organisms and spores; the projectile takes these in with it, and it implants them far in—in point of fact, far beyond the reach of any prophylactic applications of antiseptics.

A cultivation medium is now provided by the blood and lymph which are poured out into the track of the projectile; and we find in the wounds—I have in view here wounds examined immediately after arrival from the front—a mixed infection of a streptococcus with microbes derived from the faeces. This faecal infection is a special outstanding feature in this war.

Among many species of intestinal microbes which have been found in wounds, two have a quite special importance. One is the *Gas-Phlegmon Bacillus*, or *Bacillus Aerogenes Capsulatus* of Welch—a large Gram-staining, anaerobic and actively gas-forming microbe. It is found both in infiltrated superficial wounds and in deep wounds, and is particularly abundant in the frothy and offensive faecal-looking discharges which anaerobic wounds furnish. The other is the tetanus bacillus. This is more rarely encountered, and is also less abundant when present. Sometimes, however, it may show up in every field of the microscope.

The presence of streptococcus and these two faecal microbes makes the first period of the wound infection—the period of imprisoned discharges—a specially critical time for the patient—I have in view the patient who has not been operated upon at the front. During this the streptococcus may invade the tissues, and set up cellulitis or, more rarely, erysipelas. Or the tetanus bacillus may find opportunity to grow out and manufacture its poison and induce tetanus. Or the bacillus of Welch may make its way into the body and set up a gas-phlegmon in the region round about the wound, and an obstructive gangrene in the distal portion of the

[1] Reprinted from the *Proceedings* of the Royal Society of Medicine, vol. viii, 1915.

limb. Or, again, the bacillus of Welch and the streptococcus may join forces, and may in conjunction produce the gas-phlegmon or cellulitis.

As soon as the wound has been opened up its bacterial flora changes. The ordinary pyogenic infection, which has up to this been in abeyance, now gains the upper hand, and instead of an '*infection of the imprisoned discharges*', or, as the case may be, *an infection of tissues*, we have now an '*infection of the granulating wound surfaces, and of the flowing discharges*'. The chief bacterial agents here at work are the streptococcus and staphylococcus, and *Bacillus proteus*.

This pyogenic infection may, after lapse of time, subside—the wound healing up when this occurs; or the mixed infection may narrow itself down to a streptococcic infection and become chronic, the wound in this case remaining open indefinitely in the form of a discharging sinus. Or, lastly, when there is an obstructed outflow, the infection may go from bad to worse until the patient succumbs to continued suppuration and septicaemia.

Some Fundamental Considerations in regard to Treatment.

Those are, in very brief summary, the facts with regard to the evolution of wound infections, and I would venture, in passing on to discuss with you their treatment, to remind you that the ideal we ought to approximate to is the healing of the wounds by *first intention*—that is, without sensible interference by bacterial infection. And we are so far from the attainment of that ideal that nearly all our wounded are suffering from bacterial infections; that very many are ill of these infections; and that not a few are, through these, in danger of their lives.

We have at our disposal for the treatment of these wound infections three distinct therapeutic measures. Let me enumerate them in the order in which they would naturally suggest themselves to you.

First in that serial order would come *treatment by antiseptics*. After this would come what I propose to call *treatment by physiological methods*—I mean procedures such as the opening and draining of the wound—which bring the antibacterial powers of the blood to bear on the infecting microbes. And lastly would come the reinforcement of the antibacterial powers of the blood, that is, *treatment by vaccine therapy* and similar methods. I believe it is really beyond question that of these three the second is far the most important, and I would submit that—all loud talk about it notwithstanding—antiseptic treatment is at best an ancillary method of treatment. And of course the same applies also to treatment by vaccines.

Let me also here suggest to you another quite fundamental consideration. It is this: It will be clear that we cannot apply physiological treatment aright, nor can we use any antiseptic or vaccine to best advantage in wound infections, unless we first understand the physiological processes going on in the wound. We do not yet understand these even in outline.

It will therefore be necessary to address ourselves to the task of discovering what goes on in the wound and of following up its biological evolution. And the only way of doing this will be to formulate to ourselves in clear terms the questions which require answers; then to consider how to set to work to get our answers—for merely looking at the wound will not help; and finally to take cognisance of the

results which the laboratory methods I am about to describe to you have already yielded.

Our first question can be formulated thus :

(1) *Can the microbes which are found in wound infections live and multiply in the unaltered blood fluids?*

In other words, if I take pyogenic microbes from the wound and implant these into the normal undiluted serum, will they grow freely? If we are going to carry out this experiment, and to carry it out repeatedly, and deal with a number of different bloods ; and if we are going to cultivate directly from the pus, we shall evidently have to work in capillary tubes with very minute quantities of pus and very small quantities of undiluted serum. The technique which I have arrived at for fulfilling these requirements is a very simple one. I have called it the *Wash and After Wash Method.*

* * * * *

A description of the Pyo-sero-culture Wash and After Wash Method which followed here is omitted, because the method is described *infra* on p. 38 and in the author's *Technique of the Teat and Capillary Glass Tube*, 2nd Edition (Constable, London, 1921).

* * * * *

Serum cultures made by the Wash and After Wash Method furnish a very striking and uniform result. We obtain in the cultures implanted with the higher dilutions of the pus a pure culture of the streptococcus, and in the cultures more heavily implanted with the pus the streptococcus mixed with a certain number of other microbes : in particular, a few staphylococci and an anaerobic wisp-like diphtheroid bacillus which often is abundant in pus, being found both intracellularly and extracellularly. All the other pyogenic microbes appear to be inhibited in undiluted normal serum, and when they put in an appearance it is only after fairly heavy sowings with pus, and comparatively late.

Out of these facts would come what we shall presently see to be a practically important classification of pyogenic microbes—a classification into, on the one hand, *serophytes* ; and, on the other, *sero-saprophytes.* The serophytes would be those which, presumably because they find their foodstuffs ready made in the blood fluids, are at home there, and can, in the absence of phagocytes, grow and multiply there without restraint, or practically without restraint.[1] The sero-saprophytes would be those which cannot grow and multiply in the blood-fluids until a change —which we may, pending nearer investigation, call simply a *degenerative* change— has passed over those fluids.

What holds true of the blood fluids themselves might perhaps justifiably be assumed to hold true also of the lymph which pours into the wound. None the less, it will be well specially to investigate this point.

(2) *Does the lymph which pours into the wound provide a favourable nutrient medium for the microbes which have been growing in that wound?*

[1] I introduce this qualifying clause because I have on several occasions found the serum of the infected patient to give cultures of streptococcus with a planting of his pus much smaller than that which was required to give a culture in the serum of a normal man.

To pose this question is already to go a long way towards getting an answer to it ; for we can, by the aid of a very simple device, obtain the lymph from the walls of the wound. I employ for this purpose what I may perhaps call a *lymph leech*. This consists, as you see, of a small glass tube. It is sealed up at one end, drawn out at the other in the form of a nozzle, and is furnished with a lateral mouth with a raised rim—the whole being very easily made out of a piece of glass tubing, or small test-tube. To the nozzle we fit a piece of fairly thick-walled rubber tubing, and this is blocked at the end with a piece of glass rod.

When we want to obtain the exudate from a wound we bring down the lateral opening of the lymph leech upon a granulating surface, and then, transfixing the rubber tube with the needle of a hypodermic syringe, we draw out the air and make a negative pressure (*vide* Fig. 1, p. 5). It will be appreciated that the lymph leech is in principle merely a small cupping glass, and that it will, by means of the vacuum we establish in it, hold on tight for whatever period may intervene between dressing and dressing, and furnish an exudate free from all contamination with residual pus left behind in the wound. We can now proceed to compare the fluid in the cavity of the leech with the fluid in the wound outside ; or, in connexion with work on antiseptics, to compare the contents of leeches applied respectively to treated and untreated surfaces in the same wound.

And lymph leeches also can be put to other uses. We can introduce for this purpose with a syringe any fluid we may select into the lymph leech, and investigate the effect that fluid exercises upon transudation and emigration. Again, where the nature of a deep-lying infection of a mucous or other surface remains uncertain, the application of a lymph leech might clear up the difficulty. We can also, in the case where we are testing the effect of a vaccine upon a wound, take to our aid the lymph leech. For the effect of a vaccine would probably show itself in the exudate in the cavity of the leech long before it would manifest itself in the cavities of the wound. And, lastly, the application of a lymph leech to the site of inoculation might, perhaps, help to resolve the problem as to whether or no protective substances are there developed.

But it will be realised that for us—at the moment—what is of chief interest is the comparison of the fluid in the cavity of the leech with the fluid in the wound outside.

When, after washing out a heavily infected wound with an antiseptic or simple saline solution, we apply a lymph leech to the walls, and then at the next dressing compare the contents of the lymph leech with the fluid outside, we think at first that there must be some mistake. Outside we have an opaque exudate presenting all the ordinary physical characters of pus containing leucocytes in all stages of degeneration, and swarming with all manner of pyogenic organisms. Inside we have a transparent and slightly blood-stained exudate containing streptococci in practically pure culture, and in addition a few leucocytes, all of which are actively phagocytic. Except in this latter respect, we have, in fact, identically the same result as when we made our thin implantations of pus into normal serum.

The problem now stares us in the face—What is it that makes all this difference between the contents of the lymph leech and the contents of the wound? How

has the lymph, which gives in the cavity of the lymph leech only a culture of streptococcus, been converted in the wound outside into a fluid which is ideally favourable to the growth of a great number of different species of micro-organisms?

(3) *What is the cause of that 'corruption of the lymph' which converts it into a favourable nutrient medium for sero-saprophytic microbes?*

The proper way to go to work upon a problem of this kind is to keep it unremittingly before the mind; for then some hypothesis will in the end suggest itself. That found, there will invariably come to notice a certain number of accepted data which the hypothesis will fail to explain. These must then be carefully re-examined to see whether they will stand fast and discredit the hypothesis, or whether they also will come in and support it. And, finally, before launching our theory, we ought to think out all that would follow from it, and then make inquisition to see our theoretical anticipations are borne out.

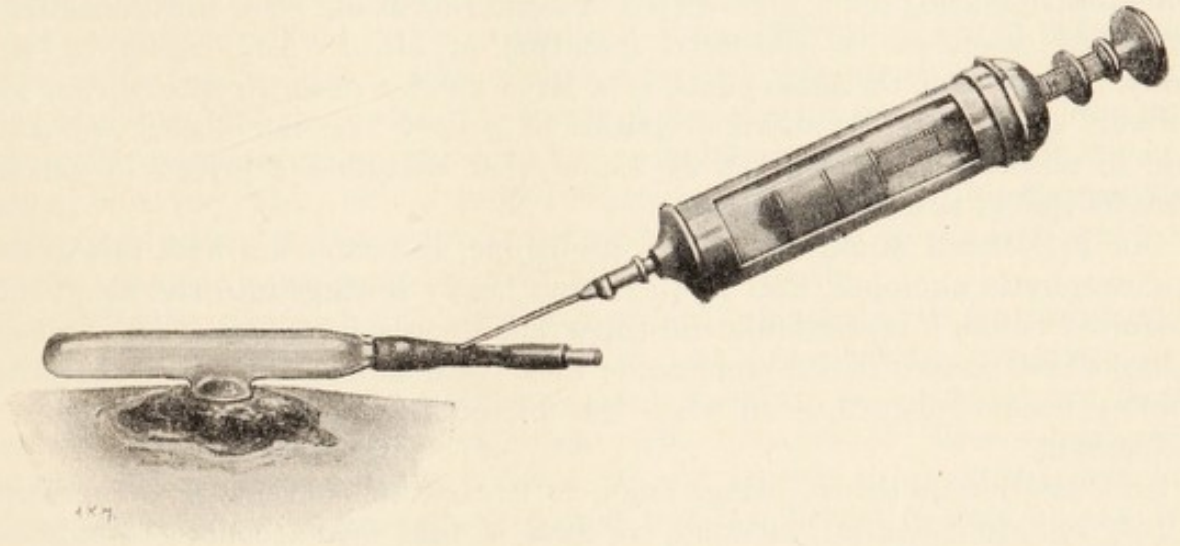


FIG. 1.—Lymph leech.

At any other time one would wish, before promulgating a far-reaching hypothesis, to have controlled it at every point. But we have on our hands in Europe, I suppose, already two or more millions of wound infections, and every other consideration must give way to that of accelerating the researches which we must look to in order to guide us in treating these infections.

I will therefore, before completing its verification, venture to put before you what is, I believe, the solution of the problem of the corruption of the lymph in the wound.

Let me take my departure from those facts which we were considering a moment ago, relating to the culture of pyogenic microbes in the blood fluids. You will remember that I suggested in connexion with serophytic microbes that these must find all the food materials they require ready formed in the blood fluids; and in connexion with sero-saprophytic microbes, that for these no nutrient substances

would be available until the albuminous substances of the blood had undergone some sort of preparatory transformation.

I conceive that that transformation could come only by a digestive process. Now, supposing this to be so, there would come into account a counteracting influence in the serum. For we have there an antifermentative, or, as we usually style it, an antitryptic element, which would directly counteract any digestive element which might be struggling to come into operation. And it is clear that microbes which were dependent for their sustenance upon the products of digestive action could establish themselves in the blood fluids only on condition that this antitryptic influence was overborne.

This hypothesis furnishes, as it seems to me, an explanation of the fact that heavy sowings of non-serophytic microbes into blood are effective in giving cultures, while light sowings are not only ineffective, but lethal to the implanted microbes. For it would be only natural that the resistance offered by the antitryptic power of the blood should be overborne by the mass effect of a number of microbes operating upon a restricted or—and this would come into consideration in localised infections—a cloistered quantum of blood. And, again, it would be only natural that the mass effect of a large volume of antitryptic serum would effectively quench the digestive activities of a very few microbes; and also, I think, in accordance with what we know, that microbes deprived of access to foodstuffs should perish of inanition.

Our hypothesis would also make intelligible, in connexion with infections by sero-saprophytic microbes, that frequent and heavy sowings into the blood should be required before a septicaemia can supervene upon a local infection. And again our hypothesis makes it comprehensible that there should be serious difficulty in obtaining haemo-cultures, even when the microbes have gained a footing in the blood-stream.

And, lastly, our theory brings home to us that, in considering the defence of the body against bacterial infection, we have to take into account not only *active defence* in the form of phagocytes and bacterio-tropic substances which make a direct attack upon micro-organisms; but also *passive defence*—that is, protection against infection obtained by preventing microbes converting to their uses the nutrient substances of the blood-fluids.

These, however, are general considerations with applications far beyond the sphere of wound infections, and we must return to the particular problem of the corruption of the lymph in the wound.

When, after treating a wound with antiseptics and leaving it clean, we find it a very few hours afterwards teeming with microbes, we are in presence of something which, in my view, urgently stands in need of explanation; for our findings both in the lymph leech and in serum cultures made with the Wash and After Wash method from pus would seem to teach us that the sowing of microbes left on the surface of an infected wound cannot be nearly heavy enough to produce the voluminous culture which grows out in the wound, nor yet to account for the rapidity with which the sero-saprophytes have started to grow. And, moreover, upon consideration it will appear that another powerful factor must constantly come into

operation in the wound. The factor in question is the tryptic ferment which is elaborated in the phagocytes and which is, when these break up, discharged into the surrounding medium. This tryptic ferment will come into operation under two different conditions. It will come in whenever a residue of disintegrated pus—for this would contain free trypsin—is left behind in, or afterwards makes its way into, the wound. Trypsin will again come into account whenever, after the washing of the wound, leucocytes once more begin to emigrate, and phagocytose, and break down.

I see in the reduction of the antitryptic power of the lymph thus effected the prime cause of its corruption. Before attempting to obtain confirmation of this from crucial experiments, there was a set of findings to be cleared up. I had found in connexion with pus implantations made into serum that when this was heated to 60° C. for ten minutes one no longer obtained the same differential growth of streptococcus as with unheated serum ; but obtained instead mixed cultures of streptococcus with sero-saprophytes, in particular staphylococcus and the wisp-like diphtheroid bacillus already made mention of. It seemed at first sight as if this could not possibly be related with a reduction in the antitryptic power of the serum ; for it has, in view of the high quality of Opie's work on this question, been generally accepted from him that the antitryptic power of the serum is unaffected by exposure to heat until a temperature approaching the coagulation point of serum is reached. In reality, however, when this is re-investigated quantitatively,[1] it emerges that the antitryptic power of the serum is reduced by one-third to one-half when we subject the serum to a temperature of 60° C. for ten minutes.

That difficulty removed out of the way of our hypothesis, we may proceed to take cognisance of the results of the crucial test experiments—experiments in which graduated additions of trypsin are made to serum as a preliminary to the implantation of sero-saprophytic microbes. The outcome of these experiments can be summed up in a sentence. When we add trypsin in quantities sufficient to reduce appreciably the antitryptic power, but insufficient to give us any free trypsin, the serum is converted into an eminently favourable nutrient medium for sero-saprophytic microbes.

Our hypothesis is thus very strikingly confirmed. It will be necessary hereafter to follow it into all its consequences. For the present it will, however, suffice if we ponder on the fact that the antitryptic power of the blood would appear to be increased in every case of severe wound infection. We have, perhaps, here a defensive reaction of the organism directed against a possible invasion of the blood by sero-saprophytes. And we may perhaps look in this direction for an explanation of the non-specific benefit which has been observed to follow upon the inoculation of bacterial vaccines. It is clearly not impossible that the inoculation of a bacterial vaccine *might* contribute both to active and passive defence—to the active defence

[1] The quantitative method here employed was in essentials that described in my *Technique of the Teat and the Capillary Glass Tube*. It was varied only in the respect that the series of trypsin, serum, and calcified milk mixtures, which are employed in that method, were taken up, not into a many-stemmed pipette, but into a long, unmounted, wide-bored capillary stem, which had, for the purpose of convenient filling in, been bent round at one end in the flame of a Bunsen into a siphoning curve.

of the body against a particular microbe by calling forth a production of specific bacteriotropic substances, and to the general passive defence of the organism by calling forth a production of antitrypsin. And these two forms of immunising response would not necessarily be linked together. The production of specific bacteriotropic substances would no doubt depend upon the quantum of bacterial antigen incorporated ; while the production of antitrypsin might perhaps depend upon the breaking down of phagocytes and the liberation of their trypsin.

What are the Factors which influence the Emigration of White Blood Corpuscles into the Wound?

I pass now to consider yet another subject-matter—the emigration of leucocytes into the wound. I need not labour the point that this is a factor which may determine the issue of an infection. Nor need I point out that it behoves us to acquire a control over the movement of leucocytes, and then to turn this to account, as the case may be, by activating or restraining emigration.

Broad foundations for our work have, as you know, already been laid by the brilliant researches of Metchnikoff. But it was with Metchnikoff always a question of experiments *in vivo*—that is, of experiments carried out under conditions which cannot be sufficiently simplified to give quite unambiguous answers. And we require for the elucidation of our problems and for all detail work connected therewith, absolutely simple crucial experiments, such as can only be made *in vitro*.

The line of thought which I have followed in elaborating a laboratory method for the study of the phenomena of emigration is the following : The leucocytes in extravascular blood are known to retain their emigrating power. A difficulty, however, when we are working with extravascular blood, will beset our observations, inasmuch as we have not at disposal such a containing membrane as the capillary wall. We are, in fact, in dealing with extravascular blood, confronted with a situation similar to that which would be encountered in observations *in vivo* if the capillary walls were to give way and we had to make observations on emigration in a portion of tissue which was flooded out by red corpuscles.

I had hoped at first to be able to circumvent this difficulty by taking advantage of the fact that when clotting occurs the red blood corpuscles become enclosed in a meshwork of fibrin, after the manner of fish in a net. But all my efforts to make the fibrin meshwork take over the office of a containing membrane were defeated. No matter how tenderly the clot was treated the meshes of the net broke, and haemorrhage from the clot interfered with the observations.

A second difficulty also presented itself. When in the living body white corpuscles emigrate into connective tissue it is possible to register their travel because they move forward through a retaining meshwork. It would not be possible to do so if they merely passed out into fluid, to be afterwards carried hither and thither by every chance convection current. Exactly the same applies to the extravascular blood. The emigrating leucocyte must be provided with some sort of scantling to move forward upon, and come to rest in.

After a time I alighted on a method which satisfies the two afore-mentioned experimental requirements, and which, as I think, provides all that is required for a quantitative estimation of emigration. Let me first tell you the general lines upon which the method proceeds, and then set out the details of the technique.

Principle of the Method employed for making Observations on Emigration.

The principle of the method is as follows : We fill in flat plane-walled capillary tubes [1] with blood from a prick in the finger, immediately place these tubes in the centrifuge, and centrifugalise until we have carried down all the corpuscles. We have now in the upper half of the tube a plasma which has been completely freed from all formed elements ; and in the lower half of the tube, at the bottom, the red blood corpuscles intermixed with a certain number of polynuclear white blood corpuscles ; and above this a layer made up predominantly of white blood corpuscles—these last in the front ranks consisting almost exclusively of small and large mononuclears. The blood now clots. And this gives in the upper half of the tube a clot consisting of fibrin without any formed elements—let us call this the *white clot*—and in the lower half of the tube a clot—let us call this the *red clot*—which holds all the corpuscles in its meshes. When a chemotactic stimulus now comes into application from above, the white blood corpuscles will come out from the red clot and will travel upwards through the meshes of the white clot—afterwards maintaining their positions so as to allow of our making measurements and enumerations.

Here it will suffice to consider some general points about the movement of leucocytes.

General Considerations relating to the Movements of White Blood Corpuscles.

We have to take into account in connexion with white blood corpuscles two kinds of movements. There is, on the one hand, a process of wandering at large ; and, on the other hand, a directed movement—that is, a movement along some particular axis—undertaken under the impulsion of a chemical stimulus. We may call the first kind of movement an *eleutherotropic* [2] movement. The second is usually known as a *chemotactic*—I prefer to call it a *chemotropic*—movement. It is, of course, the latter, not the former, kind of movement which we are here primarily concerned to study. For clearly it is the chemotactically impelled movements of the leucocytes towards the bacterial focus, and not their wanderings at large, which come into consideration in any conflict against infection.

None the less, a word may be said about *eleutherotropic movements*. One finds in every specimen of blood which has been simply centrifugalised and placed in an incubator, always a certain wandering at large of the leucocytes—in particular, the mononuclear white blood corpuscles, which have been tightly packed together by

[1] The method of making and using these tubes (we may conveniently call them *Emigration Tubes*) is described in the author's *Technique of the Teat and Capillary Glass Tube* (Constable, 2nd Edit., 1921).

[2] The word is compounded out of two Greek words : *eleutheros* (free) and *tropic*—from *trepo* (I turn towards).

the action of the centrifuge, and are ranged at the top of the red clot, leave their ranks and wander out into the adjacent regions of the white clot. The polynuclear luecocytes also are affected by eleutherotropic wandering. They come out from the hinder ranks of the leucocytic layer, and also from deeper down in the red clot, and wander free. In our observations we leave out of account all those leucocytes that have wandered outside the white clot. We regard them as having run to waste.

A further point which claims attention in connexion with emigration is the *nature of the emigrating leucocytes.*

Eleutherotropic emigration (I refer to such emigration studied in blood filled into emigration tubes and then centrifuged) is primarily mononuclear, this being probably accounted for by the fact that the white blood corpuscles which are ranged up along the line which divides the red from the white clot are almost all mononuclear. In *chemotactic emigration* we have either a differential emigration of polynuclear white corpuscles, or a mixed mononuclear and polynuclear emigration in which either the one or the other of these varieties of leucocytes may predominate. In all such mixed emigrations the polynuclear, presumably because they are faster of foot, overtake the mononuclear leucocytes and pass on and occupy the more distal portion of the field of emigration.

Survey of the Data which the 'Emigration Method' has already given.

We may now pass on to consider some of the data that the method has already given. White blood corpuscles will move out in any direction towards a chemotactic substance. They will, however, emigrate more freely downwards than horizontally, and more freely horizontally than upwards.

Anaerobic conditions are more favourable to emigration than aerobic conditions. Leucocytes will travel out farther in the direction of a chemotactic substance when we absorb the oxygen in the tube with caustic alkali and pyrogallic acid and seal, than when we leave the end of the tube open to the air.

Leucocytes emigrate more abundantly in tubes standing at a temperature of 40° C. than in tubes standing at 37° C. They do not emigrate at temperatures of 10° to 15° C.—the temperatures which prevailed on our laboratory bench. After exposure to temperatures of 0° C. for periods of half to one hour they emigrate apparently as freely as before.

Emigration apparently goes on unaffected in the presence of ether. It is abolished or suspended in an atmosphere of chloroform.

Physiological salt solution—superimposed upon the clotted or unclotted blood—induces a very vigorous emigration of polynuclear white blood corpuscles. Weaker salt solutions induce a less vigorous emigration, and water again a less vigorous. Strong salt solutions—for example, 5 per cent. salt solutions—suppress emigration.

It will be appreciated in connexion with these and all findings obtained by this method that they do not tell us the effect of reagents acting in the specified dilutions directly upon leucocytes, but only the effect of these reagents operating from

a distance. In other words, our experiments do not furnish information as to what would be the effect of bringing the chemical agents in the specified concentrations directly in relation with the capillary wall.

Bacterial suspensions which have been sterilised by heating evoke, according to the dilution in which they come into application, quite different effects. The general rule applying to bacterial suspensions would seem to be as follows: Concentrated suspensions usually completely suppress emigration. Ten or hundred fold diluted, these evoke vigorous emigration. When we employ progressively higher dilutions we arrive in time at a point when the effect is exactly the same as that of the particular fluid which we are employing as a diluent.

Normal bloods tested with one and the same series of bacterial suspensions exhibit quite different degrees of chemotropic sensibility. Chemotropic sensibility, not alone to bacterial suspensions but also to physiological salt solution, is very strikingly modified in the case of patients suffering from bacterial infections. This also applies to persons inoculated with streptococcal vaccines. In five out of six men, inoculated with a streptococcal vaccine and examined both before and afterwards, the emigrating response to streptococcus was very strikingly increased subsequently to inoculation. In the case of the sixth man it was diminished.

Results somewhat similar to those obtained with dead cultures are obtained with suspensions of living microbes (streptococci and gas-phlegmon bacilli), but here the prolonging of the incubation period may strikingly alter the situation.

What generally happens in emigration tubes may be summed as follows: When, by superimposing microbes on the unclotted blood and then centrifuging, a heavy implantation of microbes has been made, the colonies come up all along the white clot, and emigration into this is completely checked. Where only a moderate implantation of microbes has been made we have in different parts of the clot different results: Bacterial colonies develop freely in the distal area of the clot which is not invaded by emigration. In the intermediate region—that is, in the region where the microbes can grow out before the leucocytes arrive—one sees, with the low-power of the microscope, areas crowded with leucocytes—and here the bacterial colonies are being attacked by the emigrated leucocytes—and with the oil immersion one sees that every one of these leucocytes is gorged with microbes. In the base of the white clot—that is, in the area where emigration has occurred earliest and most vigorously—one finds absolutely no trace of microbial growth.

The appearances which have just been described correspond, of course, to a period of conflict. This conflict is generally at its most interesting phase in tubes which have been incubated from three to six hours. When we come later—for instance, after twelve or more hours—the conflict is over. We then find either that the white corpuscles are masters of the field and the microbes have disappeared, or else that the microbes have invaded the whole clot, and that this crumbles away as soon as it is blown out into water. There can be little doubt that the crumbling away of the clot, and the overrunning of the blood with microbes, are due to the digestion of the fibrin, and to the corruption of the blood fluids by trypsin set free from the disintegrated leucocytes.

Experiments such as these just outlined, in which living microbes are brought into application on blood, provide, in point of fact, a valuable test method. They tell us the resultant of the *chemotropic sensibility* of the leucocytes, the *opsonic power* of the blood fluids, the *digestive capacity* of those phagocytes which come into action, and of the *antitryptic* and, where such comes into account, the *bactericidal* power of the blood fluids. We are, in fact, furnished with something like a complete evaluation of the antibacterial powers of the blood.[1]

All that has been recounted above is, of course, only a beginning. But I think we may be confident that the method for the study of emigration which has here been proposed will resolve important problems in connexion with infection generally, and also—and this is what specially concerns us here—some of the problems in connexion with wound infections which are now urgently pressing for a solution.

In the matter of general problems of infection it would, I think, be possible, by implanting bacteria into blood in combination with chemical agents which would respectively promote and hinder emigration, to resolve for each particular bacterial infection the question as to whether it is the leucocytes or the blood fluids which come most into consideration as destructive agencies. That problem once resolved, we should know whether we ought, in the infection in question, to direct our chief efforts to increasing the efficacy of the blood fluids or to modifying the chemotropic sensibility of the leucocytes and encouraging emigration.

Again it looks as if it might be possible by very simple experiments to resolve the problem as to why in gonorrhoea, and also in other surface infections, the purulent discharge is suddenly arrested when the microbes succeed in invading the blood-stream, or establishing themselves in an articulation or elsewhere in the interior of the body. It would seem possible (for something of this kind would seem to occur in septicaemias supervening on wound infections) that we may be dealing here with a paralysis of the emigrating powers of the leucocytes. Or, again, it is possible that in these cases emigration may be simply suspended by a redistribution of the chemotactic forces. In other words, the cessation of the external discharge may simply mean that there is now in the blood a bacterial poison ; and that this chemotactic element, acting upon the leucocytes as a *vis a tergo*, counterbalances the *vis a fronte* of the chemotactic substances produced by the bacteria on the external surfaces.

In connexion with the particular problems of wound infections we may hope at no distant date to come into possession of information which will enable us to activate or restrain, according as the one or the other may approve itself the better policy, the emigration of leucocytes into the wound. And we may hope also to determine in connexion with every antiseptic or other solution which is brought into application in a wound, whether it promotes or hinders emigration.

Finally, let me point out—for everything that concerns bacterial vaccines concerns the treatment of wound infections—that experiments on emigration will

[1] It will be observed in connexion with tests thus conducted with centrifuged blood that, if we leave out of regard the centrifugalisation, they are in all essentials the same as the *phagocyto-bactericidal* tests with freshly drawn uncentrifuged blood which I have already described (*Vaccines and Drugs in Pneumonia*, Constable, 1914).

almost certainly resolve a number of important outstanding questions in connexion with vaccines. They ought very easily to resolve the question as to what is the best excipient for a vaccine—whether a menstruum which would restrain emigration, or one like physiological salt solution which would call forth a vigorous emigrating response at the point of injection. And lastly—and this would be one of the most important applications of observations on emigration—we ought to be able to determine what is, in the case of each bacterial vaccine, the dose which will induce the earliest possible and the most effective determination of phagocytes to the focus or foci of infection.

We may, with such new knowledge as we have acquired from the experimental methods I have described, now revert to the consideration of those three ways of combating wound infections enumerated earlier in this discourse. It will be remembered that these were : *Treatment by Antiseptics*, *Treatment by Physiological Methods*, and *Vaccine Therapy*. We will take them one by one.

(I) Treatment by Antiseptics.

If we adopted the Socratic method, and were to inquire of the first man we found engaged in washing out a wound what were the grounds for his confidence in the utility of the procedure, he would probably make some such answer as the following : ' I know that the antiseptics which I am bringing into application are agents which directly kill and inhibit the growth of microbes. There is no other agency known which would be competent to do the bactericidal work that these antiseptics do in the wound. And, again, it is everybody's knowledge that Lister, by introducing his antiseptic treatment, extirpated those septic infections of wounds which before the advent of his method devastated the surgical wards of every hospital.'

And if we were to push our question further, and ask of the surgeon to what particular end and object his procedures were directed—whether it was the sterilisation of the wound ; or the killing off of a large proportion of the microbes ; or the imposition of a check upon the survivors ; and if we were further to ask, whether the particular antiseptic in the particular strength in which he was employing it could be relied upon to achieve the end in view ; we should probably be told that, supposing that the antiseptic did not completely sterilise the wound, it would inevitably kill a large number of microbes ; and it would probably also inhibit the growth of any survivors. And, inasmuch as one or other of these objects would be sure to be achieved, there could be no question but that advantage would accrue to the patient.

We should, in short, get an answer which proceeded upon at least one erroneous assumption, and which betrayed loose and inconsequent thinking, and a reluctance to come to close quarters with the question. But the reasonings of the larger part of humanity are neither better nor worse than this ; it is not for that less necessary to take them into very serious account, and to do our best to correct them when they mislead.

Let us begin, since Lister is the fount and origin of all antiseptic treatment,

with what relates to his work. Lister's name is associated with two discoveries. The *first* of these is the discovery that we can, by an *anticipative prophylactic application* of antiseptic, hold off microbes from surgical wounds, and so avoid wound infections. The *second* is that in cases of compound fracture where the wound is already infected we can still, by what I may perhaps call a *retrospective application of antiseptics*, inhibit the wound infection. The first of these is a discovery of absolutely universal application, and it will carry the name of Lister down to remotest posterity. The second discovery has reference only to a particular kind of traumatic wound, and shows that prophylactic applications of antiseptics can be usefully employed also in connexion with some wounds which are already infected.

It is clear that neither of these discoveries finds any direct application either in connexion with prophylaxis or the treatment of the infections which occur in projectile wounds.

What it is necessary to say on the possibility of preventing septic infection by sterilising projectile wounds can be said in a very few words. The principle that microbes can be held off from wounds by an antecedent employment of antiseptics has no application to projectile wounds, for these are infected before they are seen by the surgeon. Nor, again, is the Listerian discovery that prophylactic applications of antiseptics in the ordinary compound fractures of civil life can stave off wound infection related to conditions such as obtain in projectile wounds. Retrospective, or, as we may also call them, *ex post facto* applications of antiseptics will give good results only when the microbes are accessible. In the case of the ordinary compound fracture of civil life this is often the case. For here the microbes lie exposed on the external surface of the bone which has been thrust through the skin. The contrary holds for projectile wounds. Here the microbes are inaccessible. They have been carried down deep into the tissues, and lie on the inner face of a torn and ragged track ; and that track is blocked by blood-clot and hernia of muscle.

It is clear that the utmost that prophylactic applications of an antiseptic could under such conditions achieve would be an incomplete sterilisation. And an incomplete sterilisation would leave us with a wound infection, and in a few days with as bad an infection as before.

Coming now to actually subsisting wound infections, we see that exactly the same thing would apply. We are not entitled to infer from the fact that the method of Lister is within its limitations an effective method of prophylaxis that it is also an effective method of treatment. That is clearly a question which must be determined as an independent issue.

When we approach the question in this way we see that the first point which has to be determined is : What particular concentration of each particular antiseptic will, when applied to the wound, exert there a bactericidal action on the microbes? In connexion with this we must beware of the fallacy of taking the figures for an antiseptic acting on microbes in watery suspension and seeing in these an all-round formula of efficacy for that particular antiseptic.

A formula of efficacy of this kind might, of course, find a useful application where the sterilisation of skin surfaces and instruments was concerned. For here the antiseptic comes into operation on exposed microbes in full strength. In practically

every other case the conditions would be entirely different. The antiseptic would have to come into operation in a medium which quenches its antibacterial action.

I have recently, in dealing with internal medication by antiseptics in pneumonia, brought forward [1] an array of experiments which show that the quenching of the antibacterial power of antiseptics by the medium in which these come into application, is the essentially important factor to be considered in connexion with their medicinal use. In particular I have shown in connexion with drugs like lysol, creosote, and guaiacol, that doses which would almost certainly be lethal would have to be administered before these antiseptics could come into operation in blood.

The same sort of thing holds true of pus. But here the situation will be different in two respects. It will be different in respect that, as compared with serum, pus exerts a greater quenching effect upon antiseptics. It is, if I may put it so, more *antisepticotropic*. This will prevent us taking the antisepticotropic values for the serum and applying them to the pus in the wound. Again, the conditions under which an antiseptic comes into application in a wound will contrast with those which come into application in internal medication. In connexion with internal medication we have to take into consideration the quenching influence which would be exerted by the totality of blood. In applying antiseptics to the wound it lies with us to make the conditions much more favourable to the antiseptic. We can, if it is a question of washing out a wound with antiseptics, make the relation of antiseptics to pus anything that we please. And where it is a question of leaving an antiseptic behind in the wound for the purpose of inhibiting growth, we can also, within limits, lay down our own conditions, and make provisions which will prevent the conditions becoming too unfavourable to the antiseptic.

If there are, in the published literature on antiseptics, any papers dealing with the investigation of the efficacy of antiseptics from this point of view, they have escaped my observation. I have accordingly in conjunction with my fellow-workers, Dr. W. Parry-Morgan and Dr. A. Fleming, set to work to supply the missing data. To find out what concentrations of antiseptic ought to be brought into operation in washing out a wound we took nine volumes of antiseptic to one of pus. To determine what inhibitory effect would be exerted by an antiseptic left behind in a wound we took one portion of the antiseptic to—as the case might be—two or four volumes of pus. It will be seen that by this plan of operation we conduct our experiments directly on the microbes and pus furnished by the wound ; in other words, instead of dealing with any abstract issue, we deal with the concrete question which presents itself in the particular wound infection which happens to lie before us.

The general results obtained in this investigation will be separately set forth. At the moment it will suffice to call attention to the fact that when employing nine volumes of the antiseptic solution to one of pus from the infected wound, and leaving the antiseptic in application for ten minutes, a strength of 1 in 40 of carbolic acid, and strengths of 1 in 400 of biniodide of mercury, and 1 in 500 of tincture of iodine all failed to sterilise. Again, in experiments on inhibition, one volume of a 1 in 30 dilution of lysol, and 1 in 400 of tincture of iodine, and 1 in 200 solution

[1] *Drugs and Vaccines in Pneumonia*, Constable, 1914.

of biniodide of mercury did not avail to prevent bacterial growth in four volumes of pus. But I must not delay over the question as to what will with a particular antiseptic be the particular concentration required for the attainment of a particular antibacterial effect. Let us revert to our task of trying to bring the whole question of the employment of antiseptics in wounds into some sort of proper perspective. It will help us to do this if we consider the following questions :

(1) *Is there any reasonable prospect of sterilising the wound by an application of antiseptics?*

So far as the pus which is brought into intimate contact with the antiseptic is concerned, it would probably be possible to sterilise this by methods which will elsewhere be explained. But we have in the wound not only pus which can be reached by our antiseptic washings, but also pus which is locked up out of reach in blind alleys and pockets. And, again, we have in the infected wound not only a microbic infection of discharges, but also a microbic infection of the granulation tissue. And assuredly the really formidable difficulty in connexion with the sterilisation of the wound is that of getting sufficient penetrating power to deal with these sheltered microbes.

Now the ordinary antiseptics which we employ in wounds have as good as no penetrative power, and, though it is possible to undertake comparative experiments, and as an interesting academic exercise to determine for a series of antiseptics how far their antibacterial influence may extend in agar or any other artificial medium, academic exercises like this ought not to divert our attention from the fact that there is not, among all the competing antiseptics, one which can penetrate into and sterilise the walls of an infected wound. In fact, if ever an antiseptic sterilised a heavily infected wound, that would well deserve to be announced in all the evening and morning newspapers. Nor is it matter for surprise that antiseptics should not be able to penetrate into granulation tissue. Let us call to mind the fact that this is composed of continuous layers of cells ; that the cell wall is a quasi-impenetrable membrane ; further, that we have in the granulation tissue a well-developed system of capillaries, capable of absorbing and carrying away any antiseptic that might penetrate : and, lastly, that we have also in the granulation tissue an outflowing lymph current. Having realised the inefficacy of antiseptics for the purpose of sterilising an infected wound, let us now pass to the next question. It may be formulated thus :

(2) *Is there, in point of fact, any ground for the confident belief that a reduction in the number of microbes, such as would be obtained by washing out the wound with antiseptics, must carry advantage to the patient?*

We have realised that it is a firmly established conviction that every procedure which leaves behind in the wound fewer microbes would, like a smaller sowing of seed, sensibly reduce the ultimate crop, and so sensibly advantage the patient. The bacteriologist does not see in this a matter of course. He thinks not only of the sowing, but of the soil. He reflects that when we are dealing with a microbe which reproduces itself rapidly on a particular medium—let us say the typhoid

bacillus in peptone broth—the lightness or heaviness of the sowing would after the lapse of a comparatively short time hardly come into account. Again, in the case of a microbe which multiplied itself very slowly in a particular medium the sowing would, unless the incubation period were indefinitely extended, make very little difference to the result. Finally, where a microbe grows very slowly on a particular medium, but very rapidly as soon as this undergoes transformation, the population of microbes found in the culture would clearly depend less on the number implanted than on the time taken to convert the nutrient substratum from a bad into a good cultivation medium. It is, in the light of what has gone before, quite easy to see the application of this to the wound. Whether few or many serophytic microbes are left behind in the wound will make comparatively little difference to the number found in an uncorrupted lymph. For serophytes will, unless constantly kept down by phagocytosis, multiply rapidly in such lymph. Again, in the same way, whether few or many sero-saprophytes are left behind would not make much difference to the number found in a corrupted discharge. For sero-saprophytes grow very rapidly in this medium. So the factor which will really exercise a dominant influence on the result will be the rate at which the lymph becomes corrupted. And the practical conclusion emerges that what is really difficult in dealing with an infected wound is not to thin out the microbes, but afterwards to keep down their numbers. We are here carried along by our train of thought to the ' dressing of the wound ' ; and in connexion with this we may put the following question to ourselves :

(3) *What conclusions can be drawn from the fact that frequent re-dressings are indispensable in connexion with the treatment of infected wounds by antiseptics?*

This is one of those questions of which we realise the fundamental significance as soon as they formulate themselves in the mind. When our treatment has miscarried, and the wound has filled up again with pus, and this has become tryptic and has begun to digest the granulations and skin surfaces with which it comes into contact, and when bacterial poisons are being absorbed into the system, we are compelled to re-dress the wound. In other words, when we have been falling away we have to try to get back to the position which was reached at the previous dressing. And let us in this connexion note that it is one thing when unsuccessful to fall back upon dressing, and to make of this a point of departure for trying a new way ; and quite another thing to accept dressing as a necessary and inevitable element in our programme of treatment, and then not even to propose to make it a point of departure for a new therapeutic effort, but calmly to contemplate an everlastingly repeated setting out into a blind alley, and an everlastingly repeated return to our point from which we started. If grace had been given us to see things with unsophisticated vision, it would be clear to us that to make constant re-dressing an integral and indispensable element in our programme of treatment is really as much a confession of failure in the case of an infected wound as in a surgical operation. It is equivalent to saying that our method of treatment leaves the wound in a condition which makes healing impossible. And this leads on directly to the question :

(4) *How are we, in view of all the above, to account for confidence in the utility of the antiseptic method of treatment?*

We may here begin by emphasising that in all probability the antiseptic method, considered as a method for preventing the importation of foreign germs into the wound, has deserved everything in the way of praise that may have been said of it. For it is no doubt owing to the fact that antiseptic solutions have everywhere been employed for washing out the wounds, that there have not developed in the military hospitals in this war any of those graver forms of infection which in pre-Listerian days never failed to put in an appearance. When, however, we pass from prophylaxis to treatment, and from the consideration of the effects in connexion with the patients, taken as an aggregate, to the effects which manifest themselves in the individual who is under treatment, it is then that we come face to face with the problem as to how it has come about that the obvious non-success of the antiseptic treatment is not generally appreciated. It seems to me that this also must be put down to sophisticated vision and to the effects of education. We must remember that the practitioner of to-day has been educated to expect to find, within a few hours after washing out an infected wound with antiseptic, as much pus and as many microbes as when he last came to dress it.

Finally we may ask ourselves one more question.

(5) *May eventual harm result from applications of antiseptics?*

In dealing with this question we must send adrift that verbal formula ' injury to tissues ', which meets the eye everywhere in surgical literature. And we must realise that so long as we talk only of an undefined injury to undefined tissues we shall never make any progress. Precise answers can come only from precise questions.

We ought here to ask ourselves in connexion with particular concentrations of particular antiseptics (*a*) whether they hinder or promote, to the disadvantage of the patient, the emigration of leucocytes ; (*b*) whether they paralyse phagocytic activity ; (*c*) whether they favour the ' corruption of the lymph ' ; and (*d*) whether they stimulate microbial growth. I hope in future to deal with all these questions. For the moment let it suffice to say that antiseptics in various dilutions can do all these things ; and to emphasise the following. An addition of carbolic acid may, as shown by my fellow-worker Dr. W. Parry-Morgan, diminish the antitryptic power of the serum. And it has long been known that antiseptics in high dilutions—dilutions which will be temporarily realised when antiseptics are left in the wound—powerfully stimulate microbial growth. This has, by my fellow-worker Dr. A. Fleming, recently been demonstrated to the eye by implanting the *Bacillus Aerogenes Capsulatus* of Welch into nutrient media which had received graduated additions of antiseptics, and using the amount of gas formed as a measure of microbial growth.

We now pass to :

(II) Treatment by Physiological Methods.

We shall do well to begin by putting quite away from us the current preconception that to abandon antiseptics would be equivalent to abandoning the pro-

gramme of killing microbes in the wound. A moment's reflection will show that Nature has from the very beginning of things been bringing to bear her own antibacterial agents on infecting microbes ; and that we have in antiseptics merely a recent substitute for these. Moreover, the surgeon, in treating wounds, has all along, though not with conscious aim, been bringing the antibacterial agencies of the body to bear on the infecting microbes.

In treating a wound infection by physiological methods we have therefore only to follow the surgeon's lead. But we may hope, as we go along, to improve upon his methods. For we shall fix our attention on the guiding principle which he has missed.

The chief points which the surgeon has insisted upon in connexion with the treatment of infected wounds and tissues are the following : Where there is an abscess sac or a closed cavity containing pus, this must be laid open, and outlet for the discharge must be provided—if possible in the most dependent part. Where an infection has spread diffusely in the tissues, free incisions must be made ; and where these incisions pass through infiltrated tissues they must be carried from sound skin to sound skin, and all the way down to the healthy structures underneath, and after that hot fomentations should be applied. Lastly—and this is one of the teachings of the present war—when amputating through infected tissues unrestricted drainage must be provided : either by leaving the wound unsutured, or (in cases of gas phlegmon) by reverting to the mediaeval method reintroduced by Fitzmaurice Kelly, of cutting the limb squarely across, and dispensing entirely with flaps.[1]

Let me now try to show you that all these procedures—and it will not be necessary to consider them all in detail—will in the ordinary case bring the antibacterial agencies of the body into play. And let me further try to show you that when they fail to do this satisfactorily, they never, even when they accomplish all that the surgeon asks, do any effective good in combating the infection.

I shall begin by considering the *rationale* of opening up the abscess sac. The popular explanation accounts for the utility of this procedure by telling us that it provides issue for the infected discharges. But that is quite inadequate. For not only does the operation provide issue for the infected discharges, but when it succeeds it brings about the destruction of the microbes which are embedded in the walls of the abscess sac. In reality it alters the whole situation. In the unopened abscess the antibacterial agencies of the body are overborne by the mass effect of the infecting microbes. The white blood corpuscles in the abscess sac are paralysed, or killed ; and all the antibacterial power of the lymph has been lost. In the abscess that has been laid open and emptied, the infected bacteria are overborne by the mass effect exerted by the antibacterial agencies of the body. Fresh antibacterial lymph is streaming in through the walls ; and phagocytically active leucocytes are emigrating into the empty cavity. But for all that the infecting bacteria are overborne, the infection is not necessarily extinguished. The laying open of the abscess does not always put everything right. The mechanical conditions may leave much to be desired. It may be necessary to obtain a larger outpouring of lymph to wash

[1] *Lancet*, January 2, 1915, p. 15.

the embedded bacteria out of the walls of the wound, and to prevent them accumulating in the abscess cavity and effluent channel. Again, the antibacterial agencies of the body may require to be brought into more effective operation. It may be desirable to bring to bear on the microbes both a greater volume of antibacterial lymph and a larger force of phagocytes ; or it may be proper to repress the emigration of leucocytes so as to prevent any breaking down of these in the wound.

Now the supplementary surgical procedures which were enumerated above, all contribute, more or less effectively, to the accomplishment of one or other of these ends.

Drainage-tubes are devices for preventing the accumulation of infected discharges. But they do not really keep down bacterial growth in the walls of the abscess cavity. There ought to flow out from a wound not a pus composed of disintegrated leucocytes and microbes, but a lymph which is inimical to microbes, and favourable to phagocytic activity ; and things do not begin to clear up in a wound till its effluent runs clear.

Free incisions carried down into infiltrated tissues are intended to furnish an ample outlet. But in reality the dimensions of the outlet do not necessarily correspond to the superficial area of the incisions. In point of fact the effective outlet will in infiltrated tissues correspond only to a small section of that area. For the lymph spaces are blocked with leucocytes and fibrinous exudation. And there will, moreover, ooze out from the cut surfaces a highly coagulable lymph, which very quickly seals up any open pores.

Hot fomentations, in addition to macerating and bringing away the inflammatory exudate, will induce active hyperaemia, and so increase the outflow of lymph.

Leaving operative wounds unsutured and dispensing with flaps will, as already explained, give unrestricted drainage—so far at least as the mechanical conditions are concerned.

We have now arrived at some sort of a general idea as to what would be embraced under the term ' Treatment by Physiological Methods ', and we have realised that the empirical procedures of the surgeon furnish us with something to work with and improve upon.

It will be taking a first step to the improvement of these methods if we draw up for ourselves a complete list of desiderata. We shall, in setting these out, have to bring them into relation with the actual types of wound infection which come up for treatment.

In reality our infected wounds conform, nearly all of them, to one or other of two types : In the *first* type we have an infection of either the naked tissues which form the walls of the wound, or of granulation tissue coating these walls. Examples of the first type of infection are furnished (*a*) by recent projectile wounds whose walls are implanted with microbes ; (*b*) by suppurating cavities which have just been opened up and evacuated ; and (*c*) by old-standing suppurating wounds which have just been washed out and left clean. In our *second* type of wound we have an infection in an infiltrated wall and in the tissues contiguous to this.

In the former type of wound infection it would be a desideratum to wash the

infecting microbes out of the walls of the wound by means of a powerful effluent stream of lymph ; and it would be desirable in connexion with this lymph that it should carry in with it into the infected cavity whatever force of phagocytes might be required ; that it should furnish a favourable medium for, and directly assist, phagocytosis ; that it should repress bacterial growth ; and that it should not suffer any sensible diminution of antitryptic power if, after ineffective phagocytosis, a certain number of leucocytes broke down in it.

In the second type of infection, while everything that applies to the first type would apply, it would probably be desirable, as special measures, to repress further emigration of leucocytes, and to render the lymph incoagulable so as to prevent any stanching of the lymph outflow.

For the complete realisation of these desiderata we should require to have at disposal an agency for powerfully increasing the outflow of lymph. (I propose almost immediately to show that we have this at disposal.) Further, it would probably be necessary to have at disposal—but till further research has been carried out it is impossible to speak with certainty on this subject—means for promoting and repressing emigration. And lastly, it would almost certainly be necessary to be in a position to increase at need not only the antibacterial power of the lymph with respect to the infecting microbes, but also its general power of repressing the growth of sero-saprophytes. This, however, will come up for consideration in connexion with treatment by vaccine therapy.

As just announced, I pass now to consider what agents we have at disposal for increasing the outflow of lymph. In this connexion we have already seen that the lymph flow from the wound can be increased by the application of hot fomentations. It can be increased also by introducing ether into the wound—the ether, like the hot fomentations, no doubt acting by inducing active hyperaemia.

But I think that better than either of these, because it is more continuous in its action, and because it renders the lymph incoagulable, and also perhaps because it represses emigration, is the lymphagogic application which I have been recommending now these many years back. This consists of a 5 per cent. solution of common salt, mixed with $\frac{1}{2}$ per cent. of sodium citrate. This brings into play osmotic forces, and ' draws ' the lymph out of the walls of the wound by a *vis a fronte*. The sodium citrate is added with a view to decalcifying the outflowing lymph and rendering it incoagulable.

I may perhaps be allowed to say with regard to this lymphagogic solution—or, rather, with regard to the simple 5 per cent. salt solution, which I find works in most cases equally well—that it has in this war proved itself pre-eminently useful. When brought into action upon a dry and infiltrated wound, or a wound that is foul and covered with slough, it resolves the induration, brings back moisture to the surfaces, and cleans up the wound in a way that no other agent does. Applied in gaseous gangrene in the form of a wet dressing to incisions which have been carried down into infected tissues it causes lymph to pour out of the wounds, and arrests the spread of the infection. And, again, applied in gaseous gangrene to an amputated stump in cases where it has been necessary to leave infected tissues behind, it draws out the infected lymph—saving life in almost desperate conditions.

What would be the proper culmination and end to the treatment of wound infections by physiological methods?

We have now arrived at a point when it will be proper to keep our eyes somewhat less closely upon the ground, and to ask ourselves what kind of a coping-stone is to be placed upon our edifice of physiological treatment. For it is clearly unthinkable in connexion with such treatment carried out on scientific lines that it should lead to nothing better than to that everlasting dressing and re-dressing of the wound which all antiseptic treatment seems to consist of. I am convinced that, when once we shall have learned exactly how to regulate the outflow of lymph, and to control emigration and phagocytosis, it will be practical policy to make an end, once and for all, to a wound infection, and to close up the wound.

Even as we stand at present that seems to me to be to some extent a realisable ideal. While it would lead too far to follow up this question in detail, it will, perhaps, not be amiss to direct attention to the following points :

It will always and ever be impossible to sterilise a wound within the space of a few minutes. To wash out microbes from the granulation tissue will always take time. And we shall always have to allow time for the leucocyte to find the microbe ; and for phagocytosis ; and for the digestion of the microbe in the interior of the phagocyte. And again, and above all, we shall always have to allow a very large margin of time for the miscarrying of lymph lavage, emigration, phagocytosis, and the intracellular destruction of the microbes, and for the necessary going back over all these processes.

In view of this it will be clear that when we embark upon physiological treatment we ought to carry it out unremittingly. And our treatment will perhaps best take the form of continuous irrigation or continuous baths.

When by these means we think we have rendered our wound sterile, or nearly sterile, we must, in closing up the wound, or in giving it an opportunity of healing up under a scab, always proceed by the method of trial and error and provide for the possibility of the microbes again assuming the upper hand.

(III) Treatment by Vaccine Therapy.

I emphasised at the outset of this discourse that treatment by vaccine therapy could take rank only as ancillary to treatment by physiological methods. In *Treatment by Physiological Methods* we take the antibacterial agencies of the patient just as they are, and do our best to bring them into more effective application on the infective microbes. In *Vaccine Therapy* we seek to reinforce those agencies. We endeavour to increase the bacteriotropic power of the blood, and to modify the chemotropic sensibility of the leucocytes. And, now that we have come to appreciate its importance, we should seek to increase also the antitryptic power of the blood fluids.

Let us try to see how the case for vaccines and vaccine-therapy stands, keeping always before us the great practical issue as to how much clinical benefit can in the particular case be secured for the patient, and arranging, for the purposes of our survey, the manifold applications of vaccines under six subheadings.

(1) *Prophylactic Employment of Vaccines.*—This is not only from the theoretical point of view the best of all methods of employing vaccines, but it is also the method which gives, in practice, the maximum of advantage. We have only to look to the results obtained by prophylactic vaccination against small-pox, cholera, plague, and typhoid fever.

(2) *Employment of Vaccines in the Treatment of Localised Bacterial Inroads.*—Next to prophylactic inoculations, this gives the best results. And the results, in respect of their being almost immediately manifest to the eye, are even more dramatic than those of any preventive inoculation. Perhaps the most rapid and convincing results are those obtained by small doses of streptococcic vaccine in lymphangitis and erysipelas ; by staphylococcic vaccine in furunculosis, when the boil is just beginning to develop ; and by minimal doses of tuberculin in phlyctenular affections of the conjunctiva.

(3) *Employment of Vaccines in dealing with Unopened Abscesses and other Localised Infections where the Microbes cannot be reached from the Blood-stream.*—Vaccines are here, so far as appears to clinical inspection, quite inoperative.

(4) *Employment of Vaccines in the Treatment of Localised Infections associated with heavy Auto-inoculations.*—The scientific application of vaccines in these cases is extremely difficult and laborious, and the results which are obtained—and those obtained in the treatment of developed phthisis by tuberculin supply a good example—are not very convincing.

(5) *Employment of Vaccines in the Treatment of Undrained Wounds infected by Sero-saprophytes.*—There is not yet a sufficient body of experience to decide the question as to whether benefit can be obtained from vaccines in these cases. The question will be further discussed below in connexion with the wound infections of the war.

(6) *Employment of Vaccines in the Treatment of Septicaemic Infections, and, in particular, Streptococcic Septicaemias.*—Up to the present—except perhaps in certain series of experiments relating to typhoid fever—vaccines have, on the whole, given, in septicaemias, very disappointing results. But it will be obvious on consideration, that as we advance through the whole series of applications—from prophylactic application to the employment of vaccines in septicaemias—the conditions are becoming progressively more difficult, so that success in treatment of septicaemias, if it is ever attained, will be the very final achievement of vaccine therapy.

We have now prepared the ground for considering what has been obtained by the use of vaccines in the treatment of wound infections in this war.

I have, in connexion with this, heard the opinion of a very distinguished French surgeon—pronounced after watching the effect of vaccines upon, I should think, undrained wounds and septicaemic infections—that they had never done any good. I shall, by my general survey above, at least have put you on your guard against generalising from one class of cases to all other cases. Let us now take each class of case separately, and ask ourselves whether, in this, vaccines have rendered any service. I think we shall then see that things work out everywhere in accordance with scientific law.

(1) *Prophylactic Inoculations of 'Antisepsis Vaccines'.*—If prophylactic inocula-

tions of this kind have not been undertaken in our army, it has not been because a supply of antisepsis vaccines has not been at hand, but because the idea of undertaking such inoculations has not appealed to the individual medical officers who have given first aid to the wounded. And if any prophylactic inoculations have been undertaken, this can have been only on a very small scale ; and the fact has not transpired. To be considered therefore here is only the question as to what we should on *a priori* grounds be justified in expecting from prophylactic inoculations against wound infections, undertaken upon the wounded. The answer is, I think, not doubtful. We might justifiably hope, in a proportion of cases, to sterilise the upper reaches of the wound which would be less heavily implanted ; and perhaps in isolated cases—those in which we have a comparatively light sowing of microbes —to sterilise the whole wound. Moreover, if we could employ vaccines in combination with *physiological drainage* (I mean, by that, free outpouring of lymph obtained by the use of a lymphagogic solution) we might, I think, hope to stave off infection in a fairly large proportion of cases. But—and I have already, though perhaps not emphatically enough, drawn your attention to this in connexion with prophylactic applications of antiseptics—it will, when we set out to sterilise a wound, nearly always be a question of achieving either all we want or nothing. To leave behind, especially in the upper reaches of a wound, a few microbes, which immediately set to work and multiply, amounts, from the point of view of the future of the wound, to exactly the same as leaving behind alive the whole original population. If one really intends a war of extermination there must be no remissions ; and if our first effort with vaccines and physiological drainage fails, we must immediately follow up with further efforts.

(2) *Employment of 'Antisepsis Vaccines' in Cases where the Microbes make an Irruption into the neighbouring Tissues.*—In connexion with projectile wounds it is not very uncommon to see the infecting microbes breaking bounds, and making an irruption into the neighbouring tissues. This will occur either in a wound which has not been laid open, or where the lymph flow has stanched, and the microbes have been imprisoned in an infiltrated wall. The bacterial irruption may follow the course of the lymphatics as a lymphangitis ; or it may take the form of an erysipelas or cellulitis. In these forms of infection occurring in connexion with projectile wounds, vaccines give exactly the same dramatic effects as in the small wounds of civil life—the only difference being that, when the irruption has been beaten back, we have in the case of projectile wounds still the original focus of infection to deal with ; and have, unless we improve the condition of the wound, always to be upon our guard against a renewal of the irruption.

(3) *Employment of 'Antisepsis Vaccines' in connexion with well-drained Wounds.* —When we have in a wound quite unobstructed mechanical drainage—such, for instance, as is provided by amputation without flaps—we have, from the point of view of the immunologist, conditions exactly parallel to those which obtain when microbes make a first irruption into healthy tissues. In other words, we have here —and probably also where we have good physiological drainage—brought to bear upon the microbes an ample force of phagocytes in conjunction with a rapid, percolating or outflowing, as the case may be, stream of lymph. As a consequence,

vaccines give in these cases results which are so strikingly favourable as to arrest the attention of every beholder.

(4) *Employment of 'Antisepsis Vaccines' in imperfectly drained Wounds.*—An overwhelming proportion of projectile wounds which are under treatment in hospital would, regarded from the point of view of the mechanical conditions, come into the category of imperfectly drained wounds. And this is as it must be. The conservation of the wounded limb is clearly the first object of the surgeon ; and the treatment of the bacterial infection is quite subordinate. For example, no one could ask that a leg which had been perforated by a bullet should be cut free from all its attachments to give better drainage to the infected track.

Now it might be legitimate to say that these undrained wounds were analogous to the unopened abscesses referred to above, were it not that this comparison would do much less than justice to the difficulties which confront the immunisator in the wound where pus accumulates. Not only have we in the recesses and backwaters of such a wound conditions which make it impossible for the antibacterial agencies of the body to establish by their mass effect a position of superiority over the microbes ; but we have in the corrupted discharges and the multiform bacterial growth which they harbour, obstacles to successful immunisation such as are encountered in an unopened abscess cavity. It is therefore not to be expected that we should in these cases see—and in point of fact we do not see—after the exhibition of vaccines any diminution in the pus which pours from the wound.

None the less we shall do well carefully to consider certain questions in connexion with the employment of vaccines in the treatment of imperfectly drained wounds. It is clearly a matter for consideration whether—despite the fact that the output of pus from the wound is not diminished—there may not be some useful clinical result from the vaccines. It is quite likely that there is such an effect ; and that it takes the form of a ' nibbling ' at the infection in those parts of the wound lying above the ground level of the pus ; a better entrenchment against the microbes ; and, behind this, a massing of reserves which would be brought to bear if the microbes were to irrupt into the surrounding tissues. In short, it is not unreasonable to think that the antisepsis vaccines might aid the surgeon in his conservative surgery, and might enable him to hold on longer when trying to save a limb.

Two further questions—questions which also cannot yet find answers—come up for consideration in this place. The one is the question whether it would not be possible in many cases to convert by physiological drainage an undrained into a drained wound, and then to obtain good results by the use of vaccines. The other is the question as to whether or no the bacteriotropic substances produced in response to antisepsis vaccines would come into operation upon sero-saprophytic microbes in corrupted discharges, and in lymph whose antitryptic power has been artificially diminished.

(5) *Employment of 'Antisepsis Vaccines' in Septicaemias supervening on Wound Infections.*—On this question there is nothing that can be usefully said other than that until scientific knowledge has progressed much beyond where it is now, it might be well to act upon the suggestion made above with regard to the possible utility of antisepsis vaccines in staving off septicaemic infections.

We now at the end of our survey come to the summary. That summary would clearly be, that the results of the inoculation of 'antisepsis vaccines' have conformed in everything to scientific expectation. Of the five possible applications of vaccine therapy, the *second* and the *third* have, according to anticipation, given strikingly favourable results. The *fourth* and the *fifth*—but perhaps certain reserves may be made in connexion with the *fourth*—have given, as anticipated, very unfavourable results. And that prophylactic employment of antisepsis vaccines, which has not yet been put to probation, would seem eminently deserving of an extended and careful trial, preferably in conjunction with physiological drainage.

Epilogue.

And now, except for a few concluding words, I have completed what I had to say. Up to this point we have considered only the scientific problems which confront us in wound infections. What we have now to consider is how this, and similar researches, and all that new clinical experience which has been won in this war, can be made useful to the wounded.

This is a question of setting up machinery for directing and co-ordinating the work of the medical officers engaged in the treatment of the sick and wounded. And, I take it, on a question of that kind the medical profession at home will have a voice, and, if unanimous, perhaps even have a deciding voice.

In order to enable you to judge what changes in the system would be required to give effect to the idea that medical officers should bring into application the latest lessons of experience and science, I will venture to remind you how the Medical Service of the Army is at present organised.

We have in the Army Medical Service, as it seems to me, three different and distinct services—a *Service of Administration*, a *Service of Hygiene and Sanitation*, and a *Service for the Treatment of the Sick and Wounded.*

The *Service of Administration*—and among the three services it comes easily first in order of importance—takes charge of the wounded man on the battlefield; conveys him first to the dressing station, field hospital, and clearing hospital which are ranged one behind the other at the front; thence transports him in an ambulance train to the hospitals at the base; afterwards embarks him in a hospital ship; and, at the end of his journey, provides him with hospital accommodation at home. The Service of Administration has further to see to the feeding, clothing, bedding, nursing, and medical treatment of the man in hospital, and in transit; has to look after all manner of surgical and medical stores and equipment—besides providing in a thousand other ways for the proper working of the hospitals and hospital camps.

The *Service of Sanitation* has to protect the Army against epidemic disease by attending to water supply, conservancy, and antityphoid inoculation. It has to keep a watchful eye on every case of infectious disease; to detect carriers; to equip, and man, the bacteriological laboratories required for this purpose; and to intervene in ways too numerous to mention to prevent the dissemination of infection.

The duties in connexion with the aforesaid services devolve almost exclusively

upon the permanent officers of the Royal Army Medical Service. Their work, as every one at the seat of war knows, has been quite marvellously well done. And what stands already very high in the esteem of all the world needs no more words of praise from me.

There remains the *Service for the Treatment of the Sick and Wounded.* After supplying all the multifarious duties just enumerated, there are very few medical officers of the permanent staff of the Royal Army Medical Corps left over. Hence nearly the whole care of the sick and wounded has fallen to the civil practitioners enlisted for temporary service with the Royal Army Medical Corps. For this, if for no other reason, it must be the special concern of the civil profession to do all that in it lies to help the Medical Staff of the Army to employ to the best advantage the civil practitioners now serving as medical officers in military hospitals.

What has been done in the way of regulating the work of these new-joined medical officers has been to transplant practically unaltered into the military hospitals the organisation under which medical practitioners work in civil life and in peace.

The treatment of the sick and wounded is committed, as it is in private and hospital practice at home, into the hands of individual practitioners, there being assigned to each a certain number of patients, or a ward. And, just as at home, where each medical man is in practically independent charge of his cases, and is free to follow whatever treatment appeals to him, so it is in the military hospitals. And just as at home the free exercise of private judgment carries with it an exclusive responsibility, saving only in those cases where a consultant is called in to advise, so also is it in the military hospitals.

Now, I submit that this unchartered freedom can work for good only in conditions such as those which surround us at home. At home, the practitioner finds himself practically always upon ground with which he is familiar. The cases which he deals with in his practice are similar to those he has seen treated in hospital. And if he should find himself upon unfamiliar ground he will, before he need take action, have time to inform himself. Moreover, though new science filters in slowly, it does filter in. And, finally, when the medical practitioner at home makes a new experiment in treatment, he—and this is the all-important point—does learn what results. He can, therefore, profit by the teachings of experience.

Now, the conditions in military hospitals abroad are quite different from these. The practitioner is there on quite unfamiliar ground. He has to confront unfamiliar problems—problems in connexion with projectile wounds and wound infections. He has to take immediate action. He has very little opportunity to find out what has happened in similar cases. And lastly—and you will see that upon this point everything pivots—he has very little opportunity of seeing the results of his work, and learning whether his treatment has been wrong or right. For the military hospitals in France, both at the front and also at the base, have now, through military necessity, become little more than clearing hospitals, from which cases, if at all fit to travel, are immediately sent upon their homeward journey.

There are thus lacking in the military hospitals in France all those provisos and safeguards which alone can make successful a system in which each medical

man is a guide to himself. And carried out without those safeguards that system is unjust both to doctor and patient.

The doctor feels himself left in the lurch when he is not warned off from trying experiments in treatment which a hundred others have unsuccessfully tried. He fain looks for a lead where a successful treatment has been discovered. And, where there are a number of alternative treatments, he would be glad to see comparative experiments instituted to tell him which method is best. Nor is the doctor the only person interested. The patient, his relatives, and the whole nation would, once their thoughts were directed to the matter, feel that they had the vital interest in making the work of the medical officer as effective as possible.

If this is to be done it will, I believe, be necessary to make a fundamental change in the organisation of the Medical Service—to break away from the principle of free arbitrament in treatment for the Medical Officer, and to provide that all treatment shall be regulated by orders and instructions.

These are, as you see, very big issues. It is a question of a conflict between our cherished professional tradition that every medical man must be quite unfettered in his choice of treatment ; and the very foundation principle of the Army, that every man shall work, not as he individually thinks best, but as part and parcel of a great machine.

The question as to which of these shall give way to the other must, of course, be decided by the balance of public advantage. And we cannot seriously doubt as to which side that balance inclines. We have only to consider what has been achieved in this war by antityphoid inoculation, and the preventive injection of antitetanus serum ; and to compare the brilliant results of these measures, enjoined as they are by direct instructions from headquarters, with the results which would have been obtained if their carrying out had been committed to the individual judgment of medical men who had not had before the war any opportunity of convincing themselves by personal experience of the utility of either antitetanus or antityphoid inoculation.

If now, as we see is the case, considerations of public utility commend the control of treatment of the sick and wounded by orders and regulations, let me in conclusion very briefly consider with you how under such a system there might be obtained a maximum of advantage with a minimum of disadvantage. I shall, of course, indicate only in very broad outlines what would seem to me to be the requirements.

I believe there would require to be a Professional Head to the Service for the Treatment of the Sick and Wounded. He would, of course, be subordinated to the Director-General, and his duties would be to bring up the work of the medical officers everywhere to the highest standard, and to co-ordinate their work from hospital to hospital.

It would further, I think, be necessary to have an Advising Committee who should be charged with the duty of synopsising the clinical experience won in the war ; of finding out what results the various therapeutic procedures had given ; and of drawing up on the basis of these inquiries general instructions and recommendations for the treatment of different categories of cases. On a Committee of

this sort one would, of course, wish to see representatives of surgery, of medicine, of the various specialities, and of pathology and bacteriological science. But one would wish to see the membership restricted to those who were actually at work at the seat of war, and who were prepared to take full responsibility, and carefully to watch the working of the recommendations, and at any moment to revise them in the light of accumulating experience or further laboratory experiments.

Finally, one would wish to see attached to such a committee a Research Department for the resolution of all bacteriological questions arising in connexion with hygiene, surgery, and medicine. And I may perhaps be allowed, in connexion with this last, to point out that the Medical Research Committee of the National Insurance Act, under whom I have the honour to serve as Director of Bacteriological Researches, has, since the outbreak of the war, been placing not only large funds but a carefully selected corps of skilled workers at disposal for the prosecution of researches directly contributory to the better treatment of the wounded. It is for you to see that full advantage be taken of the results as they are obtained.

A LECTURE ON WOUND INFECTIONS AND THEIR TREATMENT[1]

Delivered (with Demonstrations) at the opening of an Exhibition of Fracture Apparatus, held at the Royal Society of Medicine from October 8 to 14, 1915

Gentlemen,—In undertaking to deliver an introductory lecture on such an occasion as this I feel myself under a very heavy disability. While I am impressed—very profoundly impressed—with the ingenuity and value of the mechanical devices and appliances which have been brought together within these walls, I am, as you know, quite lacking in that expert knowledge required for the proper appraisement of such things. There is, however, one—and it is, I would urge, by far the most important—aspect of wounds which does fall within my particular department of study. It is this that emboldens me to address you on this occasion.

I would, at the very outset, put it to you that the distinction between *sick* and *wounded* is from the point of view of science an entirely improper one. Those who are classed as wounded are as universally as, perhaps even more universally than, those classified as sick suffering from bacterial infection.

Ever since the days when Lister demonstrated that sepsis in surgical wounds was avoidable, very little study has been devoted to the bacterial infections which here come into consideration. For the surgeon has set before himself as his goal, not the successful treatment of septic infections of wounds, but their avoidance. And who will say that he is wrong? Less excusable, as it seems to me, was it for him to think that he had in antiseptics—if he should ever require it—an effective ready-made method of treatment for septic infection of wounds. After a year of war there are on that point very few illusions left.

There has in the meanwhile, I hope, been growing up a conviction that we shall not arrive at an effective treatment of wounds without strenuous study of the infecting microbes, the conditions in the wound, and the therapeutic agents which we employ, and the defensive operations of the organism.

Let me, drawing upon the research work which my fellow-workers and I have been doing in France, try to put before you, as briefly as may be, in connexion with these questions such points as seem to me most deserving of attention.

The wounded man seen just after he has received his wound is a man seen in the *incubation period* of his infection, just after the microbes have been implanted —these being, as you know, carried into the wound, upon particles of infected skin and clothing.

[1] Reprinted from the *Proceedings* of the Royal Society of Medicine, vol. ix, pp. 1–72, 1915.

The problem presented by the patient when first seen accordingly shapes itself thus: What is here the chance that the defensive mechanism of the body will prove adequate for the destruction of the microbes; and may we reasonably look to see the infection aborted? And in the event of the infection not being extinguished, what kind of course will it shape?

The extinction or non-extinction of the infection will depend upon the amplitude of the microbial implantation, and the favourable or unfavourable physiological conditions in the wound.

Rifle Wounds traversing only Soft Parts.

The first type of wound which we have to consider is the perforating rifle wound where the bullet traverses the soft parts without touching bone. Here, nearly always, the bullet will cut into the wall of blood-vessels. As a result there will be haemorrhage from the wound, and when the blood coagulates the track will become plugged with clot. Later, when the patient is moved, and the wound thereby disturbed, oozing may take place from the track.

Here we have a very light microbic implantation—only small numbers of microbes having been left behind by the missile on its passage through the soft tissues. Further, the walls of the track will have been scoured by the outflowing blood. And finally such microbes as are here left are enveloped in clot—in other words, there will be brought to bear upon the residual microbes the full bactericidal power of the volume of blood which occupies the lumen of the wound. We have, in fact, exactly the same conditions as in experiments conducted in capillary tubes with a very small number of microbes implanted into a unit volume of blood.

At a subsequent stage, we may, as indicated above, have oozing. It is not, as might be supposed, blood which escapes from the mouth of an oozing wound. It is a thinner incoagulable fluid containing only a small proportion of red corpuscles. It is, to come to the point, serum expelled from the clot by the *vis a tergo* of blood pouring into the upper reaches of the wound. There attaches, as I think, to this oozing a therapeutic significance. It is, in point of fact, equivalent to a reinforcement of the clot in protective elements.

You have already seized the point that when oozing occurs the serum of the clot—and that serum will, by contact with microbes, have lost some of its antibacterial power—is replaced by blood-fluids fresh from the vessels. And you also appreciate that the outflowing stream of serum will tend to wash microbes out from the clot and convey them out of the wound. But it might perhaps be overlooked that when oozing takes place the clot is reinforced by red, and—this is important—by white, corpuscles.

Rifle Wounds where the Bullet has Comminuted Bone.

Where a projectile comes up against a bone it will shatter it and make a large exit wound by blowing out the fragments and splinters, at the same time scattering the charge of microbes, which would otherwise have been sown only on the walls of the track, far and wide through the tissues.

We have here obviously very unfavourable physiological conditions. For not only is the circulation in the wound completely disorganised, but the wound will contain bone and soft tissues cut off from their blood supply and bound to necrose and slough. And deep in the tissues we have an implantation of microbes which no outflowing blood will wash away. And even more important, the outflow of lymph from the wounded surface—an outflow which meant the continuous replacement of invalidated by potent lymph—is going to be arrested by desiccation of the external wound surfaces. The wound, in other words, will, if left to itself, become *lymph-bound*. And, finally, the wound is, by virtue of its large exposed surface, going to lie open to all manner of after-infection from without.

These same unfavourable physiological conditions are associated also with shrapnel, shell, and bomb wounds. We shall consider them further in connexion with these.

Severe Shrapnel, Shell, and Bomb Wounds.

The essential feature about this class of wound is that we have here blunt or flat missiles, and that by consequence, as compared with bullet wounds, we have less penetration and perforation, and proportionately more bruising; and at the same time larger portions of infected skin and clothing are carried in by the missile. In other words, we have in the wound much worse physiological conditions; and along with this a heavier microbial implantation.

It will be a convenient arrangement to consider, in connexion with the severer types of wound, the effects of the bruising and the cutting off of the blood supply and the implantation of microbes into devitalized tissues; and then, in connexion with the lighter types of wound, to deal with the effects of the bacterial implantation into tissues not devitalised.

The disorganisation and the shutting off of blood supply which is the feature of all severe wounds is followed, of course, by mortification; and thereafter the necrotic tissues fall a prey to every type of microbe: serophytic and sero-saprophytic, aerobic and anaerobic, non-sporing and sporing. And all these influences, working in combination, will cause the tissues to turn black and putrefy and disintegrate; giving, where the wound is allowed to desiccate, a condition of *dry gangrene*. Under the black gangrenous coating there will, if the infection fails to spread to the underlying tissues, and if things are not disastrously ended by the growing out of the tetanus bacillus in the necrotic tissues, gradually be formed a line of demarcation. And finally, the gangrenous layer will be exfoliated, leaving underneath a granulating membrane and a surface infection. Essentially the same sequence of events will supervene if the wound is kept moist. Only here we shall have *moist gangrene*, and the necrotic tissues will be converted into sloughs; and there will be earlier and more profuse suppuration.

'Punched-in' Wounds produced by Shrapnel, Shell, and Bombs.

We come now to the lighter wounds which are inflicted by blunt missiles, to the wounds which we may call *punched-in wounds*. They are comparatively superficial wounds with steep sides going down to a floor sunk below the level of the

surrounding skin. Here the microbes have been carried in over an area corresponding to the superficies of the wound, and they are implanted into the walls and the floor. What is important in connexion with this implantation is, that it is made not into an open track from the walls of which the microbes might be washed off by outflowing blood, nor yet into effused blood, which is up to a point a very uncongenial culture medium for microbes ; but into lymph standing in lymph spaces. Now the lymph in such spaces is only under very low pressure—a pressure as low as, or lower than, that of the capillaries—and by consequence when lymph spaces are broken into we have nothing resembling the outflow of blood from a wounded vein or artery. There will at most be a little weeping of lymph, and the conditions will be comparable with those produced by dealing a heavy blow with a hammer upon the bark of a tree. In the analogous case of the wound we should, it is clear, have, instead of a washing away, an embedding of microbes in the subjacent tissues and these would then close over the wound.

The conditions in the punched-in wound are, as you will now see, very unfavourable. They will be unfavourable, first, because the antibacterial power of the lymph with which the microbes are brought in contact is bound to be quickly exhausted ; and further, because with the arrest of the outflow there will no longer be any renewal of the lymph. Again, the conditions are unfavourable also in the respect that the emigrating leucocytes coming, as they do in such a case, only tardily into a zone which is already poisoned by microbes, cannot press home their attack, and will effect nothing but a choking up of the tissues round the bacterial infection.

In this way we get in the course of a very few days all round our punched-in wound a hard infiltrated edge, margined towards the healthy skin by a zone of pale pink ; and in the indurated walls of the wound there confronts us an *imprisoned infection*. That infection will now extend, and—if its way outwards to the surface is too solidly obstructed—it will spread inwards ; giving rise, according to circumstances and the character of the microbic infection, to *cellulitis* or *gas gangrene*. Ultimately, however, the infection will manage to break through to the surface, and then we have again an *infection of flowing discharges*.

It is important to appreciate that the processes that have just been described take place not only in the punched-in wound, but everywhere where we have microbes implanted into lymph spaces, and afterwards an effusion of lymph which desiccates and seals up the wound.

And precisely the same sequence of events as follows upon the original implantation of microbes will, just so long as the microbes still maintain themselves in the walls, recur if at any moment the wound is allowed to desiccate and become lymph-bound. A set-back of this kind will, for instance, almost inevitably follow when, by the transporting of the patient from hospital to hospital, the outpouring of lymph from the infected walls of the wound is interrupted by drying.

Nature of the Microbic Infection met with in Wounds.

We now pass to consider very briefly the nature of the microbes which are carried into wounds from the soiled skin and clothing of the soldier. These microbes

may, as I pointed out in a previous lecture, be classified—and the classification is important for treatment as well as for the understanding of the mode of infection and of the evolution of the wound—into two main classes, a class of *serophytes* which (either because they elaborate or find pabulum in the normal serum) can live and multiply there ; and a class of *sero-saprophytes* which, so far as we know, can develop in the blood-fluids only when these have lost their antitryptic property—the property in question being that which inhibits those digestive processes which would be capable of converting the native albumens of the serum into pabulum for microbes. Intermediate in character between the serophytes and sero-saprophytes is a class of microbes which cannot grow in the serum when we make only a small implantation, but which, no doubt owing to the fact that they bring into operation powerful digestive ferments,[1] succeed in establishing themselves when we make a heavy implantation. We may call these *imperfect* or *secondary serophytes*.

To the category of *serophytes* belong the streptococcus and the staphylococcus —the latter being far inferior to the former with respect to its power of multiplying in unaltered serum. To the category of *imperfect serophytes* belong the *Bacillus aerogenes capsulatus* of Welch (*Bacillus perfringens*) ; the *Bacillus proteus* ; its close congener, the *Bacillus pyocyaneus* ; and the wisp-shaped diphtheroid bacillus commonly found in foul suppurating wounds. To the class of *sero-saprophytes* belong the larger number of microbes found in such wounds.

It will suffice here to bring out a few of the more important points in connexion with the serophytes and imperfect serophytes found in wounds.

The microbe most universally present is a streptococcus. It differs in very many respects from the classical *Streptococcus pyogenes*, which is met with, though much more rarely, in wounds. In film preparations of pus the streptococcus here in question shows up nearly always as a diplococcus. As obtained from agar and broth cultures, the elements of the diplococcus are lancet-shaped, and they are bent into an angle. To follow the French description, they resemble a circumflex accent or take the form of saddle-bags (*formes en besace*). In broth cultures we have interspersed with these a few short chains. The colonies as they grow upon agar are more opaque, less sharply margined, and somewhat larger than those of the *Streptococcus pyogenes*. Instead of being as colourless as glass and severely discrete, they show up as very faintly grey-green, and, when planted closely, tend to run together. As compared with the ordinary *Streptococcus pyogenes*, growth is also much more rapid—luxuriant cultures being obtained at 37° C. on broth and agar in four or five hours. Moreover, growth is obtained, not only at 37° C., but also at the temperature of the laboratory bench.

The most remarkable characteristic of this streptococcus is, however, the freedom with which it grows out in normal serum, and also upon agar when transplanted in blood. When we implant into blood in emigration tubes, and then

[1] The suggestion here made wins support from the fact that the streptococcus, which we may take as the type of a true serophyte, does not, when growing in clear serum, effect any reduction in its antitryptic power, whereas both the *Bacillus proteus* and the bacillus of Welch do this. And it will be remembered in this connexion that the streptococcus does not liquefy gelatine, while the *Bacillus proteus* and the bacillus of Welch rapidly digest albuminous substances (even coagulated white of egg) and gelatine, and, as the case may be, fat, urea, and other substances.

centrifuge, and incubate, we obtain after three to five hours with a moderate implantation a growth in the form of diplococci and short chains permeating the whole white clot ; or, with very light implantation, a growth in the form of colonies clearly visible to the naked eye and consisting of typical convoluted chains made up of indefinitely numerous elements. In the case where we implant into blood and then implant the blood culture on agar, we have very opaque white convex colonies which may be as much as ½ cm., or even 1 cm. in diameter ; and which, except for the fact that they are rather moister, closely resemble staphylococcus colonies. These are made up of lancet-shaped diplococci which might easily be taken for pneumococci. The surrounding blood is not haemolysed.

There will be no doubt in the mind of anyone who has studied descriptions and illustrations of the *enterococcus* and its mode of growth on ordinary media as given in French bacteriological textbooks that the streptococcus here in question is the enterococcus of the French authors. Moreover, it may be taken as assured—for we have compared our cultures of streptococci from wounds with a series of cultures of streptococci obtained by Professor Dreyer and his colleagues from the stools of patients who were being searched in the ordinary way for typhoid and paratyphoid bacilli—that the streptococcus we are here considering is the ordinary streptococcus of the faeces. And assurance is made still more complete by the fact that when searching normal faeces by the *faeco-sero-culture method* [1] my fellow-worker, Lieutenant A. C. Inman, invariably obtained from the faeces in his after-washes a pure culture of a streptococcus which was, in all the above-mentioned morphological and biological characters, indistinguishable from that which is practically invariably present in the wounds. We may therefore take it as unquestionable that the streptococcus which is commonest in wounds is of faecal derivation, and both our *faeco-* and *pyo-sero-cultures* show that if the smallest possible implantation of this microbe is made, in no matter what bacterial admixture, into serum, it will immediately grow out there.

With regard to the presence of staphylococcus in wounds, it may be pointed out that, by reason of its wide distribution in the skin and its serophytic properties, it is bound to be present in practically all wounds. We shall, however, presently, in discussing the results of our pyo-sero-cultures, appreciate that its growth in the wound is very quickly restricted by changes produced by the immunising responses of the patient.

Like the staphylococcus and the *Streptococcus faecalis* which we have just been discussing, the *bacillus of Welch*—which is also, of course, a constant inhabitant of the faeces—is implanted, one may take it, into every wound. This microbe, be it noted, is only an imperfect serophyte. In point of fact, as my fellow-worker, Captain d'Este Emery, has succeeded in showing, the serum exerts upon the bacillus of Welch a very considerable bactericidal power ; and it is therefore in serum implantations of this microbe only the survivors which grow and multiply, and in blood implantations only those which elude destruction by phagocytes and resist the action of the serum. All this means—and clinical experience amply bears this

[1] This method is modelled in all respects upon the *pyo-sero-culture method* presently to be described.

out—that if we can bring the blood fluids and leucocytes to bear on Welch's bacillus, we have very little indeed to fear from it.

What little requires to be said about the *Bacillus pyocyaneus* and *Bacillus proteus* and other members of the class of imperfect serophytes may for the moment be reserved.

Before passing on something may appropriately be said about methods of cultivation, and I may limit myself to the description of methods of obtaining cultures in serum. For it is only by implantation into serum that we learn what microbes threaten danger, and how far the body is protecting itself against these. And again it is only by the method of serum culture that we can, when dealing with a complicated mixture of microbes, choose out from among these those which we ought to employ as vaccines.

* * * *

Here follows in the original paper a description of the Wash and After-wash method of implantation into serum.

All that is really essential about the procedure will be described below (pp. 37–39); and the details of the technique may be read up in the author's *Technique of the Teat and Glass Capillary Tube.*[1]

Response of the Wounded Man to his Wound Infection, and Blood Changes induced in him by Auto-inoculation.

In wound infections, as everywhere where bacterial toxins are elaborated and absorbed into the blood, the machinery of immunisation is after a time called into operation, and as a result the blood is put into a better condition for defence. And then begins a serious conflict between the invaded organism and the invading microbes.

It is in connexion with septicaemic invasions, such, for instance, as typhoid fever, gradually coming to be understood that it is by the event of this conflict that the issue is decided; and that the physician in attendance is not following, much less directing, events. But it is as yet a quite unfamiliar thesis that the wounded, like the typhoid, patient is reacting to his infection with a systemic immunising response; and that the changes so induced in the blood exert a quite decisive influence on the course of the infection, while the surgeon who is dressing the wound and making local applications is only in a subordinate way helping or, as the case may be, hindering the curative procedures of Nature.

It will be well before considering the surgeon's task to take cognisance of what the immunising responses of the patient are doing in the matter of fortifying his blood.

We have, of course, in connexion with this only very imperfect knowledge, and we shall therefore have to keep very close to our experimental data. It will be convenient to marshal our facts under headings supplied by our methods of blood-testing.

Data furnished by Measurements of the Antitryptic Power of the Patient's Serum.—Reference has already been made to the antitryptic power of the blood-fluids. In

[1] 2nd Edition, Constable, London, 1921.

point of fact, the antitryptic power of the serum acts as a check upon all microbial growth.[1] In the case of *sero-saprophytic bacteria* it completely balks their efforts to establish themselves in the serum. In the case of *imperfect serophytes* it places a very formidable obstacle in the way of growth. And in the case of *serophytes proper*, as a comparison between sera of low and high antitryptic index, and between sera which have, and sera which have not, received an addition of trypsin shows, it also determines whether the culture in serum [2] shall be scanty or luxuriant.

It will be obvious from the above that an increase of the antitryptic power of the blood-fluids would operate in restraint of any blood invasion, and that it would also, so far as the blood-fluids came into application unaltered, restrain the growth of all forms of microbes, both in tissues and in the wound. In other words, an increase of antitryptic power would operate as a non-specific factor in immunisation. Now we have, as already indicated in the lecture I delivered here six months ago, in every, or practically every, wounded man a notable increase in the antitryptic power of his serum. Already within thirty-six hours or less after the infliction of the wound the antitryptic index has risen far above the level of the normal ; and reckoning the antitryptic power of the normal serum as *unity*, antitryptic indices of four and five are very common in the patients under treatment at the base.

More than that, we have found a quite similar but smaller increase in the antitryptic power of the blood after inoculating ourselves—one of us with typhoid vaccine, another of us with streptococcus vaccine, and a third with staphylococcus vaccine.

And let me here recall to you that attention has, in connexion with inoculations against plague, typhoid fever, and pneumonia, been time and again called to the probability that these vaccines give some protection against diseases other than the particular disease which the inoculation is designed to ward off. Particularly convincing in this respect are the results in the form of *diminished incidence of 'other diseases'* which were obtained in South Africa by the inoculation of pneumococcus vaccine upon the Premier Mine.[3] And I think all those who have had much experience of vaccines will have seen cases where therapeutic effects lying quite outside the range of the particular vaccine employed, and therefore, as we thought, not quite creditable to science, have been obtained by vaccine-therapy.

Data furnished by Pyo-sero-culture.

The method of pyo-sero-culture was referred to in my last lecture.[4] We may, however, substitute for the lengthier procedure there spoken of, the method described and illustrated overleaf.

[1] The antitryptic power of the blood fluids represents, be it noted, much more than merely a power of inhibiting microbic growth. With the antitryptic power go lost also the complementing, opsonic, bactericidal and coagulating powers of the blood.

[2] Where instead of implanting streptococci into serum free from leucocytes we implant into blood containing leucocytes these are broken down, with the result that the antitryptic power is diminished, and we have then, as already described in connexion with emigration tube cultures, always after a sufficient interval, luxuriant growth.

[3] *Vide* Appendix II in my treatise on *Preventive Inoculation against Pneumonia in the African Native*, Constable, London, 1914, reprinted from the *Lancet*, 3rd and 10th January, 1914.

[4] *Lancet*, April 10, 1915, p. 737.

Having introduced into companion pipettes each containing a trace of the patient's pus : into one, a series of unit volumes of the patient's serum ; and into the other, a series of unit volumes of a normal serum ; and having incubated these for from six to twelve hours, we now, beginning with the volume nearest the distal end of the stem which has received the smallest implantation, blow out our successive serum cultures in separate drops on to the surface of a sterile slide ; and then with a platinum needle or glass filament stroke out these in succession upon an agar plate, making in this way a series of linear implantations. On incubating

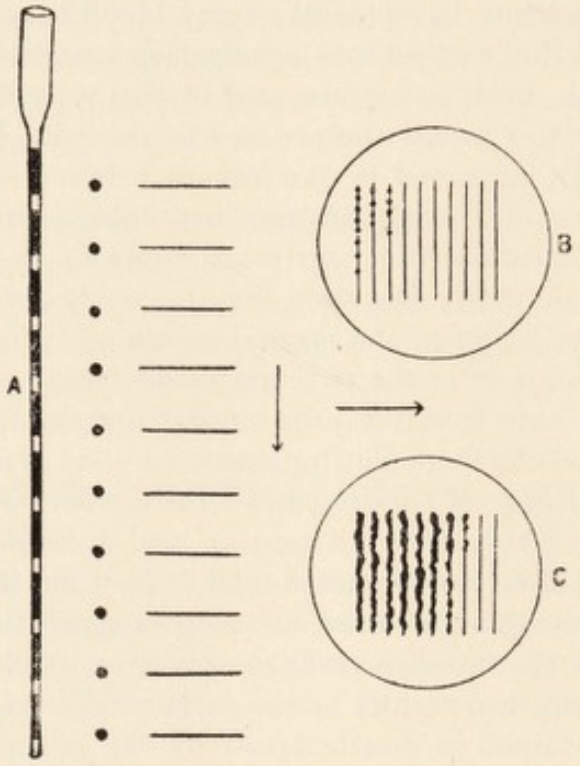


FIG. 1.—METHOD OF PYO-SERO-CULTURE.

(A) Pipette, the distal portion of whose lumen has been implanted with a wash of the patient's pus ; and has then been filled in by the Wash and After-wash procedure with unit volumes of serum. By the side of the pipette to the right are ranged a series of disks representing the series of unit volumes of serum blown out in order from the pipette, and, finally, to the right of the disks are a series of lines representing linear implantations made upon agar.

(B) Results of the series of linear implantations made with the unit volumes of the patient's serum.

(C) Results of the series of linear implantations made with the unit volumes of the normal serum which was used as a control.

our plates we then obtain with the serum of a wounded man who is uninfluenced by his infection exactly the same results as with the normal serum. In the case of a wounded man in the negative phase of his infection, we obtain cultures containing microbes (in particular, members of the class of imperfect saprophytes) unrepresented in the cultures made with the normal serum ; and, moreover, the cultures made with the patient's serum are, as compared with the cultures made with normal serum, more luxuriant and extend into higher dilutions. In cultures made with the serum of a wounded man who is making satisfactory immunising response—and the

illustration reproduces the results actually obtained, by implanting the pus of such a patient into his own serum, and into that of a normal man—we have in both cases of pyo-sero-cultures only serophytes, staphylococci and streptococci; but while the cultures made with the patient's serum (Fig. 1, B) furnish only a few discrete colonies, and these only in the first wash and two after-washes, we have with the normal serum (Fig. 1, C) in the first seven plantings massed colonies, and in the eighth, discrete colonies.

The real value of the method of *sero-pyo-culture* lies in this, that it tells up to what point the blood-fluids of the patient would, without aid received from the leucocytes, be capable of protecting themselves against an implantation of microbes, and specifically against an implantation of microbes from the wound. Now merely to tell us this is not to tell us how the microbes are going to fare in the wound. For we are not entitled to assume of the blood-fluids that they will in the wound obtain unrestricted access to the microbes; nor of the leucocytes that they will not die in the wound, converting thereby the effused lymph into a favourable culture medium for microbes. Still, evidence of satisfactory immunising response obtained by the method of pyo-sero-culture is, so far as it goes, evidence of favourable import, always with the proviso that the wound be treated in a rational manner.

Data furnished by Measurements of the Phago-incitor [1] Power of the Patient's Serum.

The changes in the serum which gradually render it a more and more uncongenial culture medium for microbial growth have their counterpart in changes in the serum which render the microbes an easier prey for phagocytes. These changes in the 'phago-incitor' power of the serum are exactly similar to those which manifest themselves in all other forms of localised infection; and we find, when we look for them, in connexion with wounds, all the phenomena of auto-inoculation with which we are familiar in other bacterial infections. And every day it becomes clearer that every displacement or movement of a fractured and infected limb—such displacements, for instance, as are associated with the transport of the wounded man, or the sagging of his limb when it is dressed, and also all those unguarded passive movements which the surgeon or orderly may inflict when the patient is under an anaesthetic, operate as auto-inoculations; and are followed by that sequence of negative and positive phases which we are accustomed to witness after the stirring up of a focus of infection by active exercise, massage, or the application of Bier's bandages.[2]

Data furnished by a Study of the Emigration Response of the Patient's Leucocytes.

As was already brought out in my last lecture, comparative experiments made with the method of testing emigration there described show that we have in patients who have made immunising response to their wound infections or to the inoculation of streptococcus vaccines, an emigration response to streptococcus implantation

[1] The term '*phago-incitor*' has for reasons which have been explained in the *Lancet* been substituted for the term *opsonic* which was employed in this lecture.

[2] *Vide* in this connexion the 'Auto-inoculation Curves' set out in the author's *Studies on Immunisation*, Constable, London, pp. 377 *et seq.*

which is strikingly greater than that of the normal man. I do not, until the method of estimation shall have been further improved,[1] desire to be more detailed on this question. I prefer to pass on to consider the bactericidal power of the whole blood, for we have in this in some sort the resultant of all those factors in immunity which we have been separately considering.

Data furnished by a Study of the Bactericidal Power of the Whole Blood.

The experiments on the bactericidal power of the whole blood which I undertook in connexion with work on pneumonia in South Africa [2] constituted a first attempt to make a complete evaluation of the bactericidal power of the blood-fluids and leucocytes working in conjunction and reinforcing each other.

Let me lead up to what I have to say upon this matter by reminding you in connexion with these experiments with the pneumococcus that the blood-fluids exert no bactericidal effect upon that microbe. And let me also very briefly go back over the procedure which I employed. That procedure was to make what I called wash or mural implantations of the pneumococcus into blood drawn direct from the finger, or, as the case might be, into washed corpuscles suspended in serum, decalcified blood, blood kept liquid upon ice, and into what I will, venture barbarously to call *excoagular* blood. I mean by *that*—the red and white corpuscles and serum which come out from the blood clot when it is mechanically churned up. The experiments conducted with all these different varieties of blood gave, as perhaps some of you will remember, very remarkable but undeniably paradoxical results. With blood drawn directly from the finger, a very striking bactericidal effect—an effect which was upon occasion equivalent to a killing off of 600,000 to as much as 1,000,000 pneumococci per cubic centimetre of blood—was achieved. But it was not in every instance achieved.

With none of the other varieties of blood was any bactericidal effect achieved ; or if there was any effect, it was very insignificant and very inconstant. The reason for these diverging results did not at that time appear. I made some guesses which fell wide of the mark.

This was the position of the question when I again, in connexion with the streptococcus, addressed myself to the study of the bactericidal power of the whole blood. And the situation to be dealt with was here essentially the same as in the case of the pneumococcus, saving only in the respect that the serum is a much better culture medium for the streptococcus than for the pneumococcus.

During many months of work only very disappointing results were obtained. The blood of normal men, the blood of wounded men who were progressing favourably, and my own blood and that of two of my colleagues after we had been inoculated with streptococcus vaccine, alike gave when implanted with streptococcus in a graduated manner as good as no evidence of any bactericidal power. Or at any rate only very inconstant results were obtained.

[1] The method in its improved form is described and figured in the author's *Technique of the Teat and Capillary Glass Tube*, 2nd Edition, Constable, 1921.

[2] *Preventive Inoculation against Pneumonia*, Constable, London, 1914.

This was even a more violent paradox than that encountered with the pneumococcus, for the blood that failed to kill streptococcus was not blood which had in any way been tampered with, but blood drawn directly from the finger ; and it is, in view of the favourable event of most streptococcus infections, and the striking

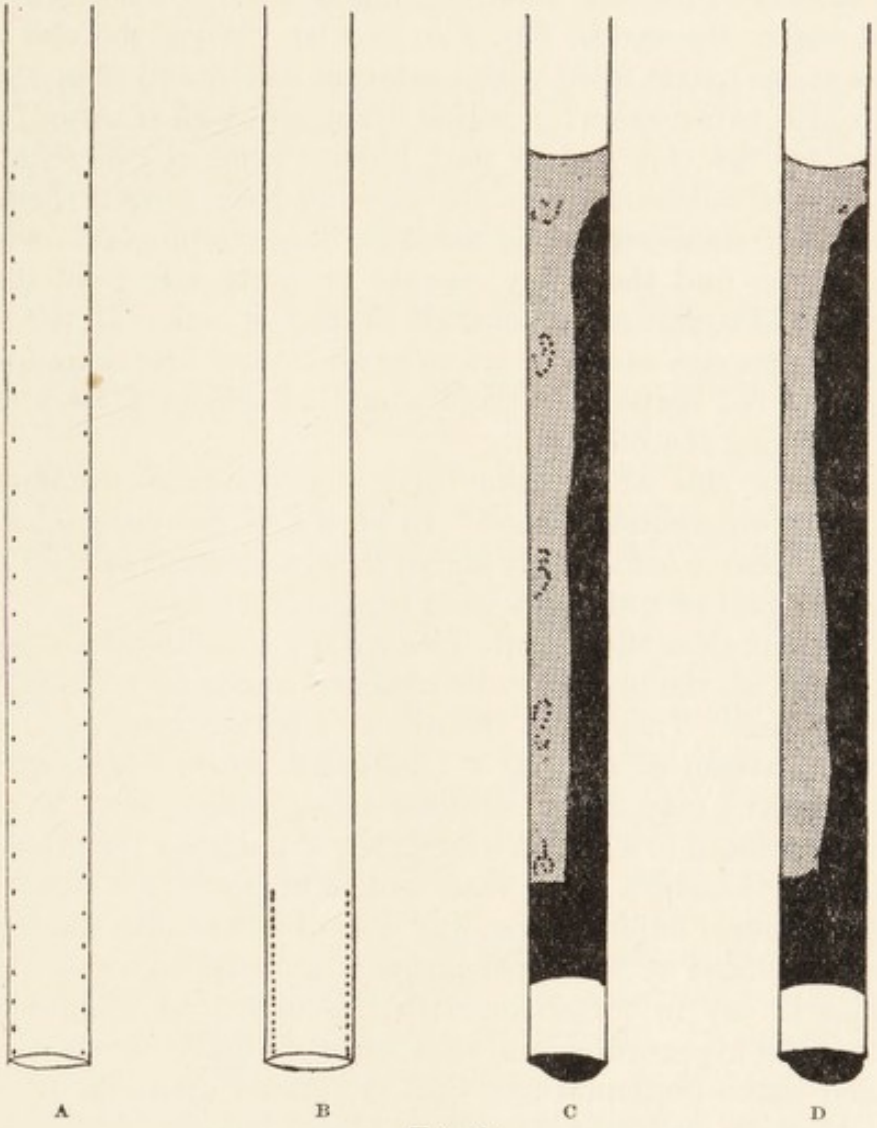


FIG. 2.

The Figure shows two forms of mural implantation into blood—in A a ' full-length mural ', in B a ' wainscot ' implantation. In A the distal end of the capillary stem has, as a first operation, been filled as far as an upper fiducial mark with blood. An air-bubble was then drawn in ; after this the tip of the tube was dipped into a microbial suspension, and then was allowed to run in as far as the distal fiducial mark. After this the microbial suspension was expelled and the blood was then, to receive its implantation, driven down to the orifice of the tube. In B, where the blood receives only a ' wainscot ' implantation, an essentially similar procedure was followed.

therapeutic effects obtained by streptococcus vaccine, difficult to doubt that streptococci are killed in the blood.

At the end a possible explanation of the contradiction between the results obtained *in vivo* and *in vitro* suggested itself. I suddenly woke up to the fact there was a flaw in the technique I was employing.

The nature of this flaw will be understood on referring to the diagrams. In my experiments the implantation of microbes into the blood was made by what I have called '*the method of mural implantation*', and the particular form of mural implantation employed was *full-length mural implantation* (Fig. 2, A).

Now what follows in the case where we implant into a blood which afterwards clots is brought before the eye in Fig. 2 (C and D). When the clot contracts the space which was at the outset filled with unclotted blood, and then with coagulum, divides itself up into two regions : a region occupied by clear serum, and a region occupied in part by the clot and in part by the loose (I call them excoagular) corpuscles which have fallen out from the clot and have ranged themselves round its base. The *first* of these regions is one in which streptococci—supposing they had once managed to find their way—would be quite safe from the phagocytic attack, and would find conditions favourable to their growth. In the *second* region, inasmuch as the phagocytes would be crawling about and fossicking for microbes in the clot and escaped red corpuscles, there would, at any rate, be a chance of the leucocytes extinguishing the infection.

Mutatis mutandis, this would apply also in experiments conducted with the different varieties of incoagulable blood. In each case the corpuscles would settle to the bottom, and there would be left above them a stratum of clear nutrient fluid in which microbes would be quite safe from phagocytic attack.

It will be obvious that these quite elementary considerations provide a very simple explanation of all the blank results obtained in our bactericidal experiments. They do more than that. They point the way to a better technique.

For clearly, if instead of making a '*full-length mural implantation*', we now limit ourselves to what I may call a '*wainscot implantation*' (Fig. 2, A) we shall be planting all our microbes into a region where they will during the whole experiment be exposed to leucocytic attack ; and there will no longer be for them, as there was with the full-length mural implantation, any way of escape into the region of safety and nourishment provided by the upper layers of the exuded serum.

It will suffice to say in connexion with this improved technique that it has answered even beyond expectation, and that when we limit ourselves to a wainscot implantation, and make implantations with graduated dilutions of streptococcus, we obtain not only with unclotted coagulable blood, but also with excoagular, and citrated blood, conclusive evidence of bactericidal power.

Let me, however, make the following point plain. Even with this improved technique the demon of chance has not been entirely exorcised from our experiments. And since chance will always, in our experiments, play a part in the ordering and disposition of leucocytes, it will be impossible in the case where the bactericidal power of the blood is centred upon these, and so operates only where gravity permits, to get regular quantitatively accurate results, such as are attainable when the bactericidal power is centred in the serum, and so operates uniformly through the medium.

* * *

The rest of the lecture is, because it deals in part with intricate therapeutic measures, more fully treated in subsequent papers, omitted.

A LECTURE ON THE CONDITIONS WHICH GOVERN THE GROWTH OF THE BACILLUS OF 'GAS GANGRENE' IN ARTIFICIAL CULTURE MEDIA, IN THE BLOOD-FLUIDS *IN VITRO*, AND IN THE DEAD AND LIVING ORGANISM

(*Delivered before the Royal Society of Medicine, 18th December*, 1916 [1])

My subject-matter to-day is not, as on previous occasions, the general question of the treatment of infected wounds. It is a much narrower issue. I would propose to consider with you the conditions which respectively promote and inhibit the growth of the 'gas gangrene' bacillus of Welch, but here also I shall have in view a purely practical end. The investigation of the conditions which favour or hinder the growth of the organism here in view has, as I see it, only one possible object. That is to conduct sooner or later to the saving of life and limb.

I may, I think, take it as certain that clinical observation is incompetent to furnish us with any precise information regarding the conditions which favour or impede the growth of the bacillus of gas gangrene, and that such information can be obtained only by laboratory investigation. But that does not mean—and we must never lose sight of this—that we can place unrestricted confidence in inferences based upon laboratory experiments. For in laboratory experiments we make for ourselves artificially simplified conditions; and confine our attention to a very limited number of factors. By virtue of this we are subject to make erroneous generalisations, concluding that what holds true under the conditions obtaining in the laboratory experiment will hold true universally. Presumptions of that kind can be avoided only by continually extending and critically revising our laboratory experiments and organising inquiries to find out whether our doctrines really give good results in practice.

And it is specially necessary to take these precautions when therapeutic procedures are based upon laboratory data. For quite a large proportion of such therapeutic procedures rest either upon generalisations which do not apply outside the conditions which are obtained in the experiments, or else upon generalisations which emphasise the thing that is unimportant to the prejudice of the thing that is important. I have in my mind, for example: the doctrine that antiseptics will sterilise an infected wound; and, in connexion with my present subject-matter, the doctrine that the growth of the gas-gangrene bacillus pivots upon the presence or absence of oxygen. It will provide me with a convenient point of departure to invite you to consider what is the experimental basis of this doctrine.

[1] Reprinted from the *Lancet*, 6th January, 1917.

I. Conditions which govern the Growth of the Bacillus of Welch in Artificial Media.

To practically all of us the most important scientific datum ascertained with regard to the bacillus of Welch is that it will not grow in the presence of air. And this datum, firmly believed, has dominated all surgical thinking in the domain of gas gangrene. It has led to the employment of oxygen or peroxide of hydrogen injected into the tissues as a sovereign remedy against the progress of gangrene. And it has suggested that the advantage of thoroughly opening up a wound infected by anaerobes is, in the main, advantage derived from letting in the air.

But the thesis upon which all this rests—the thesis that the bacillus of Welch cannot grow and multiply in the presence of air—is as a matter of fact erroneous. It was discovered by Tarozzi that when pieces of animal tissue were added to bouillon, cultures of anaerobes could be obtained in open tubes. Ori and Wrzosek, following up this work, showed that the same result could be obtained with pieces of either raw or autoclaved potato, and also with other vegetable tissues. Nor are these, as might be supposed from the fact that we have continued to think along the old lines, very recent discoveries ; nor, again, do the aerobic cultures of anaerobes here in question yield only meagre growth. Quite the contrary. The work of Ori and Wrzosek dates back already some ten years. And in reality the cultures of the bacillus of Welch grown in the open in bouillon containing a piece of potato are characterised by very rapid and vigorous growth, with gas production. So vigorous in point of fact is the growth of the bacillus of Welch in the open potato bouillon tube, that this method furnishes, it would seem, the best method for isolating the microbe from specimens of pus in those cases where the organism is present in only very small numbers.

There are displayed before you here a series of open culture tubes implanted with the bacillus of Welch, all showing by their turbidity and by foaming how vigorous is the growth. And, in order that the erroneous mental images which the appellation 'anerobes' nurtures in the mind may be obliterated, I have ranged up before you here also cultures in open of a variety of other anaerobes. And let me say that so far we have not obtained any anaerobe from a wound which cannot by proper devices be made to grow freely in open tubes.

You can see that it follows from this, that we cannot possibly promise ourselves that if we introduce oxygen into the tissues, or admit air to the interior of the wound cavity, we shall thereby inevitably arrest a gangrene bacillus infection. Or, putting the conclusion in more general form, we see that the therapeutic principle of combating anaerobes by combating anaerobic conditions cannot be regarded in any sense as an adequate therapeutic principle.

Let us be careful to read the lesson of these tubes aright. All that they teach is that anaerobic microbes can be got to grow with astonishing freedom in culture tubes fully open to the air. But it is not thereby established that the presence of oxygen is either indifferent or congenial to anaerobic microbes. And, in point of fact, it has been suggested, and the view is *a priori* tenable, that the potato may provide some reducing agent which by holding off the oxygen of the air at the outset enables the microbes to get a start, the subsequent growth being due to anaerobic growth in a medium deprived of air by the generation of gas in the culture. This

hypothesis that the potato furnishes a reducing substance which gives the culture a start seems to win support from the fact that the potato bouillon gives much less vigorous cultures when stale than when freshly prepared. And, again, the traditional view that oxygen is inimical, or at least uncongenial, to the growth of the class of microbes denoted 'anaerobes' does not entirely lack support. When after implanting I empty out the major part of the contents of a potato bouillon tube, reserving only a few c.c.'s, and then lay the tube on its side in the incubator, I get only a very meagre culture. The same holds true when I draw a continuous stream of air bubbles through the culture, and again in the case when cultivating in a capillary tube, I break up my column of fluid by intercalating a number of air bubbles. Moreover, when I endeavour to subculture from the meagre cultures of anaerobes grown under such conditions of maximum exposure to air, I am practically always unsuccessful. But all these considerations do not avail to obscure the fact that we are required to abandon the traditionary view that the growth of anaerobes pivots upon the presence or absence of oxygen. And after taking cognisance of these cultures in open tubes we are intellectually impoverished to the extent that we see that the doctrine of anaerobiotic growth that, as we thought, held unrestrictedly, holds true only with limitations.

Intellectual impoverishment is, however, impetus to research. And now that the presence or absence of oxygen turns out not to be the factor which controls the growth of the bacillus of Welch, there is stimulus to try to find out what is the controlling factor, or rather what are the controlling factors. For—it being in the order of nature that things should never be too easy—there are bound to be many controlling factors. I and my fellow-workers, Major Georges Dreyer at Boulogne and Dr. Alexander Fleming at St. Mary's, have consequently set ourselves to search for these controlling factors. In each case we set out to look for mechanical factors which might favour or hinder the growth of the bacillus of Welch.

The first question to which investigation was directed was the question as to what would be the effect of in the one case dispersing the implanted microbes through the culture medium, and in the other case concentrating the infection in some one region of the culture medium. I had already seventeen years ago, in a study [1] of the distribution of agglutinins and bactericidal substances in the body in cases of typhoid and Malta fever, called attention to the circumstance that microbes which would if carried into the blood-stream have been killed or impeded in their growth by the bacteriotropic powers of the blood succeeded in maintaining themselves alive in the internal organs, collected together in what I called 'niduses of lowered bacteriotropic pressure'—i.e. in regions where because collected together they can by active and passive chemical force maintain conditions propitious to their survival. In view of this analogy, and in view also of the circumstance that for the successful starting of a culture of the bacillus of Welch a large implantation is usually required, it appeared not unreasonable to inquire from experiment whether concentration of the infection comes into account also in connexion with growth upon artificial media.

The experiments were in each case carried out with measured volumes of

[1] The *Lancet*, 1899, ii, p. 1727.

glucose broth implanted with graduated additions of a suspension of Welch's bacillus, and cultivated anaerobically in capsules of glass tubing or capillary pipettes. In each case duplicate volumes were taken, and the one tube was cultivated lying flat and the other in the upright position—the microbes in this latter being concentrated at the bottom either by gravitation or centrifugalisation. In every series of such experiments—and in all eight were performed—the advantage from the point of view of successful cultivation of the microbe was with the series of tubes that were incubated in the upright position. The following may serve as an illustrative experiment.

Experiment 1

A 24-hours' culture of the bacillus of Welch, grown upon serum agar in an atmosphere of coal-gas sealed up in a test-tube drawn out in the blow-pipe flame, was suspended in a convenient quantity of glucose broth. This suspension, enumerated in a Thoma-Zeiss cell, was found to contain 220,000,000 microbes (the actual figure arrived at was 217,600,000). From this a graduated series of dilutions were made in glucose broth. Two 20 c.mm. volumes of each dilution were then taken up into graduated capillary pipettes and anaerobic conditions were provided by driving the column of fluid down from the proximal to the throttled distal end of the tube by the pressure of coal-gas [1] and then sealing up the two ends of the tube.

The cultural results are here set out in tabular form.

Experiment 1

Serial number of the dilution	Number of microbes in 20 c.mm. of that dilution	Cultural result in the tube standing upright		Cultural result in the tube lying flat	
		After 24 hours	After 48 hours	After 24 hours	After 48 hours
1	400,000	Growth	Growth	Growth	Growth
2	80,000	Growth	Growth	Growth	Growth
3	16,000	Growth	Growth	Growth	Growth
4	3,200	Growth	Growth	Growth	Growth
5	640	Growth	Growth	0	Growth
6	128	Growth	Growth	0	Growth
7	25	Growth	Growth	0	Growth
8	5	0	Growth	0	0
9	1	0	Growth	0	0

An effect essentially similar to that produced by collecting the infection into a restricted region of the cultural fluid ought, as reflection will show, to be achievable also by dividing up the culture medium by a series of partitions. For the chemical effort which the microbes will have to put forth for the transformation of the provided culture medium into a really propitious medium will, when that is divided up, be concentrated upon a fraction of the whole.

[1] The details of this (I call it 'the gas-piston method') are given in the author's *Technique of the Teat and Capillary Glass Tube*, 1921.

The experiment, conducted in duplicate, set out in the table below seems to indicate that this does hold true.

Experiment 2

Serial number of dilution	Number of microbes in each 100 c.mm. of the dilution	Volume of dilution employed for anaerobic culture in tubes lying flat			
		100 c.mm. as a single unit		100 c.mm. divided up by gas[1] into five units of 20 c.mm.	
		A	B	A	B
1	102,400	+	0	+ + + + 0	+ + + + 0
2	20,480	+	+	+ 0 0 0 0	+ + 0 0 0
3	4,095	+	+	0 + 0 0 0	+ + + 0 0
4	820	+	0	+ + + + +	0 0 0 0 0
5	165	+	+	0 + 0 0 0	+ + 0 0 0
6	35	+	+	+ + + 0 0	+ 0 0 0 0
7	7	+	0	0 + + 0 0	+ + 0 0 0

Other and more interesting experiments falling entirely into line with those which have been in question above are the experiments devised and carried out by Dr. Alexander Fleming. You have these cultural experiments in open tubes displayed for view here. We have, *first*, a culture of the bacillus of Welch obtained by introducing a pledget of asbestos into glucose broth left open to the air ; *secondly*, a culture obtained under the same conditions with a pledget of cotton-wool ; *thirdly*, a culture obtained by the addition of platinum black ; *fourthly*, one obtained with a rust-covered nail ; and *fifthly*, a culture obtained by introducing into the open bouillon a hair-fine capillary glass tube filled in with a minute quantum of a diluted culture. When we take cognisance of all these—and you see we have here in each case a turbid and vigorous gas-producing culture—and when we bring what we see here into relation with the fact that we obtain cultures also in open tubes containing potato, carrot, white haricot beans, bread, cabbage, cheese, earth, desiccated and ground-up albumin, and other additions, it comes home to us that the common factor here must almost certainly be a mechanical factor. And that mechanical factor would appear to be the providing of some hole or cranny to serve as a nidus in which the microbe can get a start by concentrating its chemical effort at first upon a fractional portion of the provided culture medium. Again, when we look beyond these test-tube experiments to clinical facts we see that the supervention of gangrene is very frequently correlated with the leaving behind in the wound of infected portions of clothing ; we see, in other words, that the same mechanical factor which is operative in the test-tube experiment would seem to come into account also in the body.

[1] The dividing up of the column of fluid by bubbles of gas was carried out by the technique described under the name of the 'Gas-lock Method' in the author's *Technique of the Teat and Capillary Glass Tube*, 2nd Edition, 1921.

II. Conditions which govern the Growth of the Bacillus of Welch in the Blood-fluids.

(*a*) *Bactericidal Factor*

In the matter of the culture of the bacillus of Welch in the blood-fluids the factor which more than any other factor comes into account is—and this was shown by Captain d'Este Emery when he was my fellow-worker at Boulogne—the bactericidal action of the serum. The following experiment shows how considerable is this restraining and bactericidal action of the normal serum. It brings out also the fact that the implanted microbes have a better chance of surviving and establishing themselves when collected together than when dispersed through the blood-fluids.

Experiment 3

This experiment was a companion experiment to Experiment 1 (*supra*), and is to be read in connexion with it. The same bacterial suspension was employed and the procedure was, except in the respect that the dilutions were made in the author's serum instead of in glucose broth, the same.

Experiment 3 (*Companion to Experiment* 1)

Serial number of the dilution	Number of microbes in 20 c.mm. of that dilution	Cultural result in the tube incubated upright	Cultural result in the tube incubated lying flat
1	400,000	Growth	Growth
2	80,000	Growth	0
3	16,000	0	0
4	3,200	0	0
5	640	0	0
6	128	0	0
7	25	0	0
8	5	0	0
9	1	0	0

We see here (computing from the figures for the tubes lying flat, i.e. the tube in which the microbes were dispersed through the culture medium) that 1 c.c. of normal serum was capable of disposing of an implantation of 4,000,000 (80,000 × 50) gas-gangrene bacilli, all of which bacilli were (as the control experiment, Experiment 1, shows) living bacilli.

(*b*) *Mechanical Factor*

Also we can see here that advantage accrues to the blood-fluids when the microbes are dispersed and cannot co-operate, and disadvantage when the microbes are collected together and afforded an opportunity of making a combined attack. The influence of this factor of dispersing or concentrating the infection comes out more clearly when we make similar implantations into duplicate volumes of serum, we centrifuge the tube containing the one portion and incubate it upright, and leave the other tube uncentrifuged and incubate it lying flat.

In the following experiments the cultures were made anaerobically by the 'gas-piston' method. The implantations were in Experiments 4 and 5 made by the 'method of washes', i.e. they were made by filling into the pipette one or more volumes of the microbic suspension, or one of a graduated dilution of this suspension, expelling this culture, and incorporating the microbes left behind into one unit volume of serum. In Experiment 6 graduated dilutions of the bacterial suspension were made in serum.

Experiment 4

	Amount of microbic suspension implanted into serum					
	Washes					
	4	3	2	1	½	¼
Centrifuged tubes incubated upright	Growth	Growth	Growth	0	0	0
Uncentrifuged tubes incubated lying flat	Trace	0	0	0	0	0

Experiment 5

	Amount of microbic suspension implanted into serum				
	Washes				
	2	1	½	¼	⅛
Centrifuged tubes incubated upright	Growth and gas	—	Growth and gas	Growth and gas	Growth only
Uncentrifuged tubes incubated lying flat	Trace	Trace	Trace	0	0

Experiment 6

	Bacterial suspension progressively diluted with neutralised serum						
	2 fold	4 fold	8 fold	16 fold	32 fold	64 fold	128 fold
Centrifuged tubes incubated upright	Gr.	Gr.	Gr.	Tr.	Tr.	Tr.	0
Uncentrifuged tubes incubated lying flat	Tr.	Tr.	Tr.	0	0	0	0

Gr. = growth ; Tr. = trace.

It comes out, as you will see, quite clearly in these experiments that the doctrine of the 'non-bacteriotropic nidus'—which I suggested to explain the survival of microbes in an organism which has in its blood-stream an ample provision of pro-

tective substances—is a doctrine which applies also to cultivations in serum conducted *in vitro*. And the full details of the experiments, if there were room to give them here, would bring out that the more rapidly the concentration of the implanted microbes is effected, and the shorter the preliminary exposure to the full bactericidal action of the serum, and again the less bactericidally potent the serum, the greater becomes the chance that an implanted microbe will get a start and go on from that to produce a generalised infection.

Up to this point the problem of the conditions which govern the growth of the bacillus of Welch in the blood-fluids has been treated as if practically all that was of moment was to withdraw by mechanical methods the implanted microbes from full exposure to bactericidal power of blood-fluids. But even here the factor which is in ultimate analysis the operative factor is, of course, the chemical factor. What comes into account is, on the one hand, the diminished mass effect exerted by the bacteriotropic action of the serum upon the microbes ; and, on the other hand, the increased mass effect exerted upon the phylactic elements of the blood-fluids by the products elaborated by the chemical activity of the microbes.

When the bacillus of Welch grows freely in serum it reduces the antitryptic power of the medium and it elaborates acid. Concurrently, as it would seem with this, the microbe starts to grow with phenomenal rapidity after the manner of an avalanche gathering force as it goes. Our next task must be to inquire whether there is any causal relation between the reduction of antitryptic power and the avalanche-like progression of the culture.

(*c*) *Experiments showing that the Culture of the Bacillus of Welch in Serum is largely governed by the Antitryptic Power of the Blood.*

The question as to what it is that converts the pus of neglected wounds into an ideally propitious culture medium for the gangrene bacillus and every other species of microbe presented itself very early in the course of this war. To that question I proposed an answer, and I think with every day it has become clearer that it was the right answer. That answer was to the effect that what stands in the way of free growth of all micro-organisms in the blood-fluids is the antitryptic power. We have to suppose in connexion with this that the antitryptic power inhibits the digestive processes which must precede the conversion of the native albumins of the blood into congenial pabulum for microbes. It therefore seemed to follow that if trypsin were directly added to the blood-fluids, or else if trypsin were indirectly added, and this is what occurs in stagnant pus by the disintegration of the leucocytes, we should have a corruption of the discharges, every manner of microbe cultivating itself there without restraint. In brief, what I suggested was that the antitryptic power is the guardian of the blood. In connexion with this I would point to the experiments of my fellow-workers, Captains S. R. Douglas and L. Colebrook. They have shown that haemocultures, otherwise so frequently infertile, can very often be rendered fertile by the addition of trypsin to the culture medium. And the following experiments, conducted with the bacillus of Welch, show exactly the same thing.

Experiment 7

A 24-hours' culture of the bacillus of Welch grown upon agar flushed with serum was suspended in a convenient quantum of glucose broth. This was found to contain 350 millions of bacilli per c.c. Graduated dilutions of the suspension were then made in a serum (A. E. W.'s) which neutralised an equal bulk of a 25-fold dilution of trypsin. Another precisely similar series of dilutions was made in another sample of the same serum to which had been added 1/25th of its bulk of the same sterile trypsin undiluted. Six 20 c.mm. volumes of each successive dilution of either serum were then taken up into calibrated capillary pipettes for anaerobic cultivation. The cultural results as determined by microscopic examination were as set out below.

Serial number of the dilution	Number of microbes in the 20 c.mm. volume which was cultivated	Unaltered serum	Trypsinised serum
		Number of fertile cultures	Number of fertile cultures
1	7,000,000	6 out of 6	6 out of 6
2	1,400,000	5 ,, 6	6 ,, 6
3	280,000	0 ,, 6	6 ,, 6
4	56,000	0 ,, 6	5 ,, 6
5	11,200	0 ,, 6	2 ,, 6
6	2,240	0 ,, 6	0 ,, 6
7	450	0 ,, 6	0 ,, 6
8	90	0 ,, 6	0 ,, 6
9	18	0 ,, 6	0 ,, 6

We see here that for the infection of normal serum there were required more than 25 times more microbes than for the infection of trypsinised serum.

Experiment 8

Here in the one set of tubes a wash of trypsin followed by a wash, or fraction of a wash, of the bacillus of Welch were added to serum ; in the control tubes larger quanta of microbial culture were implanted.

Control tubes :	
Serum + 3 washes of bacterial suspension - - -	No growth
,, + 2 ,, ,, ,, ,, - - -	,,
,, + 1 wash ,, ,, ,, - - -	,,
,, + $\frac{1}{2}$,, ,, ,, ,, - - -	,,
,, + $\frac{1}{4}$,, ,, ,, ,, - - -	,,
Trypsin tubes :	
Serum + 1 wash trypsin, 1 wash bacterial suspension -	Abundant growth with gas
,, ,, ,, $\frac{1}{4}$,, ,, ,, -	,, ,, ,,

Experiment 9

Here the same procedure was followed.

Control tubes containing normal serum :	
Serum + 4 washes of bacterial suspension - - -	No growth
,, + 3 ,, ,, ,, ,, - - -	,,
,, + 2 ,, ,, ,, ,, - - -	,,
,, + 1 wash ,, ,, ,, - - -	,,
,, + $\frac{1}{2}$,, ,, ,, ,, - - -	,,
,, + $\frac{1}{4}$,, ,, ,, ,, - - -	,,
Tubes containing trypsinised serum :	
Serum + 2 washes of bacterial suspension - - -	Abundant growth with gas
,, + 1 wash ,, ,, ,, - - -	,,
,, + $\frac{1}{2}$,, ,, ,, ,, - - -	,,
,, + $\frac{1}{4}$,, ,, ,, ,, - - -	,,

Experiment 10

Here again the same technique was employed except in the respect that the trypsinised serum was prepared by adding 1 unit volume of trypsin respectively to 9, 19, and 39 unit volumes of serum. The serum was A. E. W.'s serum, which neutralised an equal volume of a 25-fold dilution of trypsin. The cultural results were as set out below.

—	Amount of bacterial suspension implanted					
	Washes :					
	3	2	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$
Serum without addition -	Trace	Trace	0	0	0	0
Serum + 1/40th of its volume of trypsin - - - -	Growth	Growth	Trace	Trace	Trace	0
Serum + 1/20th of its volume of trypsin	Growth and gas	Growth	Growth	Growth	Growth	Growth
Serum + 1/10th of its volume of trypsin	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and gas

To this experiment may be added the following which brings out that there is a general but not a perfect correlation between the antitryptic power of the serum and its power of resisting infection by the bacillus of Welch.

Experiment 11

Derivation of the serum	Antitryptic power [1] of the serum	Infection-resisting (phylactic) power					
		Amount of culture implanted					
		Washes					
		3	2	1	½	¼	⅛
Patient with serious compound fracture	10 units (reciprocal of T/10)	0	0	0	0	0	0
Patient with perforating wound of chest	6·6 units (reciprocal of T/15)	Tr.	0	0	0	0	0
Patient with gangrene infection of leg	6·6 units (reciprocal of T/15)	Gr.	0	0	0	0	0
Patient with serious flesh wound	5 units (reciprocal of T/20)	Gr.	Gr.	Gr.	Gr.	Gr.	0
Patient with serious flesh wound	5 units (reciprocal of T/20)	Gr.	Tr.	0	0	0	0
Normal man	5 units (reciprocal of T/20)	Gr.	Gr.	Gr.	0	0	0

Tr. = trace ; Gr. = growth.

[1] Here, as elsewhere, the antitryptic power was measured by finding out what dilution of trypsin was neutralised by an equal volume of serum. By dividing in each case the figure representing this dilution into 100 we obtain the reciprocals, figures which provide a very convenient expression for the results of antitryptic measurement.

(*d*) *Experiments showing that the Growth of the Bacillus of Welch in the Blood-fluids is promoted by the Addition of Acid.*

When one notes that the bacillus of Welch when growing freely in serum turns it acid ; and when we then reflect upon the fact that all serum cultures of the microbe, whether *in vitro* or in the living body, begin with difficulty, and then, after reaching a certain critical point, progress at the rate of an avalanche, one inevitably, as in regard to the reduction of the antitryptic power of the serum, asks oneself whether the characteristic avalanche-like acceleration of growth may not be a direct result of this particular change in the medium.

The answer is given in the following experiments.

Experiment 12

Seven unit volumes of serum were neutralised by the addition of 2 unit volumes of a N/10 sulphuric acid—the control sample of serum being diluted to the same extent with physiological saline solution. This done, the antitryptic power of the two samples of serum was measured. It worked out in each case as 3 (approximately) —i.e. a unit volume of each of the sera neutralised a 40-fold and failed to neutralise a 30-fold dilution of the trypsin. These preliminaries completed, the resistance of the two sera to infection by the bacillus of Welch was investigated by aspirating into a capillary pipette a unit volume of a thick bacterial suspension, and following

up in each case (I call this the Wash and After-wash method) by a series of unit volumes of serum. These successive after-washes were divided off by bubbles of coal-gas introduced by the Gas-lock method. The results after 24-hours' culture were as shown in the following table.

—	Cultural results						
	After-wash						
	1st	2nd	3rd	4th	5th	6th	7th
Neutralised serum - - - - -	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.
Correspondingly diluted unneutralised serum	0	0	0	0	0	0	0

Experiment 13

As in the last experiment 7 unit volumes of serum were mixed in the one case with 2 unit volumes of N/10 sulphuric acid, and in the other with 2 unit volumes of physiological salt solution. Graduated dilutions of a suspension of Welch's bacillus were then made upon slides by the wash volume (W/V) method—i.e. in the first case a unit wash of bacterial suspension was implanted into a volume of serum ; and then in each case a wash of implanted serum was carried over into the next unit volume of serum. An unmeasured sample of the whole series of dilutions was then drawn up into the stem of a capillary pipette, the successive volumes being separated by bubbles of coal-gas. The experiment was in the case of each serum carried out in duplicate. The cultural results were as follows.

	Cultural results						
	Dilution :						
	2	4	8	16	32	64	128
Neutralised serum :							
Pipette No. 1 - - - -	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.
,, No. 2 - - - -	Gr.	Gr.	Gr.	0	0	0	0
Control serum :							
Pipette No. 1 - - - -	Tr.	0	0	0	0	0	0
,, No. 2 - - - -	0	0	0	0	0	0	0

Experiment 14

Normal serum was neutralised by the addition of N/10 sulphuric acid and then mixed with one-ninth of its bulk of a five-fold dilution of trypsin. The control sample of serum was diluted to the same extent with 0·85 per cent. NaCl solution. Both specimens were then implanted with a suspension of the bacillus of Welch by the wash and after-wash method.

Tr. = trace ; Gr. = growth.

—	Cultural results							
	After-wash							
	1st	2nd	3rd	4th	5th	6th	7th	8th
Neutralised and trypsinised serum	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.	Gr.
Control serum - - - -	Gr.	0	0	0	0	0	0	0

Experiment 15

This experiment given in tabular form below is self-explanatory.

Serum implanted with 3 washes of bacterial suspension - - -	No growth
,, ,, ,, 2 ,, ,, ,, - -	,, ,,
,, ,, ,, 1 wash ,, ,, - -	,, ,,
Serum neutralised (by adding 2 volumes of N/10 sulphuric acid to 7 volumes of serum) and implanted with 1/5th wash of bacterial suspension	Copious growth
Serum acidified (by adding 3 volumes of N/10 sulphuric acid to 7 volumes of serum) and implanted with 1/5th wash of bacterial suspension	Copious growth

This series of experiments make it, as it seems to me, quite indubitable that additions of acid convert the serum into an eminently favourable medium for the bacillus of Welch, and it is clear from the data set forth in connexion with Experiments 12 and 13 that this effect is obtained quite apart from any reduction of the antitryptic power. We have seen that the converse of this last also holds true, the reduction of antitryptic power, quite apart from any addition of acid, converts the serum into a very favourable culture-medium for micro-organism. And I think there can be no question that when these two factors co-operate we have a combination which adequately accounts for the 'avalanche phenomenon' (if I may so call it) which is the outstanding feature in the biology of the bacillus of Welch both when it grows in the blood-fluids *in vitro*, when it grows in the dead body, and when in the living body it invades the tissues, giving rise to spreading 'gas gangrene'.

We have next to study the growth of the bacillus of Welch in the dead body.

III. Conditions which govern the Growth of the Bacillus of Welch in the Dead Body.

Already in Welch's very first publication upon the *Bacillus aerogenes capsulatus* —the microbe which now bears his name—it is put upon record that if a small volume of culture is introduced into the blood-stream of a rabbit, and the animal is then killed and put into the incubator, the whole organism will be rapidly invaded, gas being generated in the blood, the condition known as 'foaming liver' being produced, and the peritoneal cavity being, after six or more hours, blown out with gas. As soon as we set ourselves to think out what all this imports, we see that it

must mean that the chemical changes occurring in the blood and liver after death transform the blood-fluids into an eminently favourable medium for the cultivation of the bacillus of Welch.

The following experiments show that this surmise is quite correct.

Experiment 16

Rabbit No. 1.—The animal, injected intravenously with 3 c.c. of a broth culture of the bacillus of Welch, was killed five minutes after, and was then placed in the incubator. A sample of blood was taken before and a series of samples after injection. In each case film preparations were made and examined, and measurements of the antitryptic power and of the blood alkalinity were undertaken. These are recorded in tabular form below. In regard to the film preparations, it will suffice to say that no microbes were microscopically discoverable in any but the last specimen ; here they were numerous. After six hours the animal was blown up with gas and the liver was foaming.

Times when the samples of blood were collected	Measurements of antitryptic power and chemical reaction of the serum	
	Antitryptic power	Chemical reaction [1]
	Units	
Immediately before injection - - -	3	Alkaline, N/40
5 min. after injection - - - -	2	—
10 ,, ,, ,, (heart blood) - -	1·6	Alkaline, N/50
3 hrs. ,, ,, ,, ,, - -	1·6	,, N/60
6 ,, ,, ,, ,, ,, - -	—	Acid

[1] Here and elsewhere in this paper the alkalinity of the blood was measured by the method described in the author's *Technique of the Teat and the Capillary Glass Tube.*

We have here evidence that, presumably as a result of a destruction of leucocytes, the antitryptic power of the blood is progressively reduced, and that, no doubt as a consequence of lactic acid production in the muscles, the blood-fluids lose their alkalinity and finally become acid. One can hardly doubt that it is these changes which help forward the growth of Welch's bacillus in the dead rabbit.

That the anaerobic conditions do not play here any significant rôle will appear in connexion with Experiments 19 and 20.

Experiment 17

Rabbit No. 2.—The animal was injected intravenously with 1 c.c. of an aerobically grown potato-broth culture, and was killed immediately after. As in the last case, film preparations of the blood were examined and measurements of the antitryptic power and alkalinity carried out. In films made $3\frac{1}{2}$ hours after death hardly any microbes could be detected. In preparations made $4\frac{3}{4}$ hours after death they numbered 6–8 to the microscopic field. At the end of six hours the animal was

blown up with gas, and the liver was honeycombed with small cavities containing a foaming and tryptic fluid.

Times when the samples of blood were collected	Measurements of anti-tryptic power and chemical reaction of the serum	
	Anti-tryptic power	Chemical reaction
	Units	
Immediately before injection - - -	4·5	—
15 min. after injection (heart blood) - -	5·5	Alkaline, N/35
3½ hrs. ,, ,, ,, ,, - -	4·5	,, N·80
4¾ ,, ,, ,, ,, ,, - -	3·6	—
6 ,, ,, ,, ,, ,, - -	2·2	Acid

Experiment 18

Rabbit 3.—This received intravenously 1 c.c. of a culture of the bacillus of Welch grown aerobically in potato broth, and the animal was killed 15 minutes after the injection and placed in the incubator. Samples of blood were taken and examined as in the previous experiments. A single microbe was found in the blood film made 2 hours after death. The liver 7 hours after death was torn to pieces by gas and looked, except for the fact that its colour was a dark brown-red, like a mass of coral as obtained from the swimmerets of a hen-lobster; films prepared from it showed an almost solid mass of microbes. The results of the measurements of anti-tryptic power and blood reaction are subjoined.

Times when the samples of blood were collected	Measurements of anti-tryptic power and chemical reaction of the serum	
	Anti-tryptic power	Chemical reaction
	Units	
Immediately before injection - - -	3	Alkaline, N/30
15 min. after injection - - - -	3	,, N/30
2 hrs. ,, ,, (heart blood) - -	1·8[1]	Acid
4 ,, ,, ,, ,, ,, - -	1·6[1]	Acid

[1] Measured after serum had been neutralised with washes of N/10 NaOH.

Experiment 19

Rabbit 4.—A sample of blood was taken from this animal, and it was then, without receiving any injection, killed and placed in the incubator. The second samples of blood were taken 3 hours after death respectively from the S.V.C. and from the I.V.C. and hepatic vein. Sample 3 was taken from the heart 5 hours after death.

The results of the measurements of antitryptic power, blood reaction, and infection-resisting power are subjoined.

—	Antitryptic power	Chemical reaction
Serum, Sample 1 - - -	3 units	Alkaline, N/30
,, ,, 2 - - -	3 ,,	,, N/80
,, ,, 2B - - -	Tryptic [1]	Acid N/150
,, ,, 3 - - -	,, [1]	,, N/75

Infection-resisting (Phylactic) Power

—	Amount of culture implanted							
	Washes—							
	3	2	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$	$\frac{1}{32}$
Serum, Sample 1	0	0	0	0	0	0	0	0
,, ,, 2	–	–	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and Gas
,, ,, 2B	–	–	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and Gas

[1] Determined after serum had been neutralised by washes of N/10 NaOH.

Experiment 20

Here a sample of blood was taken from a cat and the animal was then immediately killed and placed in the incubator. Sample 2 was taken from the heart three hours after; Sample 3 six hours after. As in the last case, the antitryptic power,

—	Antitryptic power	Chemical reaction
Serum, Sample 1 - - -	4	Alkaline, N/50
,, ,, 2 - - -	4	,, N/150
,, ,, 3 - - -	4	Faintly acid

Infection-resisting (Phylactic) Power

—	Amount of culture which was implanted				
	Washes				
	3	2	1	$\frac{1}{2}$	$\frac{1}{4}$
Serum, Sample 1	0	0	0	0	0
,, ,, 2	Growth and gas	Growth and gas	Growth and gas	Growth and gas	Growth and gas
,, ,, 3	—	Growth and gas	Growth and gas	—	Growth and gas

the blood reaction, and infection-resisting power of these samples were measured. It will be seen that except for the fact that the antitryptic power is maintained unaltered the results are precisely the same as those obtained in the rabbit.

It is evident from the results set out here that the blood changes which convert the blood-fluids after death into an eminently favourable culture medium for the bacillus of Welch are chemical changes which occur spontaneously, and quite independently of the inoculation of the bacillus of Welch. Furthermore, when we consider the cultural results set out in the second of the two tables, bearing in view that the cultures were in each case made anaerobically, we recognise that the circumstance that the fact that anaerobic conditions such as these prevail in the dead body is a fact which can have nothing to do with the rapid pullulation of the microbe.

IV. Conditions which govern the Growth of the Bacillus of Welch in the Living Organism, in particular on the Blood Changes which supervene (a) when the Bacillus of Welch is inoculated into the Blood-stream or Subcutaneous Tissue, and (b) when the Microbe invades the Tissues from a Wound producing Gas Gangrene and the Characteristic Toxaemia which is associated with this.

Disposing my data in accordance with the scheme thus indicated I may set forth first, adding here and there brief comment, certain data furnished by blood examinations undertaken upon rabbits inoculated intravenously with cultures of the bacillus of Welch.

(a) *Experiments in which the Bacillus of Welch was Inoculated intravenously into Rabbits*

Experiment 21

Rabbit 5.—This was a companion rabbit to Rabbit 4 (Experiment 18), and it was inoculated intravenously with 1 c.c. of the same potato-broth culture as was there employed. A comparison of the figures given below with those given in connexion with Experiment 18 shows in the 19 hours after the injection profound differences between the living and the dead rabbit. For in the living here, the alkalinity of the blood remained practically unaffected and the antitryptic power sank away only very slowly. Thereupon, apparently quite suddenly the rabbit became collapsed and the circulation flagged so much that blood was unobtainable

Times when the samples of blood were collected	Measurements of antitryptic power and alkalinity	
	Antitryptic power	Alkalinity of blood
Immediately before injection	3·6	N/30
15 minutes after injection	2·2	—
4 hours ,, ,,	3·0	—
19 ,, ,, ,,	2·5	N/35
21 ,, ,, ,,	4·0	N/50
23½ ,, ,, ,, (1¼ hours after death)	1·6	N/180

from the ears (these were stone cold) and had to be drawn off from the femoral artery. Respiration was 80 to 100 in the minute, and the clinical picture corresponded to that of the classical 'acid rabbit' of Walther and Stadelmann—i.e. to the clinical picture seen when a rabbit is overdosed with hydrochloric acid.

Owing to the difficulty of procuring sufficient rabbits only two more experiments of this kind were made. Both of these, so far as the first hours of observation are concerned, confirmed the results of Experiment 21 ; but neither of them gave any evidence in corroboration of the view that death in infection by the bacillus of Welch is ushered in by an acidaemia. In view, however, of the circumstance that there was in each a formidable lacuna in the observations, the animal in each case dying unexpectedly in the night, the fact that evidence of the supervention of acidaemia is wanting must be discounted. The data relating to one of the two rabbits—a rabbit that was found dead in 18 hours after the intravenous injection of a small quantum of culture—are given below.

Experiment 22

Times when the samples of blood were collected	Measurements of antitryptic power and alkalinity	
	Antitryptic power	Alkalinity of blood
Immediately before injection	3·0	N/40
10 minutes after injection	2·6	N/40
30 ,, ,, ,,	2·0	N/40
2 hours ,, ,,	2·0	N/40
6 ,, ,, ,,	1·5	N/45

We pass now from the consideration of rapidly fatal intravenous inoculations to which there is no obvious immunising response, to study the effects of subcutaneous inoculations in the case of animals who for the most part respond and survive.

(*b*) *Experiments in which the Bacillus of Welch was Inoculated subcutaneously into Guinea-pigs and White Rats*

Here also observations were made upon the antitryptic power and the alkalinity of the serum from the circulating blood. In addition—for it was possible to do this until such time as the local effusion was either absorbed or broke through the skin and was lost—determinations were made also of the antitryptic power and alkalinity prevailing at the seat of the inoculation. In each case the results are set out in the form of charts. Upon these the unbroken line is the curve obtained from the circulating blood ; the interrupted line the curve from the oedema fluid. And in each case the scale is a scale of reciprocals—i.e. the figures are the quotients obtained by taking the dilution of the reagent which neutralised the effect of an equivalent volume of serum and dividing this into 1000.

Experiment 23

Guinea-pig No. 1.—The animal was inoculated subcutaneously in the leg with 0·1 c.c. of a 24-hour-old potato-broth culture aerobically grown. Beginning in the leg the effusion gradually spread over the whole of the belly, and finally after three days the skin broke down and the animal afterwards recovering and the wound healing over. The film preparations made from the effusion showed at first very numerous and afterwards only few bacilli. (See Chart I, G 1.)

Experiment 24

Guinea-pig No. 2.—The animal was inoculated subcutaneously with 0·3 c.c. of a 24-hour-old potato-broth culture aerobically grown. Local effusion was well

CHART I.

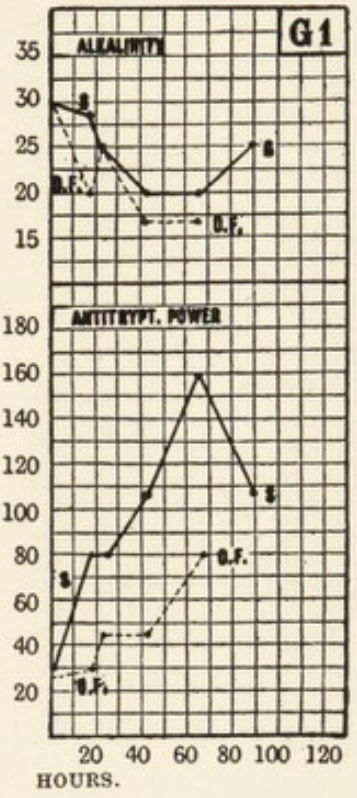
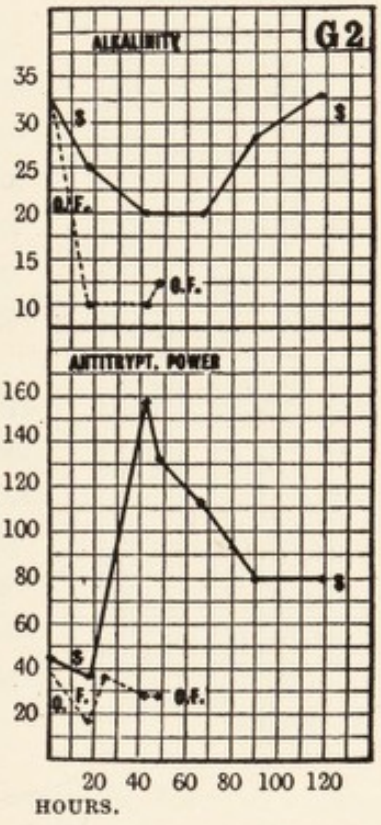


CHART II.



developed after 18 hours; it increased in quantity up to the 48 hours and then broke through upon the skin and leaked away, the wound afterwards healing up and the guinea-pig making a good recovery. (See Chart II, G 2.)

Experiment 25

Guinea-pig No. 3.—The animal was inoculated subcutaneously with 0·3 c.c. of a 24-hour-old potato-broth culture aerobically grown. Local effusion was well developed after 21 hours. After 27 hours the subcutaneous tissue, as soon as it became flaccid through withdrawal of fluid, filled up rapidly with gas, and the animal died 33 hours after the injection. See Chart III, G 3.)

Experiment 26

White rat No. 1.—The animal was inoculated subcutaneously with 0·7 c.c. of a 24-hour-old potato-broth culture aerobically grown. Local effusion was well developed 16 hours after, and from the second day onwards the lesion became indurated and the oedema gradually disappeared, the animal making a perfect recovery. (See Chart IV, R 1.)

Experiment 27

White rat No. 2.—The animal was inoculated subcutaneously with 0·6 c.c. of a 24-hour-old potato-broth culture. The local lesion ran the same course as in the first rat, and the animal, after being very ill for two days, made a perfect recovery. (See Chart V, R 2.)

CHART III.

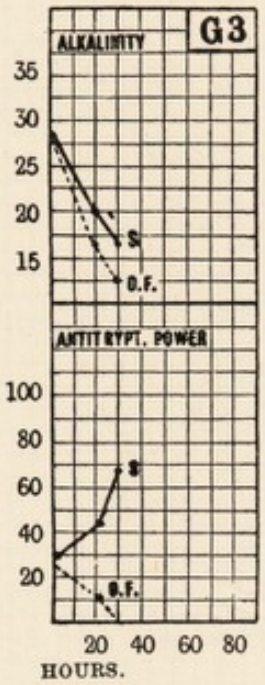
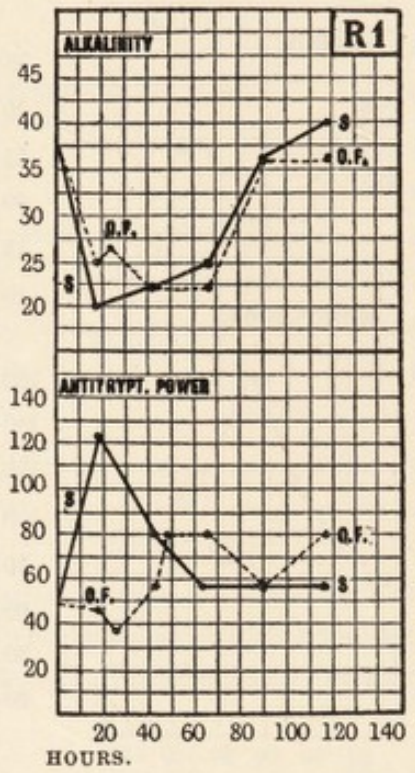


CHART IV.



Experiment 28

White rat No. 3.—The animal was inoculated subcutaneously with 0·6 c.c. of a 24-hour-old potato-broth culture. There was less effusion than in the case of the first two rats, and by the second day it had been completely absorbed. The animal was never really ill. (See Chart VI, R 3.)

It is brought out very clearly in these charts that infection by the bacillus of Welch produces as a rule both a local and a general acidosis, and it will be seen—and, of course, this was to be expected *a priori*—that we have always a more pronounced acidosis in the local lesion than in the general blood-stream. Where, as in Chart III, the acidaemia becomes very pronounced the animal succumbs. And where, as in Chart VI, there is no acidaemia the animal is never seriously ill. Turn-

ing to the antitryptic power, we see that in all cases without exception—and when we turn back we can see indications of this also in the rabbit experiments (*vide* Experiments 21 and 22)—the curve which represents the antitryptic power of the blood rises. It rises very steeply where, as in Chart VI, the animal deals triumphantly with its infection; and it rises only very little where, as in Chart III, the animal puts up only a very feeble fight.

It also holds true of the curve of the antitryptic power of the oedema fluid in Charts I, II, IV and V that as the animal begins to recover it rises, following the curve of the blood, and we see in Chart III that the oedema fluid may become tryptic in the case where the animal fails to stand up against the infection.

CHART V.

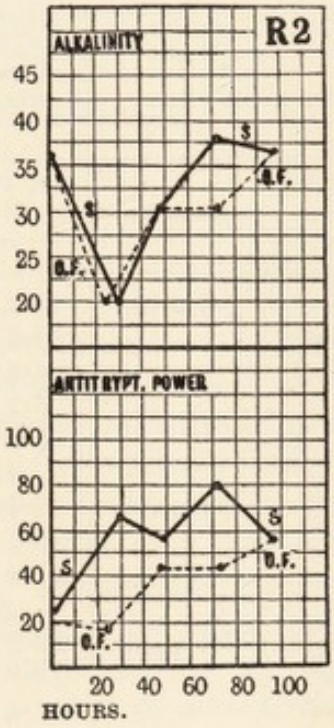
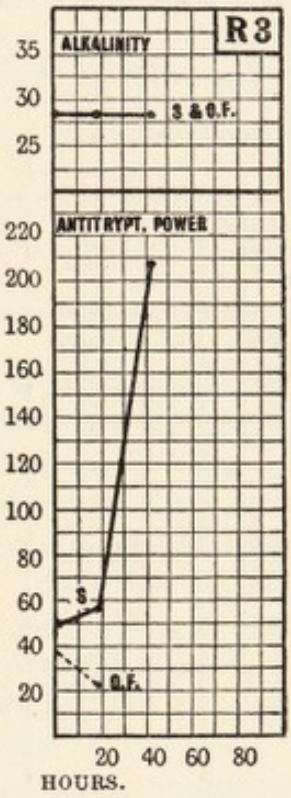


CHART VI.



(c) Observations made on Man

We have now by experiments conducted *in vitro*, and in the dead, and living animals, collected sufficient data to enable us to construe aright such observations as it may be practicable to make upon men suffering from wounds infected by the bacillus of Welch, or from that spreading tissue infection which is spoken of as 'gas gangrene', or again from that sharply characterised toxaemic condition which is the ultimate outcome of that infection.

A commencement may be made by setting out in tabular form the results of a series of antitryptic measurements made by me on three consecutive days in a casualty clearing station. These results relate to men all recently admitted to hospital with severe and highly infected wounds—cases of manifest 'gas gangrene' being here specially excluded. I may further explain that many of the men who

were examined on the first day were examined also on the second, and similarly many of the cases examined on the second were re-examined on the third day. (See Table I.)

It is brought into clear view by the summary that—and I have already on previous occasions emphasised this point—every microbic infection of wounds (and the same probably holds on all microbic infections and inoculations of vaccine) is followed by a rise in the antitryptic power constituting a non-specific immunising response—that response being greater or less in accordance with the degree of the severity of the infection. Moreover, consideration of the figures for the successive

TABLE I.—*Measurements of the Antitryptic Power of the Blood of Normal Men, Slightly Wounded Men, and Heavily Wounded Men, excluding those affected with 'Gas Gangrene'.*

—	Normal men		Slightly wounded men		Heavily wounded men, excluding cases of gas gangrene	
Date	A.T.P. of the individual men	Average	A.T.P. of the individual men	Average	A.T.P. of the individual men	Average
5 : 1 : 16 -	4·4 4·4	4·4 units	5·7 3·6 4·4 4·4 11·4 4·4 4·4	5·5 units	11·4 8·0 11·4 8·0 4·4 11·4 5·7 6·6 5·0 8·0 13·3	8·5 units
6 : 1 : 16 -	5·7 4·4	5·0 units	5·7 5·7 5·7 5·7 5·7	5·4 units	11·4 10·0 16·0 16·0 11·4 5·7 5·7	10·9 units
7 : 1 : 16 -	4·4 5·0	4·7 units	8·8 4·4 4·4 5·7 5·7 8·0	6·3 units	22·2 11·4 18·1 18·1 11·4 13·3 18·1	16·1 units
Summary - - -		4·7 units	—	5·8 units	—	11·3 units
Antitryptic index -		1		1·23		2·4

days indicates that as the septic condition develops the antitryptic power gradually increases. I next take from Table I the figures relating to the antitryptic power in heavily infected patients not affected with 'gas gangrene'; and supplement these with data furnished by measurements of their blood alkalinity; and then contrast these with data furnished by measurements of antitryptic power and blood alkalinity carried out on 'gas gangrene' patients, adding also for comparison figures which apply to normal men.

These data are set out in Table II.

TABLE II.—*Summary of Measurements of Antitryptic Power and Blood Alkalinity made upon Heavily Infected Patients not suffering from and Patients suffering from 'Gas Gangrene'.*

	Antitryptic power	Blood alkalinity
Heavily infected patients exclusive of cases of spreading gas gangrene bacillus infection :		
Number of patients tested in each way - -	25	10
Range of variation within the group - - -	5·7–22·2 units (*vide* Table I)	N/30–N/35
Average for the group - - - - - -	11·3 units	N/31·5
Patients suffering from spreading gas gangrene bacillus infection and intoxication :		
Number of patients tested in each way - -	14 [1]	15 [1]
Range of variation within the group - - -	5–22 units (*vide* Table III)	N/40–N/80
Average for the group - - - - - -	11·2 units	N/55
Normal men - - - - - - - - - -	4·7	N/30–N/35

[1] The majority of these patients are those included in Table III.

Scrutiny of this table reveals that there is with regard to antitryptic power absolutely no difference between heavily infected patients not suffering from 'gas gangrene' and patients suffering from that infection. When, however, we turn to the column headed 'Blood alkalinity', we see that the blood alkalinity of the heavily infected patient who is not suffering from gas gangrene corresponds exactly with the normal; while the 'gas gangrene' patient's blood alkalinity is very markedly reduced. In other words, the figures here brought together bring out the fact that the toxaemia of gas gangrene is an acidaemia.

In Table III, concentrating here upon cases of 'gas gangrene', I go more into detail and set out a series of measurements of the antitryptic power and alkalinity of the circulating blood in 'gas gangrene' and also measurements of the antitryptic power and alkalinity of lymph obtained from the infected tissues. At the end of the table I add, for purposes of comparison, the details of the examinations made in two cases which might—though, in point of fact, the error was in neither case committed—have been regarded as 'gas gangrene' cases. I further include in the table six observations bearing on the treatment of gas gangrene acidaemia by the intravenous administration of alkalies.

Data furnished by Measurements of the Antitryptic Power and Alkalinity of the Circulating Blood and of the Lymph from the Infected Tissues in Cases of 'Gas Gangrene'.

Consideration of the data which are set out in Table III makes, as I think, quite clear that we are, in the so-called 'gas gangrene infection' of man, dealing with essentially the same phenomena as in our laboratory experiments. We saw in

in vitro cultures in serum that the bacillus of Welch diminishes the antitryptic power of the medium and renders it acid ; and we saw that the serum is by these means converted into a pre-eminently favourable medium for the growth of the bacillus. In experiments on the blood in the dead body we saw that it is these chemical changes which furnish the conditions required for the avalanche-like inroad of the bacterial infection. And, finally, experiments upon living animals showed that we have in infections by the bacillus of Welch, *with respect to alkalinity*, a reduction in the fluids taken from the focus of infection, and also a reduction in the circulating blood ; and, *with respect to antitryptic power*, in the circulating blood, a marked immunising response, while we have in the infected tissues a diminished or abolished antitryptic power, especially where the animal is only unsuccessfully combating or succumbing to the infection.

Every one of these points obtrudes itself again upon our notice in the records dealing with human 'gas gangrene' which are brought together in Tables II and III. We have there, to begin with, the high antitryptic response in the circulating

TABLE III

Serial number	Brief outline of the case	Data with regard to the antitryptic power and alkalinity of the blood	Data with regard to the antitryptic power and alkalinity of the lymph in the infected tissues
1	Spreading gangrene bacillus invasion in subcutaneous tissue of arm, with coppery discoloration and crepitation. Amputation of arm.	*A.T.P.*, 8 units.	Oedema fluid from tissues close to the wound : *Tryptic.* Oedema fluid from spreading edge: *A.T.P.*, 2·2.
2	Clinical features as in Case 1.	*A.T.P.*, 6·6 units.	Oedema fluid from tissues above the wound : *A.T.P.*, 1·6.
3	Multiple shrapnel wounds of leg with spreading gangrene bacillus infection in subcutaneous tissue. Acute toxaemia, with rapid respiration, impalpable pulse, and cold creeping upwards from extremities. Intravenous injection of 16 grammes of $NaHCO_3$. Death 12 hours after onset of toxaemic symptoms.	Before intravenous injection : *Alkalinity*, N/80 ; *A.T.P.*, 6·6 units. 10 minutes after injection : *Alkalinity*, N/50 ; *A.T.P.*, 6·6 units.	—
4	Extensive wound of thigh. Spreading gangrene bacillus infection involving knee and spreading in subcutaneous tissue of the thigh with crepitation. Amputation of thigh. Death 48 hours after operation.	*A.T.P.*, 11·4 units. *Alkalinity*, N/50.	Fluid from knee : *A.T.P.*, 2 units ; *Alkalinity*, N/50. Fluid from subcutaneous tissue : *A.T.P.*, 3·3 units ; *Alkalinity*, N/40.

TABLE III—(*Continued*)

Serial Number	Brief outline of the case	Data with regard to the antitryptic power and alkalinity of the blood	Data with regard to the antitryptic power and alkalinity of the lymph in the infected tissues
5	Compound fracture of thigh with extensive flesh wound. Rapidly spreading gangrene bacillus infection of tissues. Acute toxaemia. Icteric serum [1]; culture of the bacillus of Welch from blood 4½ hours; intravenous injection of 8 grammes of $NaHCO_3$ 8 hours; and death 14 hours after onset of toxaemic symptoms.	Before intravenous injection: *A.T.P.*, 5 units; *Alkalinity*, N/50. 5 minutes after injection: *A.T.P.*, 5 units; *Alkalinity*, N/50. 6 hours after injection: *A.T.P.*, 5 units; *Alkalinity*, N/50.	—
6	Compound fracture of ankle. Acute toxaemia with collapse, precluding operation. Injection of 20 grammes of lactate of soda. Condition rapidly improved and amputation carried out. In evening patient was sitting up, next morning general condition very satisfactory, and patient made a good recovery.	Before injection: *Alkalinity*, N/50. Immediately after: *Alkalinity*, N/50. 7 hours after: *Alkalinity*, N/50. Next morning: *Alkalinity*, N/40.	—
7	Extensive wound in upper third of arm. Gangrene with dark livid discoloration and haemorrhagic blisters, with purple mottling extending over the shoulder. Profound toxaemia; 10 grammes of $NaHCO_3$ intravenously. Disarticulation at shoulder. Next morning general condition satisfactory and patient made a good recovery.	At time of operation: *Alkalinity*, N/70. 6 hours after: *Alkalinity*, N/60. Next day: *Alkalinity*, N/40.	Oedema fluid from upper arm: *Alkalinity*, N/200. Oedema fluid from lower arm: *Alkalinity*, N/60.
8	Very numerous shrapnel wounds of both legs. Gangrene bacillus infection spreading out from these in the form of infiltrated copper-coloured patches.	*A.T.P.*. 20 units; *Alkalinity*, N/50.	Oedema fluid from infiltrated copper-coloured patches: *A.T.P.*, 6·6 units; *Alkalinity*, N/60.
9	Gangrene of leg spreading upwards. Amputation at middle of thigh.	*A.T.P.*, 8 units.	*A.T.P.* of oedema fluid from spreading edge, 2·9 units.
10	Massive gangrene infection of all muscles of anterior aspect of thigh.	*Alkalinity*, N/60.	Clear fluid from wound: *Alkalinity*, N/60.

[1] The special features of the blood in gas-gangrene toxaemia are that the serum is of a characteristic deep yellow colour, there being also, as in most cases of serious bacterial intoxication, a very heavy buffy coat.

TABLE III—(*Continued*)

Serial Number	Brief outline of the case	Data with regard to the antitryptic power and alkalinity of the blood	Data with regard to the antitryptic power and alkalinity of the lymph in the infected tissues
11	Haemothorax infected with Welch's bacillus and containing many W.B.C. Icteric serum.	*A.T.P.*, 13·3 units ; *Alkalinity*, N/50.	Pleural effusion : *A.T.P.*, 6·6 units ; *Alkalinity*, N/100.
12	Haemothorax film preparations show 20 or more *B. Welch* in each microscopic field. No indications of growth in effusion when cultured, and growth on artificial media only when very large quanta are implanted.	*A.T.P.*, 22 units ; *Alkalinity*, N/40.	*A.T.P.*, 8 units ; *Alkalinity*, N/100.
13	Patient admitted with an enormous wound in groin and in a condition of collapse. Recovered sufficiently to allow of incomplete operation. 24 hours later vomiting and very feeble, rapid pulse. Intravenous injection of 20 grammes $NaHCO_3$. Next day some improvement. Day after patient succumbed.	*Alkalinity*, N/40 of blood collected *circ.* 18 hours after operation.	—
14	Amputation after 4 days in hospital of thigh for gas gangrene starting from wound of leg and knee. 24 hours after patient was still very weak. 40 hours after operation 10 grammes of $NaHCO_3$ intravenously. Patient succumbed 24 hours later.	Blood taken at time of operation : *A.T.P.*, 16 units ; *Alkalinity*, N/60. Blood taken 24 hours after operation : *A.T.P.*, 20 units : *Alkalinity*, N/60. Blood taken immediately before injection: *A.T.P.*, 20 units ; *Alkalinity*, N/50. Blood taken immediately after injection : *A.T.P.*, 23 units ; *Alkalinity*, N/40.	Fluid from oedematous subcutaneous tissue just above level of amputation : *A.T.P.*, 13·3 units ; *Alkalinity*, N/80.
15	Amputation stump of upper part of thigh with gas infection of the sloughing surface. An axial incision carried up from this upon ilium. Oedema fluid neutralised by lactic acid gives anaerobically in 4 hours a foaming culture of *B. Welch*. Unneutralised it gives anaerobically a scanty growth in 18 hours. Heart blood obtained 24 hours later at P.M. gives a pure culture of streptococcus.	*A.T.P.*, 16 units ; *Alkalinity*, N/35.	Oedema fluid intermixed with blood from incised tissue : *A.T.P.*, 16 units ; *Alkalinity*, N/35.
16	Perforating wound immediately below the knee. Limb cold and oedematous. Amputation with view to possibility of gas gangrene infection.	*A.T.P.*, 8 units ; *Alkalinity*, N/35.	*A.T.P.*, 4·4 units ; *Alkalinity*, N/35.

blood and the reduced or abolished antitryptic power in the infected tissues or infected effusions. We have, in addition, diminished alkalinity in the infected tissues or infected effusions. And we have not only a local acidosis, but we have also an acidaemia. We find that acidaemia where the infection has culminated in that 'gas gangrene toxaemia' which is ushered in by vomiting and then shows itself in collapse, with rapid respiration, ashy-grey pallor, feeble and then impalpable pulse, the body becoming stone-cold before death, first the hands and feet, then the whole limbs, finally the nose, ears, and forehead, the patient remaining with clear intellect and without suffering to the last.

It may perhaps, pending further investigation, be assumed with respect to this acidaemic condition that the acid production proceeds not only in the infected tissues standing in relation with the wound, but also in the liver and other internal organs to which the bacillus of Welch may have been conveyed—metastatic growth being favoured as soon as the alkalinity of the blood begins to be reduced by the influx of lymph charged with acid in the infected tissues.

Considerations of this kind should be present to our minds when we turn to take stock of the results of the therapeutic administration of alkalies in 'gas gangrene'. As shown by the records, this procedure gave markedly favourable results only in two cases out of the six. In those two cases, however, the effect was dramatic. Probably in the other cases, as is the case in the acidaemia of diabetes and uraemia, the evolution of acid must have gone on unaffected.

It must be left for future experimentation to determine whether better results can be obtained by earlier intravenous injection of alkali, and whether the local evolution of gas gangrene could be arrested by the injection into the tissues or, as the case may be, into an infected haemothorax of alkali or of an *alkalinised* strongly antitryptic serum, remembering here that a strongly antitryptic serum can practically always be obtained either from the patient himself or from any other heavily infected patient.

In concluding, I have to express my acknowledgments to my colleague Major Georges Dreyer for generous assistance in plotting out the curves and in some of the experiments; to my fellow-worker the late Captain H. H. Tanner for similar assistance. My thanks are also due to Captain Haycraft for help in connexion with the study of cases of gas gangrene, and to my fellow-worker Dr. Alexander Fleming for permission to incorporate in this lecture some of the results of his research work.

FURTHER OBSERVATIONS ON ACIDAEMIA IN GAS GANGRENE AND ON THE CONDITIONS WHICH FAVOUR THE GROWTH OF ITS INFECTIVE AGENT IN THE BLOOD-FLUIDS [1]

BY ALMROTH E. WRIGHT AND ALEXANDER FLEMING

In connexion with gas gangrene one of us has already shown [2] the following: (1) The bacillus of Welch when cultivated in serum renders that medium acid; (2) The normal blood-fluids by virtue of their alkalinity and antitryptic power antagonise the growth of the bacillus; (3) The blood-fluids become a very favourable culture medium for the organism when we blunt off their alkalinity by acid, or their antitryptic power by trypsin, and more conspicuously when we do both; (4) The septicaemic gas infection which develops in an animal killed and incubated after intravenous inoculation with the microbe is associated with the development of the post-mortem acidosis; (5) In the living animal the evolution of gas gangrene marches hand-in-hand with a local and general acidosis; (6) In man the characteristic toxaemia of gas gangrene is correlated with the supervention of a very severe acidosis; and (7) An immediate improvement in the clinical condition of the patient is obtained by the intravenous injection of alkali.

We have made further observations along these lines.

Further Data showing that we have in Gas-gangrene Intoxication an Acidaemia.

We may begin with data relating to acid intoxication in the gas-gangrene patient. Blood-alkalinity examinations were made by us working independently by different methods: one of us (W.) titrating directly in capillary pipettes with dilutions of standard acid; [3] the other (F.) employing the method of Marriott. The former procedure determines only the reaction of the serum—i.e. the amount of base unoccupied by fixed acid. And the alkaline reaction of the serum stands in the normal man, the reader will remember, absolutely fast at N/35. Marriott's method [4] determines, in terms of hydrogen ion content, not only the reaction (pH) of the blood, but also the amount of the alkali (RpH) which is masked by CO_2. In the scale of notation this method employs (we here abbreviate from Marriott): 'a reaction of 7·0 is the expression for neutrality. Figures less than this represent varying degrees of acidity; figures greater corresponding degrees of alkalinity. The reaction of the normal blood before the carbonic acid is expelled (pH) is approximately 7·5; and after that (RpH) about 8·5.' We have ourselves never obtained for RpH any value higher than 8·3.

[1] Reprinted from the *Lancet*, 9th February, 1918. [2] Wright, *The Lancet*, 6th Jan., 1917.

[3] Wright, *Technique of the Teat and Capillary Glass Tube* (Constable, London).

[4] Marriott, *Archives of Internal Medicine*, June, 1916, Part I, vol. xvii.

It appears clearly in the table which occupies pp. 74–76 that the direct titration and Marriott methods both furnish evidence that we have in the toxaemia of gas gangrene a very pronounced acid intoxication. The table further shows that there is, on the whole, very close agreement between these two methods of measuring acidosis. Where the one method shows an increase or diminution of alkalinity, practically always the other also shows it. At the same time we may be allowed to remark that the longer range and unequal subdivisions of the scale of notation employed in the direct titration have over the shorter range and uniform divisions of the Marriott scale the advantage of compelling attention to those quite small progressive increments of acid which are in the later stages of auto-intoxication of fatal import for the patient. The reader will appreciate this on looking through the Table.

He will, for example, realise in connexion with Case 4 that the Marriott readings pH 7·3, RpH 7·6, (as against 7·5 and 8·3 for the normal) are not as intellectually arresting as the readings N/70 (as against N/35 for the normal) which are furnished by direct titration.

We may here, postponing for a little the discussion of the symptomatology and treatment of the acidaemia, investigate further the question of acid production in the blood, and the effect of blunting off its alkalinity upon the growth of gas-gangrene microbes, extending our observations to the gangrene bacilli of secondary rank—i.e. to the *Vibrion septique* and the *Bacillus oedematiens*, *Bac. fallax*, and *Bac. aerofoetidus* of *Weinberg*—microbes which are all occasionally found in gas gangrene.

Question as to whether the Gas-gangrene Bacilli of Secondary Rank resemble the Bacillus of Welch in producing Acid in Serum and growing more freely in Serum of Diminished Alkalinity.

With regard to the elaboration of acid by these microbes it will suffice to say : that with the possible exception of *Bac. fallax* they one and all, when they grow freely, make the serum acid. The influence of the blunting off of the alkalinity upon their growth in serum is brought out in the subjoined experiment.

Experiment

Four portions of serum were implanted in bulk with the four microbes here in question. Ten subvolumes of each implanted serum were then taken, and to each was added one-tenth of a graduated dilution of normal sulphuric acid, the control portion of implanted serum being diluted to an equivalent extent with normal saline solution. The separate portions were then filled into narrow tubes, shut off from the air by a layer of melted vaseline, and incubated. The amount of gas evolved was taken as the measure of growth, and the figures in the table are measurements in millimetres of the distance to which the plugs of vaseline were driven up by gas given off from the cultures.

Having seen that these gas-gangrene microbes of inferior rank behave in the same way as the bacillus of Welch in the respect that they grow with difficulty in normal serum and grow better and better as the serum alkalinity is blunted off, we

pass to inquire whether the gas septicaemia and 'foam-liver' *in mortuo* and the acid intoxication *in vivo* are also obtained with these microbes.

Reaction of the serum	*B. fallax*				*B. aerofoetidus*				*B. oedematiens*		*Vibrion septique*		
	Age of culture				Age of culture				Age of culture		Age of culture		
	36 hrs.	48 hrs.	65 hrs.	4 days	36 hrs.	48 hrs.	65 hrs.	4 days	40 hrs.	60 hrs.	15 hrs.	24 hrs.	40 hrs.
Acid N/37 -	0	0	0	0	0	0	0	0	0	0	0	0	0
,, N/120	2	3	3	5	2	4	5	8	3	4	L.B.	4	4
Neutral -	0	2	3	5	0	0	0	0	2	3	0	4	14
Alkaline :													
N/160 -	0	2	3	5	0	0	0	0	L.B.	2	0	5	14
N/100 -	0	0	1½	3	0	0	0	0	L.B.	2	0	5	12
N/65 -	0	0	1½	3	0	0	0	0	L.B.	2	0	5	12
N/57 -	0	0	L.B.	L.B.	0	0	0	0	0	L.B.	0	5	12
N/47 -	0	0	0	L.B.	0	0	0	0	0	L.B.	0	6	11
N/42·5 -	0	0	0	L.B.	0	0	0	0	–	–	–	–	–
N/35 [1] -	0	0	0	0	0	0	0	0	0	0	0	L.B.	4

[1] Control without acid addition. L.B. = Large bubble.

Experiment shows that we can with each of the microbes here in question reproduce, though perhaps in a less conspicuous form, the post-mortem appearances obtained with Welch's bacillus. As with that microbe, experiments on living animals do not give anything like as clear results as experiments on the dead: *first*, because a large proportion of the animals are resistant to our inoculations; and, further, because those that succumb, succumb very often without any warning, so that there is no opportunity for blood observations at the period when the acidaemia is to be expected. In the following experiment, however—and it is the only one in which the conditions were propitious for observation—the question of the production of an acidaemia is, so far as the *Vibrion septique* is concerned, resolved. And we surmise that, given a sufficient supply of animals, the question would be resolved in the same sense also in connexion with the three other microbes—for these are, of course, morphologically much more closely allied to our type microbe—the bacillus of Welch.

Experiment

Rabbit.—After taking a sample of blood from the ear the animal was inoculated in the leg with a culture of the *Vibrion septique*. Fifteen hours after the leg was found swollen. Eighteen hours after the animal appeared ill and was breathing very rapidly and deeply. Twenty hours afterwards 5 c.cm. of blood were taken from the heart and the *Vibrion septique* was obtained from this by culture. Twenty-two hours afterwards the animal was lying comatose, and it was then killed after withdrawing a further sample of blood from the heart.

Measurements of Alkalinity made by the 'Direct Titration' and the Marriott Method

Time when blood specimen was taken	Direct titration	Marriott method	
		pH	RpH
At outset - - - - -	N/35	7·5	8·2
18 hours after - - - -	—	7·45	7·9
20 hours after - - - -	N/50	7·4	7·9
At death, 22 hours after - -	N/100	7·3	7·6

Further Experiments showing that the Growth of the Bacillus of Welch is favoured when the Alkalinity of the Serum is reduced.

We now revert to the acidaemia produced by Welch's bacillus. We show, in Exp. 1 below, the extent to which the growth of the microbe is favoured in the blood-fluids of the gas-gangrene patient drawn off in the stage of extreme acidosis; in Exp. 2 the effect of graduated additions of sulphuric acid on the growth of the microbe in normal serum; and, in Exp. 3, the effect of adding to the serum CO_2 to saturation.

Experiment 1

Here we took (*a*) the serum from a moribund gas-gangrene patient; and (*b*) a normal serum. The gas-gangrene serum was the last sample from Case No. 3 (Table I.) Its *alkalinity* corresponded to N/150, and its *antitryptic power* was *eight times normal*.

In each case a series of equal volumes of serum were filled into narrow tubes. Each of these volumes was then implanted with one-tenth of progressive dilutions of a gangrene bacillus serum culture diluted down with normal serum. Melted vaseline was then poured on to the top of the serum. As before the amount of gas formed was taken as the measure of growth, and the figures in the table give the height of the gas column.

Dilutions of the gas-gangrene culture implanted	Serum from Gas-gangrene patient		Normal serum	
	Number of hours of culture when column of gas was measured		Number of hours of culture when column of gas was measured	
	18 hours	24 hours	18 hours	24 hours
Undiluted - -	Over 60 mm.	Over 60 mm.	Large bubble	3 mm.
Diluted 4-fold -	45 ,,	,, 60 ,,	0	0
,, 16 ,, -	34 ,,	,, 60 ,,	0	0
,, 48 ,, -	25 ,,	40 ,,	0	0
,, 150 ,, -	15 ,,	36 ,,	0	0
,, 500 ,, -	Large bubble	25 ,,	0	0
,, 2,000 ,, -	,,	25 ,,	0	0
,, 6,000 ,, -	0	0	0	0
,, 24,000 ,, -	0	0	0	0

We see here that, despite the restraining influence exerted by the 8-times increased antitryptic power, the acidaemic gas-gangrene serum gives a culture with an implantation 2000 times smaller than that required for the normal serum.

TABLE A

Case No.	History	When blood sample was taken	Data furnished by Marriott's method		Data furnished by titration with acid
			pH.	RpH.	
1	Wound of forearm. Gas gangrene from the wrist to the bend of the arm. No constitutional symptoms. Amputation immediately above elbow. Good recovery.	At operation.	—	—	N/40
2	Very extensive wound of the leg with gas gangrene. Intense restlessness. Has to be propped up to get his breath. Respirations irregular, about 30 per min. Death.	3 hours before death.	—	—	N/50
		Shortly before death.	—	—	N/60
3	Very extensive wound of the leg with gas gangrene. Lies cold, cyanotic, and almost comatose, breathing very deeply, about 40 per min. Death.	1 hour before death.	—	—	N/80
		Shortly before death.	—	—	N/160
4	Large wound of thigh and extensive bruising of back, with widespread gas gangrene in both regions. Patient lies quite cold and pulseless. Respirations 15 per minute. Intravenous injection of 5 per cent. NaCl and 5 per cent. $NaHCO_3$. Within an hour is eating his dinner and reading the paper. Six hours afterwards renewed pain and tension in leg. Further very extensive operation. Death during the night.	Before injection.	7·3	7·6	N/70
		Immediately after injection.	7·65	7·95	N/35
		3 hours after injection.	7·4	7·8	—
5	Perforating wound of elbow with obliteration of vessels followed 24 hours later by the development of gas gangrene in the forearm. No constitutional symptoms. Amputation above elbow. Recovery.	At operation.	7·4	7·75	N/35
6	Gas gangrene is spreading upwards upon the trunk from a high amputation of the thigh. Patient is out of his mind and is pulseless and in a moribund condition. Intravenous injection of 500 c.cm. of a 5% NaCl and 5% $NaHCO_3$ solution, patient dying immediately after the injection.	Before injection.	7·05	7·05	N/100
		Immediately after injection.	7·3	7·7	N/50
7	Very extensive wound of buttock. Patient lies cold, pulseless, and breathing very deeply 28 times per minute. Intravenous injection of 500 c.cm. of 5% $NaHCO_3$ solution. Patient immediately revives. Seven hours later the pulse again becomes feeble and the respiration increases to 40 per minute. Intravenous injection of a further 250 c.cm., 5% $NaHCO_3$, and 2·5% NaCl solution. This was followed by the oral administration of 8 g. of lactate of soda every fourth hour. Next day patient's constitutional condition is not unsatisfactory. Death in the course of the night.	Before injection.	7·3	7·7	N/70
		Immediately after injection.	7·95	8·2	N/30
		Immediately before 2nd injection.	7·4	7·95	N/50
		Immediately after 2nd injection.	7·7	8·2	N/40
		24 hours after 1st injection.	7·7	8·0	—
8	Extensive wound of thigh. Operation and removal of large mass of infected adductor muscles. General condition gives rise to no anxiety. 24 hours afterwards patient has developed an icteric tinge and a flagging pulse. Intravenous injection of 500 c.cm. $NaHCO_3$. Condition improves from day to day.	At operation.	7·5	7·9	N/45
		24 hours after, and immediately before, injection.	7·5	7·9	N/50
		Immediately after injection.	7·8	8·1	N/40
		48 hours after.	7·9	8·15	N/35
		72 ,, ,,	—	—	N/40

TABLE A—(*Continued*).

Case No.	History	When blood sample was taken	Data furnished by Marriott's method		Data furnished by titration with acid
			pH.	RpH.	
9	Extensive wounds of both legs. Patient very weak, pulse impalpable, respirations 32. Intravenous injection of 150 c.cm. $NaHCO_3$, followed by 8 g. of lactate of soda every 4 hours. 24 hours after patient is in much better condition. 48 hours after improvement continues. Towards evening recurrence of gas infection in leg. Disarticulation at knee. Next morning gas gangrene manifests itself in decumbent aspect of buttock. Further operation. Death.	Before injection.	7·4	7·7	N/70
		24 hours after.	7·4	7·8	N/40
		48 ,, ,,	7·7	8·1	N/30
		72 ,, ,,	7·8	8·1	—
10	Wound on inside of thigh. A large portion of the sartorius has been excised. Extension of gangrene downwards from lower border of incision. Patient pulseless and inoperable. Intravenous injection of 500 c.cm. $NaHCO_3$. Patient revives and an operation is successfully undertaken. 24 hours afterwards general condition is very satisfactory. Patient makes a very good recovery.	Immediately before injection.	7·4	7·65	N/60
		Immediately after injection.	7·9	8·05	N/30
		24 hours after injection.	7·6	8·15	N/35
		48 hours ,, ,,	7·4	8·0	—
11	Gas gangrene of arm. Constitutional condition satisfactory. Amputation in upper third of arm. Intravenous injection of 500 c.cm. 5% $NaHCO_3$. 24 hours after constitutional condition very satisfactory. Patient makes a good recovery.	Before injection.	7·35	7·9	N/45
		24 hours after injection.	7·65	8·3	N/35
12	Patient has had his leg disarticulated at the knee for gas gangrene and has had secondary haemorrhage.	12 hours after operation.	7·4	7·95	N/40
13	Patient's leg had been amputated above the knee for gas gangrene, and he lies cold and pulseless, breathing 42 per min. Intravenous injection of 300 c.cm. $NaHCO_3$ solution. Some improvement of symptoms. Dies 12 hours afterwards.	Immediately before injection.	7·25	7·5	N/80
		Immediately after injection.	7·45	7·8	N/45
14	Leg amputated in upper third of thigh. Gas gangrene spreading upwards into trunk and scrotum. Intravenous injection of 450 c.cm. of 5% $NaHCO_3$. Patient revives sufficiently to allow of an extensive operation. Dies 4 hours later.	Before injection.	—	—	N/60
		Immediately after injection.	—	—	N/55
15	Gas gangrene of leg. Disarticulation at knee. Patient nearly dies on the table. Intravenous injection of 400 c.cm. 5% $NaHCO_3$. Death two hours later.	Immediately before injection.	—	—	N/80
		Immediately after injection.	—	—	N/35
16	Wound of chest and haemothorax infected with *B. Welchii*. Chest has been opened and drained. Icteric tinge. Pulse very feeble. Respiration very rapid. Intravenous injection of 460 c.cm. of 5% $NaHCO_3$ solution, followed by lactate of soda, 8 g. every 4 hours. 24 hours constitutional condition no better. Death.	Immediately before injection.	—	—	N/70
		Immediately after injection.	—	—	N/40
		3 hours after injection.	—	—	N/50
		24 ,, ,, ,,	—	—	N/30

TABLE A—(*Continued*).

Case No.	History	When blood sample was taken	Data furnished by Marriott's method		Data furnished by titration with acid
			pH.	RpH.	
17	Extensive wound of thigh with gas gangrene. Multiple deep incisions. Patient has been lying pulseless and in a state of collapse for 24 hours since his operation. Intravenous injection of 500 c.cm. of 5% $NaHCO_3$ solution. Immediate great improvement in his clinical condition. 8 g. of lactate of soda 4 hourly. 24 hours afterwards condition very satisfactory. Patient makes a good recovery.	Immediately before injection.	—	—	N/60
		Immediately after injection.	—	—	N/30
		7 hours after injection.	—	—	N/35
		24 ,, ,, ,,	—	—	N/35
18	Patient has had his left arm amputated for gas gangrene. The infection now develops in the right arm above elbow. Amputation in the upper third of arm. Intravenous injection of 500 c.cm. 5% $NaHCO_3$ solution. Patient makes a good recovery.	Immediately before injection.	—	—	N/50
		18 hours after injection.	—	—	N/30
19	Leg amputated 12 hours before for gangrene. Little constitutional disturbance. Pulse good. Respiration 27. Makes a good recovery.	12 hours after operation.	7·45	8·1	—
20	Left foot amputated 12 hours before. Wound in right leg with gas infection. Amputation through middle of thigh. Pulse very rapid. Intravenous injection of 500 c.cm. 5% $NaHCO_3$ solution. Patient makes good recovery.	Immediately before injection.	7·5	8·0	—
		Immediately after injection.	8·0	8·4	—
21	Large buttock wound with some gas infection. Pulse fair. No air-hunger. Intravenous injection of 500 c.cm. 5% $NaHCO_3$ solution.	Immediately before injection.	7·3	7·9	—
		Immediately after injection.	8·0	8·2	—
22	Leg amputated through middle of thigh for gas gangrene. Pulse small and weak. Respiration 30 per minute. Injected intravenously 500 c.cm. 5% $NaHCO_3$ solution. 12 hours afterwards recurrence of gas infection and death.	Immediately before injection.	7·3	7·7	—
23	Leg had been amputated 24 hours before for gas gangrene. Very marked icterus. Pulse fair. No increased respiration. Gangrene not spreading. Oral administration of 8 g. of lactate of soda every three hours. Patient made good recovery.	Before alkali medication.	7·4	7·6	—
24	Amputation of leg for gas gangrene. Condition gives rise to anxiety. Intravenous administration of 500 c.cm. 5% solution of $NaHCO_3$. Patient makes a good recovery.	Immediately before injection.	7·3	8·0	—
		Immediately after injection.	8·8	8·3	—

Remarks

CASE 4.—Samples of lymph exuding from wound. No. 1, alkaline, N/80. Film contains streptococci and a few *B. Welchii*. No. 2, acid, contains *B. Welchii* in pure culture. Pyo-sero culture by the method of after-washes. Pus implanted into the serum of blood taken before injection gives a growth of *B. Welchii* and streptococcus in the whole series of after-washes. The same pus implanted into serum of blood taken after injection gives a growth of streptococcus only.

CASE 5.—Exuded lymph obtained by incision into arm ½ hour after amputation is brownish in colour, acid in reaction, and contains *B. Welchii* and streptococci.

CASE 14.—Lymph from incision into scrotum—alkalinity N/100. No bacterial infection.

Experiment 2

A serum was taken and was implanted in bulk with a very small quantity of a culture of the bacillus of Welch. Of this infected serum a series of equal volumes were then filled into narrow tubes. To these were added graduated quantities of standardised sulphuric acid, the quantities being such as to give, in the central tube of the series, serum of a neutral reaction ; with, on the one side, tubes of increasing acid ; and, on the other side, tubes of increasing alkali content. Melted vaseline was then poured on to the top of the tubes, and they were placed in the incubator. The amount of gas evolved was taken as a measure of growth, and the figures in the table give the height of the gas columns in millimetres.

Serial number of tube	1	2	3	4	5	6	7	8	9
Reaction of the serum	Acid N/60	Acid N/70	Acid N/110	Acid N/200	Neutral	Alkaline N/330	Alkaline N/150	Alkaline N/60	Alkaline N/55
Result after 24 hours -	—	—	—	S.B.	S.B.	—	—	—	—
,, ,, 30 ,, -	—	—	—	5·5	8·0	S.B.	—	—	—
,, ,, 46 ,, -	—	—	6·5	9·5	11·5	7·0	L.B.	—	—
,, ,, 50 ,, -	—	—	8·0	11·0	13·0	8·0	7·5	—	—

SB = Small bubble. LB = Large bubble.

Experiment 3

A thick bacterial suspension was made from a 24-hours'-old blood-agar culture of the bacillus of Welch ; and this suspension was diluted 2, 4, 8, 16, 32 and 64 times. Of the original suspension 1 wash (i.e. *circ.* $\frac{1}{25}$ vol.) and 2 washes, and of each dilution one wash—corresponding to $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$, $\frac{1}{16}$, $\frac{1}{32}$ and $\frac{1}{64}$th wash of the original suspension—were implanted into normal serum in capillary pipettes, the procedure for anaerobic culture being the ' gas-lock ' procedure referred to in the previous paper.[1] In the experiments here in question the ' butt end ' containing the serum in bulk was, for the *control experiments*, connected up with the gas-supply ; and, for the *substantive experiments*, with a Kipp's apparatus generating CO_2, and the serum was in each case saturated by letting it stand in contact with gas, and by conveying into it bubbles of the gas. The results, read off after the tubes had been incubated for 24 hours, were as set out in the following table :

Derivation of the serum, and form in which it was employed	Amount of the implantation							
	2 washes	1 wash	$\frac{1}{2}$ wash	$\frac{1}{4}$ wash	$\frac{1}{8}$ wash	$\frac{1}{16}$ wash	$\frac{1}{32}$ wash	$\frac{1}{64}$ wash
A. E. W.'s serum unaltered	0	0	0	0	0	0	0	0
Same serum saturated with CO_2	×	×	×	0	0	0	0	0
L. C.'s serum unaltered -	0	0	0	0	0	0	0	0
Same serum saturated with CO_2	×	×	0	×g	×	×	×g	×g
J. F.'s serum unaltered -	0	0	0	0	0	0	0	0
Same serum saturated with CO_2	×g	×g	×g	×g	×g	×g	×g	×
A. E. W.'s serum unaltered	×g	0	0	0	0	0	0	0
Same serum saturated with CO_2	×g	×g	×g	×g	×g	×g	×g	×g

[1] *Supra*, p. 47.

×, Culture. ×g, Culture with gas formation.

Question as to whether the Bacillus of Welch grows more rapidly, and produces more Gas, in Blood-fluids to which Glucose has been added.

In connexion with the pathology of gas gangrene another general problem suggests itself to the mind. This is the problem as to whether the special predisposition of wounded muscle to gas-gangrene infection is due to its carbohydrate content. The theory that we have here the cause of the infection finds its principal support in the circumstance that it is the liver—the organ of highest carbohydrate content—which is in the dead animal, after intravenous inoculation, the seat of the most fulminating infection. But this facile reasoning leaves out of sight that when we inject an animal intravenously and intramuscularly with the same quantities of culture, and then kill and incubate, we obtain pullulation of the microbe with enormous gas production in the peritoneal fluid, which is not, we may assume, specially rich in sugar ; and no visible effects whatever in the inoculated muscle. And, again, when we inject intravenously and then kill and immediately extirpate the liver—our principal fount of sugar—we still get our fulminating post-mortem gas septicaemia.

But even apart from this, the idea that the infection of wounded muscle is conditioned by the circumstance of the microbe finding here at its disposal a provision of sugar encounters in the thoughtful mind many difficulties. Külz showed that severe muscular exercise used up every trace of glycogen in the body. Consequently, in men wounded during the intense fatigue of the battle—and that intense fatigue has often been brought into association with the onset of gas gangrene—we may assume that their muscles contain very little or no glycogen. Nor can we know whether that carbohydrate, if still present, would pass into solution and be placed at the disposition of the microbe. And again we do not know whether the lymph in the muscles contains even as much sugar as the circulating blood. Since the muscle uses up sugar the probabilities would seem to be rather the other way. All these points would seem to invalidate the theory that it is the higher percentage of sugar which is responsible for the predisposition of muscle to gas-gangrene infection. And it is not as if we had here a theory which alone could supply an explanation of this disposition. We have seen that every addition of acid—even of carbonic acid—favours the growth of the bacillus of Welch in serum ; and we know that functioning and devitalised muscle elaborates carbonic and lactic acid ; and that we have, therefore, in muscle fatigued, or cut off from its blood supply by trauma, tourniquet, ligature, or collapse of the circulation, a local reduction of alkalinity which would be favourable to the development of the gas-gangrene bacillus.

Enough will have been said to show that the problem as to whether the special predisposition of wounded muscle is due to its containing sugar is, like all problems of causation, much more complex than immediately appears. But clearly there is nothing to prevent us determining by experiment whether an addition of glucose to normal serum aids the growth of the bacillus of Welch and promotes gas formation, and whether such serum constitutes as favourable a medium as ' acidosed ' serum.

Experiment

The method of experimentation was the same as in Experiment 3 in the previous subsection, with the difference that here coal-gas was employed in the substantive and control experiments alike, and that for the substantive experiments there was employed a serum to which there had been added one wash (*circa* $\frac{1}{25}$ volume) of a glucose solution. The results, as before, were read off after 24 hours. And in this connexion it is important to emphasise that it is the early results which differentiate most clearly between the different sera, and of course it is the early results which would come into account in connexion with infection *in vivo*.

Derivation of the serum and form in which it was employed	Amount of the implantation								
	3 washes	2 washes	1 wash	$\frac{1}{2}$ wash	$\frac{1}{4}$ wash	$\frac{1}{8}$ wash	$\frac{1}{16}$ wash	$\frac{1}{32}$ wash	$\frac{1}{64}$ wash
A. E. W.'s serum	×	0	0	0	0	0			
Same with 1% glucose	×	0	0	0	0	0			
,, ,, $\frac{3}{3}$ wash of normal H_2SO_4	×	×	×	×	×	0	0		
A. E. W's serum	×	—	×	×	×	0	0		
Same with 1% glucose	×	×	×	0	0	0	0		
A. E. W.'s serum	—	×g	×	0	0	0	0	0	
Same with 0·5% glucose	—	×g	×g	0	0	0	0	0	
,, neutralised with H_2SO_4	—	×g	×g	×g	×g	×g	×g	×g	
A. E. W.'s serum	—	×	×	0	0	0	0	0	
Same with 0·5% glucose	—	×	×	×	0	0	0	0	
,, neutralised with H_2SO_4	—	×g	×g	×g	×g	×g	×g	×g	
L. C.'s serum	—	0	0	0	0	0	0	0	
Same with 1% glucose	—	0	×	0	0	0	0	0	
,, ,, 0·5% ,,	—	0	0	0	0	0	0	0	
,, ,, 0·25% ,,	—	×	×	0	0	0	0	0	
,, ,, $\frac{5}{7}$ wash normal H_2SO_4 [1]	—	×g	×g	×g	×g	×g	×	×g	
A. E. W.'s serum	—	0	0	0	0	0	0	0	
Same with 1% glucose	—	×	×	0	0	0	0	0	
,, slightly acidified with H_2SO_4	—	0	0	0	0	0	0	0	
,, saturated with CO_2	—	×	×	×	0	0	0	0	
A. E. W.'s serum	—	×g	0	0	0	0	0	0	—
Same with 1% glucose	—	×g	0	0	0	0	0	—	—
,, neutralised with H_2SO_4	—	×g	×g	×g	×g	×g	×g	×g	0
,, saturated with CO_2	—	×g	×g	×g	×g	×g	×g	×g	×g
J. F.'s serum	—	0	0	0	0	0	0	0	0
Same with 1% glucose	—	×	0	0	0	0	0	0	0
,, saturated with CO_2	—	×g	×g	×g	×g	×g	×g	×g	×g

×, Growth. g, Gas formation.

[1] Taking a wash as equivalent to $\frac{1}{25}$ vol., $\frac{5}{7}$ of a wash of normal acid would just neutralise normal serum.

It will be seen from the above table that the addition of glucose to the serum does not exert upon the *growth of the bacillus* of Welch any constant or marked

favouring influence. And it is clear that that favouring influence, where exerted, does not admit of any comparison with that obtained by neutralisation of the serum by sulphuric acid, or the blunting off of the alkalinity by saturation with CO_2. It also comes out clearly that the *evolution of gas* is favoured far more by the blunting off of the alkalinity of the serum than by the addition of glucose. This last point is brought out in a very conspicuous manner in the subjoined experiment.

Experiment

The technique employed was that of cultivating in narrow glass tubes covered in by vaseline; and one volume of the undiluted or diluted bacterial suspension was added in each case to 9 volumes of normal serum. The amount of gas evolved was determined by measuring the height of the column of gas.

Derivation and form of serum employed	Duration of incubation	Amount of implantation				
		One-tenth volume of bacterial suspension				
		Undiluted	Diluted 5-fold	Diluted 25-fold	Diluted 125-fold	Diluted 625-fold
(*a*) Serum with 1% glucose -	24 hrs.	10 mm.	L.B.	0	0	0
(*b*) Serum neutralised with H_2SO_4	,,	14 ,,	17 mm.	11 mm.	0	0
(*a*) Serum with 1% glucose -	72 hrs.	14 ,,	14 ,,	14 ,,	14 mm.	0
(*b*) Serum neutralised with H_2SO_4	,,	23 ,,	30 ,,	30 ,,	15 ,,	0

LB = Large bubble.

Summary and Consideration of the Symptomatology and Treatment of the Acid Intoxication in Gas Gangrene.

The observations set out above have confirmed and brought into clearer light the fact that the growth of the microbes of gangrene is favoured by every reduction of blood alkalinity, and they suggest that wherever, as in the dead body and the muscles, we come upon conditions which specially favour the growth of the gas-gangrene bacillus, there the factor of acidosis is likely to be the operative factor. And it has been further demonstrated that the microbes of gangrene can by elaborating acid make for themselves favourable conditions at the site of infection, and in the blood generally.

Symptomatology

The suggestion that we have to see in gas-gangrene toxaemia an acidaemia has encountered opposition.

It has been objected: Air-hunger is not, as it ought to be, a feature, and an outstanding feature, in the clinical picture of gas-gangrene toxaemia. Nor is there in the toxaemia of gas gangrene anything else to remind us of the classical symptoms of acidosis.

From the contention that air-hunger does not enter into the picture of gas-gangrene toxaemia the appeal is to the clinical facts. We have, in the large majority of cases of gas gangrene, well-marked hyperpnoea ; in some, we have quite classical air-hunger ; and where we find this symptom absent it is, we may suggest, because the agonal cold is already creeping up over the gas-gangrene patient. In such circumstances, with internal respiration practically extinguished and the pouring into the blood of CO_2 and further acid products excluded, air-hunger is obviously ruled out.

That the clinical picture of gas-gangrene toxaemia fails to correspond with our mental picture of acidosis may depend upon our mental picture having been arrived at by erroneous generalisation.

If that picture has been built up by generalising from examples of only one form of acidosis, and if there have been admitted into it features referable to other toxic agency and unrelated to acidosis, the criterion by which we judge will necessarily mislead. If, for example, we let ourselves be dominated by the idea that diabetic coma displays the symptoms of acidosis, and allow ourselves to identify the clinical picture of acidosis with that of diabetic coma, we shall inevitably, as has been done, conclude that we cannot in gas-gangrene toxaemia be dealing with an acidosis.

But, then, let us reflect upon our position when once it stands fast that gas-gangrene toxaemia is associated with an acid intoxication. Clearly, we shall then, by parity of reasoning, be compelled to conclude that we cannot in diabetic coma be dealing with an acidosis. Such a dilemma teaches that we ought to generalise upon a wider basis, and to bring under contribution, when we are building up our clinical picture of acidosis, all the known forms of acidosis.

We have an acidosis not only in diabetic coma and gas-gangrene toxaemia, but also in many cases of nephritis ; further, as recently shown by Rogers in Asiatic cholera ; [1] and again, as one of us—on the basis of *a priori* reasonings,[2] and blood examinations of cases from the siege of Ladysmith,[3] and infantile cases [4]—has contended in scurvy, i.e. in the cachexia brought about by a dietary of cereals or dried and salted meat exclusively, or of these foods in combination. And of course we have—and this is, perhaps, the most elucidating of all—the condition of the ' acid rabbit '—the acidaemia produced experimentally in that animal by the oral administration of hydrochloric acid.

Constitutional Symptoms of Acidaemia

The constitutional symptoms common to all these forms of acidosis would, when the conditions are acute, seem to be two :

First, we have the hyperpnoea which has already been under discussion. With respect to this, it has come home to us that, though an outstanding symptom when muscular exercise puts a strain upon the respiratory mechanism, hyperpnoea may

[1] *The Lancet*, 1917, ii, 745.

[2] Wright, ' On the Pathology and Therapeutics of Scurvy ', Scientific Appendix, *Report of the Army Medical Department for* 1895.

[3] Wright, ' On the Pathology and Therapeutics of Scurvy ', *The Lancet*, 5th August, 1900.

[4] Wright, ' Discussion on the Ætiology of Scurvy ', *Transactions of the Epidemiological Society of London*, New Series, vol. xxiii, pp. 94–97, and 108.

easily cease to be apparent or even make default when the patient is at complete rest and the internal respiration is cut down.

The second important clinical feature of acidosis is that the life of the patient or experimental animal in this condition hangs upon a thread. We leave our gas-gangrene patient for an hour, and we come back and find him dead. The same, as we gather, holds of the cholera patient. 'Acidaemic sudden death' is common also in diabetic coma and nephritic patient. And in the accounts of ship-scurvy—and in particular in that memorable account in Lord Anson's *Voyage of the 'Centurion'*—there is constant reference to patients dying quite without warning, and to death being wont to follow very suddenly upon the least physical exertion. Exactly the same holds of the 'acid rabbit'.

To these clinical features may be added a third. Nephritic, and in particular scorbutic, and gas-gangrene patients have a sallow earthy aspect which immediately brings up to the mind of those familiar with the facies the possibility of acidaemia.

Local Manifestations

In the matter of local manifestations there would appear to be—but, of course, the symptomatology will here vary with the local source of the acid—a disposition to serous effusion into the tissues, and in particular—perhaps here to rectify the local acidosis—an effusion into the site of the acid production. Fischer, in his work on nephritis, has drawn special attention to acidosis as a cause of imbibition, and very probably this factor does play a part in the causation of oedema in the nephritic. The same almost certainly holds true of gas gangrene. We have there a very conspicuous serous infiltration of the tissues, and the microbic invasion of the subcutaneous tissues is here preceded by an advance wave of diminished alkalinity marked out by a purplish mottling of the skin.

In scurvy also we have, in the infant, as a characteristic early symptom, muscular pain and tenderness which probably speak of effusion; and in the accounts of land-scurvy—such as those in Calvert's collection of the *Travels of the Early Explorers of Australia*—we have frequently recurring references to painful effusions in the calf and thigh; and in Lord Anson's *Voyage* and the works of Lind on sea-scurvy we have accounts of anasarca and effusion into serous cavities.

Out of all these elements and such others as may perhaps present themselves in connexion with still undescribed forms of acidosis, the clinician of the future will build up an accurate generalised picture of its symptomatology.

In time of war, having laid a sufficient foundation of pathological observation, the pressing task is to get on to the effective treatment of the acidosis of gas gangrene.

Treatment

The treatment of the acidaemia of gas-gangrene toxaemia follows directly from its pathology. We may discuss first the constitutional, and then the local treatment.

Constitutional Treatment

We have, as has appeared in the histories embodied in Table I, employed, as is done in grave diabetic acidosis, intravenous injections of alkali, following these

up, where a relapse had to be guarded against, by lactate of soda administered by the mouth in doses of 8 g. four-hourly until the urine becomes alkaline.

For the intravenous injections we have employed a 5 per cent. solution of $NaHCO_3$, preferring this for two reasons to a solution of carbonate of soda : *first*, for convenience of dosage, the bicarbonate being, as distinguished from the water-holding carbonate of soda, a non-efflorescent salt ; and, secondly, to guard against local injury to tissues in case of any fluid escaping from the needle during the injection. We have not allowed ourselves to be influenced by the circumstance that bicarbonate is during sterilisation partially converted into carbonate, for the originally 5 per cent. or three-fifths normal bicarbonate solution remains, no matter how much is converted into carbonate, still a three-fifths normal alkaline solution.

The quantum of alkaline solution chosen—i.e. 500 c.cm.—would appear to have been appropriately chosen, for this has sufficed to restore, or just more than restore, to the blood its normal alkalinity.

The lactate of soda—made by neutralising lactic acid by soda—was chosen for the after-treatment both because it is very easily tolerated by the normal stomach and because it is after absorption very rapidly (in the normal man in the course of a very few minutes) converted into carbonate.

On account of the nausea and vomiting at the outset of gas-gangrene toxaemia the oral administration of lactate of soda cannot at that stage replace intravenous injection.

Local Treatment

Here two points may be adverted to. The *first* relates to the anaesthetic for the operation; the *second* to the after-treatment of the amputation stump or incised tissues.

In relation to the anaesthetic it would appear to be the experience of all that chloroform must be avoided ; that warmed ether gives much better results, and that nitrous oxide with oxygen is far the best anaesthetic.

It has been suggested in connexion with these findings that the chloroform, and to a less degree the ether, narcosis may in the already acidaemic patient aggravate the acidosis ; but this would perhaps not be of so much moment in the case of the patient whose blood alkalinity had before operation been restored to the normal. With regard to the after-treatment of the wound it is of fundamental importance where infected or ' acidosed ' (and because of that very easily infected) tissue has to be left behind to evacuate all the corrupted lymph, replacing it by lymph normal in alkalinity ; and normal (and that in this case means equipollent with the blood-fluids) with respect to antitryptic power.

To this end a local lymphagogue must be resorted to ; and one of us has already more than once called attention to the very striking improvement obtained in these cases by the free application of 5 per cent. salt solution.

Results in Cases of Gas Gangrene treated by Intravenous Injection of 5 per cent. Bicarbonate of Soda

It is the bane of scientific research that if ever there is suggested by it a therapeutic measure, that procedure is, despite all its advocates may do, represented as either a complete panacea, or a measure which disappoints legitimate expectation.

If a little quiet thought were given to the therapeutic problems in question, all this would be avoided. Here, for instance, in connexion with the treatment of the acidosis of gas gangrene, one ought not to have to preface one's recommendation of alkaline injections by a formal confession of faith that the toxaemia of gas gangrene must assuredly be something more than an acidosis.

After comparing in the rabbit simple acidosis with gas-gangrene infection one would wish to be credited with the power of recognising that the two conditions are not identical.

Again, even if one were supposed to believe that we are in the toxaemia of gas gangrene confronting a simple acidosis, one would wish to be credited with the power of seeing that one cannot in a severe acidaemic case, where the whole salt content of the blood has been profoundly altered, hope by an injection of bicarbonate of soda to bring about a *restitutio ad integrum*.

And even if one did think that a *restitutio ad integrum* could be effected, one would wish to get credit for seeing that one could not hope to get durable benefit from this where one has neither completely extirpated the infection nor yet successfully treated it by ' drainage of the tissues '.

And, lastly, when one recommends the injection of alkali in gas-gangrene infection, one would wish it to be borne in mind that we have in such cases nearly always an associated streptococcus infection which would not be directly affected by our injection of alkali.

In view of these considerations, we have not even attempted to collect and present any comparative statistics of gas gangrene treated with and without alkali. That, as it seems to us, would be as much a logical abuse as to try to establish by comparative statistics of tracheotomised and non-tracheotomised cases of diphtheria the advantage of tracheotomy in largyneal obstruction.

In either case resort to the particular procedure is prescribed by common sense, and is approved by the immediate striking improvement achieved in cases otherwise desperate.

But in connexion with gas-gangrene infection it may perhaps be permissible to point out that the benefit of alkali treatment is almost certainly not summed up by saying that by it the inoperable acidaemic cases become operable.

We may, in view of the data we have set out, quite reasonably hope that by the early administration of alkali the acidaemia may be forestalled ; and also that by it, so long as the circulation is still intact in the site of infection or its immediate neighbourhood, an obstacle may be placed in the way of the growth of the infective agent.

In conclusion, we wish to express our acknowledgments to Major J. W. West, R.A.M.C., for much helpful assistance in the study of cases of gas gangrene. We desire also to thank Dr. Weinberg, of the Pasteur Institute, for supplying us with cultures of the gas-gangrene microbes discovered by him. To Captain H. Henry, R.A.M.C., also we are indebted for other cultures of these microbes.

ON THE ACIDOSIS OF SHOCK AND SUSPENDED CIRCULATION[1]

BY ALMROTH E. WRIGHT AND LEONARD COLEBROOK

The suggestion that acid intoxication is an element in surgical shock we owe to Crile. For the establishment of the fact we are indebted to Cannon. His observations have shown that we have in the wounded man affected by shock a man suffering from a severe, sometimes an extreme, acidosis. This discovery has therapeutic value ; and it is of utility also as directing attention to a fundamentally important element in our vital machinery which has up to now been only very imperfectly explored, and which medicine has, one may say, completely left out of account. I refer to the large output of acid waste products from the body, and the provisions by which, despite that, the alkalinity of the blood is maintained.

Let us go to work by enquiring in connexion with the wounded man : To which of all the pathological agents brought to bear on him is his acidosis due? Whence have come the waste products which have produced that acidosis? What factors have influenced their convection into the blood-stream? And how soon after it reaches the circulation is the acid disposed of? These problems considered, the question will come up as to whether the type of acidosis encountered in the wounded is not encountered also in other morbid conditions.

The outstanding feature in the symptomatology of shock being the fall of arterial tension—and interference with the circulation at the periphery—we may inquire first into the effect of arresting and reopening that circulation. In the experiments set out in Table I below we anaesthetised rabbits with ether, clamped one or several main arteries, and removed the clamps after varying intervals—taking from time to time samples of blood for the measurement of the alkalinity.

The method employed for this was that of direct titration in capillary glass tubes with dilutions of standardised sulphuric acid, using sensitive red litmus paper as an indicator.[2] One of the advantages of this method—and it is for the purpose here in view a great advantage—is that of taking no cognisance of CO_2—i.e. of *expirable acid* —and measuring only the *non-expirable acid* conveyed into the blood.(See Table I.)

We see in these experiments that when an artery is clamped and afterwards unclamped a very appreciable quantity of a non-expirable acid is conveyed into the blood-stream. The same effect will, of course, be obtained with a ligature, tourniquet, or Ersmarch bandage. It will be obtained, also, whenever the arterial pressure sinks away and afterwards recovers. For when we have collapse of the circulation, the blood-stream is cut off from the periphery and metabolic exchanges are arrested ;

[1] Reprinted from *The Lancet*, 1st June, 1918.

[2] Wright, *Technique of the Teat and Capillary Glass Tube*, London, Constable.

and when the blood pressure is restored capillary blood-vessels are reopened and the metabolic exchanges fallen in arrear are resumed.

TABLE I

No. of rabbit	Particulars of procedure	Time when blood samples were taken	Alkalinity
1	Both femoral arteries and both carotids occluded for 1 hr., then unclamped. Animal placed in warmth beside stove; ½ hr. after reopening circulation air-hunger and convulsive seizures developed. Death.	Immediately before removing clamps from vessels	N/40
		During convulsions	N/80
2	Abdominal aorta and both carotid arteries occluded for 1 hr., then unclamped. Recovery.	Immediately after occluding the vessels	N/40
		Soon after removing clamps	N/60
3	Carotid arteries and external jugular veins, also femoral arteries and veins occluded for 1½ hrs., then unclamped. Recovery.	Before commencement of operation	N/30
		Immediately before removing clamps from vessels	N/30
		40 minutes after removing clamps	N/60
		18 hrs. afterwards	N/50
4	1 carotid artery and external jugular vein, 1 subclavian artery and vein, also 1 femoral artery and vein, occluded for 1¼ hrs., then unclamped. Recovery.	After anaesthetising	N/50
		Immediately before removing clamps from vessels	N/45
		35 minutes after removing clamps	N/60
5	Abdominal aorta occluded for 1 hr., then unclamped. Killed.	Before commencement of operation	N/35
		Immediately before removing clamp	N/40
		Few minutes after removing clamp [1]	N/55

[1] Blood from inferior vena cava.

Our next series of experiments has reference to the effect of cold immersion. (See Table II.)

It will be seen that there is a broad similarity between these results and those set out in Table I. There are, however, differences. *In the first place*, the acidaemia is here much greater. *Secondly*—no doubt in correlation with the fact that the circulation in the limbs is not immediately arrested by the cold immersion—the acidaemia is already manifest when the animal is removed from the ice-bath. And, *thirdly*, when we here test the muscle (we do this by placing a piece of washed extirpated muscle on red and blue litmus paper) we find it definitely acid instead of alkaline as normal muscle, or amphoteric as muscle extirpated after simple occlusion of the artery.

TABLE II

No. of rabbit	Particulars of the procedure	Derivation of the blood sample and when it was taken	Alkalinity
1	Ice-bath for 40 minutes, animal then placed in hot bath for 5 min., afterwards kept in incubator at 37° C. After 1½ hrs. animal's condition very satisfactory, and after 3¼ hrs. recovery apparently complete.	Before ice-bath (ear)	N/35
		Immediately after ice-bath (F.V.) -	—
		Immediately after hot bath (F.V.) -	N/60
		1½ hrs. after (ear) -	N/60
		3¼ hrs. after (ear) -	N/35
2	Ice-bath for 40 minutes. Rectal temp. went down to 15° C. and animal died from collapse few minutes after being taken out of bath.	Before ice-bath (ear)	N/35
		Immed. after bath (F.V.) - -	N/60
		Soon after death (Sup. V.C.) - -	N/100
		Blood from Vena Portae - -	N/80
3	Ice-bath for 20 minutes ; animal then left wet at room temp. After lapse of 20 minutes air-hunger and tetanic spasms developed and animal quickly died.	Before ice-bath (ear)	N/35
		Immediately after bath (F.V.) -	N/60
		At death, from Inf. V.C. - -	N/300
		Blood from Vena Portae - -	N/200
4 [1]	Ice-bath for 15 minutes ; animal then placed in hot bath for 15 minutes and afterwards kept in incubator at 37° C. Its condition showed little improvement up till 3½ hours after, when it was killed.	Before ice-bath (ear)	N/35
		Immediately after ice-bath (F.V.) -	N/60
		Immediately after hot bath (F.V.) -	N/60
		After 3½ hrs. at 37° C. (F.V.) - -	N/50
5	Ice-bath for 15 minutes, then hot bath for 7 minutes, and kept afterwards in incubator at 37° C. for 3½ hrs. Animal's condition became satisfactory after ¼ hr. in incubator.	Before ice-bath (ear)	N/35
		Immediately after ice-bath (J.V.) -	N/80
		Immediately after hot bath (J.V.) -	N/100
		½ hr. afterwards -	N/100
		1 hr. later - -	N/80
		3 hrs. later - -	N/35
6	Ice-bath for 20 minutes. Animal then left lying wet at room temp. ; it died after 6 hours.	Before ice-bath (ear)	N/35
		5 minutes after ice-bath (J.V.) - -	N/80
		20 minutes later -	—
		1¼ hrs. later - -	N/60
		3¾ hrs. later - -	N/120

F.V., femoral vein. J.V., jugular vein. Sup. and Inf. V.C., superior and inferior vena cava.

[1] Half-grown.

Resuscitation Acidosis

Passing to the effect of bringing back the circulation, we see in Table II that this increases the acidaemia, and that the blood returning from the muscles is more acidosed than the blood taken from the right heart or vena portae.

And concurrent examination of the muscle reveals that, as the acidosis of the blood increases, that of the muscle decreases until its normal alkaline reaction is restored.

A further point of practical import, brought out in connexion with rabbits 1 and 5, is that the animals, when they have to all appearance got over the effects of their cold immersion, may still be definitely acidaemic. It is shown in the table that this acidaemia disappears after a few hours. This reversion to the normal may be safely assumed to be due to the acid being burned off in the system.

Acidosis from Haemorrhage

There would have suggested itself for study next the question as to whether haemorrhage produces acidaemia.

That question has, however, already been settled in the affirmative by the experiments of Milroy,[1] and we can see that in two ways haemorrhage must favour the development of acidaemia. It carries off sodium and potassium carbonates—the alkali available for the neutralisation of acid. And it depresses the arterial tension, and so interrupts the circulation at the periphery. That, as we have just seen, increases acid production in the muscles.

Acidosis from Violent Muscular Contractions

From the study of the effect of diminishing the supply of oxygen to the muscle we may pass on to study the effect of increasing the metabolism of the muscles to the point at which the oxygen supply becomes inadequate. We can do this by powerful faradisation.

We have here, again, an acidaemia (see Table III). We see from the conditions of the experiment that it is a myogenous acidaemia ; and we have confirmation of this in the circumstances that muscle tested immediately after tetanisation is like muscle immediately after cold immersion, definitely acid. And there is also another point of resemblance between the acidaemia of tetanisation and that of arterial occlusion and cold. When it has not been carried too far the acidaemia passes off after a few hours.

Acidosis of the Wounded Man

With respect to the acidaemia of the wounded man we see no room to doubt that it is one into which the factors we have been studying all enter.

As to the nature and genesis of the acid conveyed into the blood we may, as it seems to us, in the light of Fletcher's work on the metabolism of muscle in the presence of oxygen and in its absence, with probability conclude that both in our experiments and in shock as seen in the wounded man we are dealing with an

[1] *Journal of Physiology*, 1917.

acidaemia produced by lactic acid evolved in muscles which are by reason of arrest or collapse of the circulation cut off from their oxygen supply. When we think the matter over we see that this would be an acidaemia similar in character and derivation to that which develops in the dead body. The importance of recognising the fundamental identity of the acidaemia of shock and that which develops in the dead animal will presently emerge.

TABLE III

No. of rabbit	Duration of stim. and particulars of procedure	Derivation of blood sample and when it was taken	Alkalinity
1	Ligature of femoral vein followed by faradic stim. of leg continued for 10 minutes.	From F.V., immediately before stim.	N/35
		From F.V., immediately after stim. -	N/60
2	Ligature of Inf. V.C. in lumbar region, followed by faradic stim. of both lower limbs, continued for 10 minutes.	Before commencement of experiment (ear) - -	N/30
		From Inf. V.C. before stim. - -	N/30
		From Inf. V.C. few minutes after stim. - - -	N/120
3	Faradisation of both lower limbs.	Before stim. (ear) -	N/40
		Few minutes after faradic stim. (ear)	N/100
3	On the following day faradic stim. was repeated.	Before stim. (ear) -	N/30
		Immediately after stim. - - -	N/50
		10 minutes after -	N/120
4	Violent faradic stim. of both lower limbs under general anaesthesia. Severe convulsive seizures occurred and death shortly after.	Before giving anaesthetic (ear) - -	N/35
		Immediately after death : Blood from Inf. V.C. -	N/120
		Blood from right heart - - -	N/80
		Blood from vena portae - -	N/40

F.V. = Femoral. Stim. = Stimulation.

Having won our way to this point of outlook, it behoves us to survey further from it. We have to inquire, *first*, whether there may not, under familiar labels which convey no suggestion of acidosis, lurk acidoses of like derivation with those we have been studying ; and, *secondly*, whether the acidoses which are associated with certain bacterial infections—and we are thinking here in particular of gas gangrene and Asiatic cholera—may not be wholly or in part myogenous acidoses following upon a collapse of the circulation.

Prospecting in the direction first indicated, we are conducted directly to the consideration of chilblains and trench foot.

Indications pointing to Chilblains and Trench Foot being associated with Acidosis

It will be clear that the conditions which we dealt with in our ice-bath experiments and the conditions which produce chilblains and trench foot are essentially the same. From this we may safely argue that when acidosis is examined for in these conditions it will be found. And in the meantime it is in connexion with the relation of acidaemia to gas gangrene and the data set forth in Table IV (below) of interest to note that there is in connexion with severe trench foot a quite special liability to the development of gas-gangrene infection.

TABLE IV

	Duration of incubation	Amount of culture of *B. Welchii* implanted							
		Washes							
		2	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$	$\frac{1}{32}$	$\frac{1}{64}$
Blood taken from rabbit before ice-bath. Alkalinity = N/35.	24 hrs.	—	0	0	0	0	0	0	0
Blood taken $1\frac{1}{4}$ hours after removal from ice-bath. Alkalinity = N/100.	24 ,,	—	×g	×g	×g	×g	×g	×g	×g
Blood taken from ear vein of rabbit before faradic stimulation. Alkalinity = N/30.	24 hrs.	0	0	0	0	0	0	0	0
	48 ,,	Tr.	Tr.	Tr.	Tr.	Tr.	0	0	0
Blood taken from femoral vein after faradic stimulation. Alkalinity = N/100.	24 ,,	×g	×g	0	0	0	0	0	0
	48 ,,	×g	×g	×g	×g	×g	×g	×g	×g

× = Culture. × g = Culture with gas formation. Tr., Trace.

Acidosis of Anaesthesia

The pathology of trench foot and that of general anaesthesia would seem to lie poles apart. But in reality they would seem to have in common the factor of a shutting off of the circulation and a resultant cutting down of oxygen supply from the muscles. This collapse of the circulation will, of course, be specially liable to supervene in severe and prolonged operations, in particular when undertaken in cold operating theatres. In animals—inasmuch as with them struggling, asphyxia, and terror are inevitable accompaniments of every administration of anaesthetics—we are already as soon as the animal is under the influence of the anaesthetic confronted by a fully developed acidosis, and this will, if the animal remains in good condition during the anaesthesia, subsequently diminish. We shall, a little later, have to advert again to this ' anaesthsia acidosis '. For the moment it will suffice

to bring out that Cannon has emphasised the important practical points—the risk of superinducing upon the top of a ' wound-shock acidosis ' an ' anaesthesia acidosis '; and the special risk of superinducing asphyxia when administering an anaesthetic to an already acidosed patient.

Problem of the Derivation of the Acidosis of Gas Gangrene

Two years ago one of us pointed out that gas gangrene is characterised by the development of an extreme acidosis ; and that gas-gangrene patients who are in a state of collapse and quite inoperable can be resuscitated and brought into a condition to stand operation by the intravenous administration of bicarbonate of soda. The utility of this procedure appears now to be established, and the treatment is widely resorted to. There remains, however, the problem of the source of the acidaemia. In connexion with this it was at the time suggested that the acid was elaborated by the bacillus of Welch. That was based on that bacillus elaborating acid in serum ; and on the acidaemia becoming more and more pronounced until death supervened. There did not at the time suggest itself any contributory non-microbial source from which the acid could be derived.

Now, however, in the light of the facts elicited by Cannon and ourselves, the problem has taken a quite different complexion. It has emerged that we must, in addition to acid elaborated by the microbe, take into our reckoning acid elaborated by muscle. That acid would operate first at the source. Converting as it would the alkaline muscle lymph into non-alkaline medium—i.e. in a medium congenial to the bacillus of Welch—it would provide for the infection a favourable point of departure. Again, the acid conveyed into the blood would favour the spread of the gas-gangrene infection.

In connexion with this one of us has demonstrated [1] that the fulminating gas-gangrene infection which is obtained in the dead animal is due to acid conveyed into the blood after death ; and, further, that a quite similar rapid pullulation of the microbe takes place in blood drawn off from the dead animal after the post-mortem acidaemia has developed. It is therefore conceivable that in those cases where gas gangrene develops during or immediately after shock the favouring factor may be acid derived from muscle.

The influence of this factor is shown when we implant graduated quantities of the bacillus of Welch into normal blood and into blood drawn off after tetanisation or cold immersion. The results set out in Table IV are those of typical experiments.

There is another way in which acid produced in muscle may intervene in gas gangrene. Here it will be intervention, not at the outset of the infection, but at the height of the toxaemia. In that toxaemia we nave invariably a collapse of the circulation comparable to that obtained in cold immersion ; and to this might not unreasonably be ascribed, at any rate, the rapid progress of the acidaemia.

Confirmation of that idea would seem to be furnished by the fact that very often in gas gangrene when the blood alkalinity has been brought back to normal and the circulation restored by the administration of alkali we have in a very short

[1] *The Lancet*, 1917, i, 1.

time a recurrence of the acidaemia. That recurrence would correspond to the aggravation of the acidaemia observed in animals warmed up after cold immersion.

Problem of the Derivation of the Acidosis in Asiatic Cholera

In connexion with the theory of acidosis developed above, it may perhaps be suggested as likely that the acidosis which Rogers has shown to be an important factor in cholera may, like the acidoses we have been considering, be an acidosis due to collapse of the circulation. In the algid stage of cholera when the blood has been inspissated in consequence of the alvine discharges, the circulation is obstructed and the oxygen must be as completely cut off from the muscles and outlying portions of the body as when the body is immersed in an ice-bath.

Resuscitation Procedures in Shock

The ideas which we have been developing have clearly a direct bearing on the policy to be adopted in the treatment of cases of shock—the warming up of the patient, and the intravenous injection of alkali recommended by Cannon.

With regard to the warming up of the patient there is an important distinction to be established. As a prophylactic measure the giving of hot drinks and the application of warmth is assuredly the ideal procedure. For by maintaining the circulation the acidosis will be prevented.

No such enthusiastic view can be taken of heat applied as a remedial procedure in fully developed shock. No doubt it is there urgently required for the re-establishment of the circulation and the breaking of the vicious circle. But inevitably it will convey into the blood-stream additional acid, increasing the acidaemia.

Our experiments upon rabbits subjected to cold immersion have very vividly impressed upon us that too rapid resuscitation by warmth—i.e. a too precipitate washing of muscle acid into the blood—may be perilous to life.

We venture to suggest that this possibility should, in connexion with resuscitation procedures—and not only in those applied to the wounded—be constantly kept in view. And it would seem to us theoretically desirable, for the avoidance of resuscitation acidaemias, wherever possible, to commence procedures by a bicarbonate of soda injection.

With respect to the risk of superinducing an aesthesia acidosis on the top of a resuscitation acidosis, it is clear that security against this would be only obtainable by ascertaining, before sending the patient to operation, that his blood alkalinity had returned to the normal.

We would, in connexion with this, point out that the method of measuring the alkalinity of the blood by the method of direct titration in capillary tubes is very easily learned ; and that, once a sample of serum has been obtained, the testing takes only two or three minutes.

THE CONDITIONS UNDER WHICH THE STERILISATION OF WOUNDS BY PHYSIOLOGICAL AGENCY CAN BE OBTAINED[1]

BY ALMROTH E. WRIGHT, ALEXANDER FLEMING AND LEONARD COLEBROOK

The treatment of a bacterial infection is always approached with certain *a priori* assumptions. The surgeon who treats wounds with antiseptics assumes that the organism is unable to deal with the infecting microbes. The proper assumption would be that the organism must—for else there would be bacterial infections from which nobody could recover—be competent to deal with every species of microbe. And clearly it is impossible to know what the body is capable of achieving, or to fix any limit to its bactericidal powers, before we have found out how to bring those powers effectively to bear, and before the conditions essential to success have been realised in wounds.

Let us begin by finding out what destructive effects can be obtained with the blood, and first of all with the blood-fluids. From that we must make graduated bacterial implantations into the different kinds of blood-fluid encountered in the body : (*a*) into normal serum ; (*b*) into serum whose antitryptic power is abolished, as happens when it stands stagnant upon disintegrated leucocytes ; (*c*) into serum which has been neutralised, or nearly neutralised, by acid, as happens whenever there is any collapse or interruption of the circulation ; [2] and (*d*) into whole blood. Such graduated implantations are most conveniently made in capillary pipettes by the ' method of after-washes '.

We draw into our pipette first a unit-volume of a bacterial suspension, and then follow on—so long as there is room in the stem—with unit-volumes of serum separated by bubbles of air, or, for anaerobic culture, by bubbles of hydrogen or coal-gas. This procedure gives in the successive after-washes diminishing implantations of microbes. For present purposes we may eliminate from consideration the first after-washes—for these contain a certain proportion of the medium with which we are implanting—and may focus our attention upon the later after-washes where we have undiluted serum. We set out below in the form of a table the general result of a series of aerobic and anaerobic sero- and haemo-cultures implanted with a mixture of staphylococcus, streptococcus, colon bacillus and bacillus of Welch. That we have here, despite the symbiotic factor, a substantially correct picture of the effects produced by the different blood-fluids is shown by the fact that essentially similar results are obtained with separate implantations of each variety of microbe.

Here there was used for the implantations a mixture of equal volumes of a staphylococcus, streptococcus, colon bacillus, and *Bacillus Welchii* culture.

[1] Reprinted from *The Lancet*, 15th June, 1918.

[2] Wright and Colebrook, *The Lancet*, 1st June, 1918, p. 763.

Table I

(A) *Streptococcus pyogenes.* (B) *Staphylococcus.* (C) *B. coli.* (D) *B. Welchii.*

Serial No. of after-wash	Unaltered serum from clot								Serum deprived of its antitryptic power by addition of trypsin								Serum rendered almost neutral by addition of acid								Whole blood defibrinated							
	Aerobic culture				Anaerobic culture				Aerobic culture				Anaerobic culture				Aerobic culture				Anaerobic culture				Aerobic culture				Anaerobic culture			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
1	+ +	+ +	+	0					+	+ +	+ +	+ +	+ +	+	+	+ +	+	+ +	+ +	+ +	+ +	+	+	+	+	+	+ +	+	+	+	+	+
2	+ +	+	+	0	+ +	0	+	0	+	+ +	+ +	+ +	+ +	+	+ +	+ +	+	+ +	+ +	+ +	+	+	+	+ +	+	+	+	0	+	+	0	0
3	+ +	+	+	0	+ +	0	+	0	+ +	+ +	+ +	+ +	+ +	+	+ +	+ +	+	+ +	+	+	+	+	+	+	+	+	+	+	0	+	+	+	0
4	+	+	+	0	+	0	+	0	+ +	+ +	+ +	+ +	+ +	0	+ +	+ +	+	+	+	+	+	+	0	+	+	+	+	+	+	+	0	0
5	+	0	0	0	+	0	0	0	+ +	+ +	+ +	+ +	+ +	0	+ +	+ +	+	+	+	+	+	+	0	+	+	+	+	0	+	+	0	0
6	+	+	0	0	+	0	0	0	+ +	+ +	+ +	+ +	+ +	0	+	+ +	+	+	+	+	+	+	0	+	+	0	+	+	+	+	0	0
7	+	+	0	0	+	0	0	0	+ +	+ +	+ +	+ +	+ +	0	+	+ +	+	+	+	+	+	+	0	0	+	+	+	0	+	0	0	0
8	+	0	0	0	+	0	0	0	+ +	+ +	+ +	+ +	+ +	0	+	+ +	+	+	+	0	+	0	0	0	+	0	0	0	+	0	0	0
9	+	+	0	0	+	0	0	0	+ +	+ +	+ +	+ +	+ +	0	+	+ +	+	0	+	+	+	0	0	0	+	0	0	0	+	0	0	0
10	+	0	0	0	+	0	0	0	+ +	+ +	+ +	0	+ +	0	0	+ +	+	0	0	+	+	0	0	0	+	0	0	0	+	0	0	0

+ = Growth. + + = Abundant growth. 0 = No growth.

The broad results are set forth in Table I.

In our *unaltered serum* we have in our aerobic and anaerobic tubes and in each case throughout the whole series of after-washes a culture of streptococcus. In the anaerobic tube that culture is in all the later after-washes a pure culture. In the aerobic tube we have superadded irregularly, especially in the earlier after-washes, a culture of staphylococcus, and also a scanty growth of the colon bacillus. The bacillus of Welch nowhere puts in an appearance.

With the *trypsinised serum* cultured anaerobically we have in all the after-washes an extraordinary pullulation of each of the four implanted microbes : the streptococcus, the staphylococcus, the colon bacillus, and the bacillus of Welch. In the anaerobic tube we have again in the whole series of after-washes an extraordinary pullulation of the streptococcus and bacillus of Welch. This last microbe, be it observed, grows in the anaerobic not a whit more freely than in the aerobic tube ; indeed, it would seem to grow less freely. The staphylococcus, except in the first after-washes, fails to put in an appearance, and the colon bacillus grows sparingly.

In the *neutralised serum* we have, as in every other blood medium, streptococcus growth in both the aerobic and anaerobic tube in the whole series of after-washes. The staphylococcus also grows in all but the last after-washes. The colon bacillus grows only in the aerobic tube. Lastly, the bacillus of Welch grows in the aerobic tube in all, and in the anaerobic tube in all the earlier after-washes. Here again the anaerobic conditions seem to hinder rather than to favour the growth of this organism.

Finally, in *the whole blood* the streptococcus and staphylococcus again grow both in the aerobic and anaerobic tubes—the former microbe in each tube in all the after-washes, and the latter more irregularly, especially when we come to the later after-washes. It may also be incidentally noted that in the aerobic tube the colon bacillus and the bacillus of Welch put in in the earlier after-washes an occasional appearance.

For the surgeon these are too many bacteriological details. Let us try to extract from them only what is of practical use. The important generalisations are these :

(1) *Serum from normal blood and normal lymph* constitute for the vast majority of microbes met with in foul wounds a very unfavourable culture-medium. Of the microbes encountered in wounds only the streptococcus, the staphylococcus, and certain diphtheroid bacilli can grow in unaltered serum ; and when we make a minimal implantation the streptococcus alone gives a growth. In other words, the microbes of wounds fall into two categories : *sero-saprophytes*, which grow in corrupted, and *serophytes* in uncorrupted blood-fluids. Two practical points emerge : (*a*) when a wound contains sero-saprophytic organisms we may know that we have there corrupted discharges. And (*b*) if we can then flood the wound with wholesome serum and keep that serum uncorrupted the sero-saprophytes will disappear and the infection will be reduced to a purely serophytic, generally to a streptococcic and staphylococcic, infection. We have then, instead of a foul, a ' clean ' wound.

(2) *Trypsinised serum*—in other words, the kind of serum we have in the wound cavity and tissues when any exudate stands stagnant upon disintegrated leucocytes

—provides an excellent culture medium for practically every species of microbe. In this medium the bacillus of Welch, the streptococcus and countless other microbes

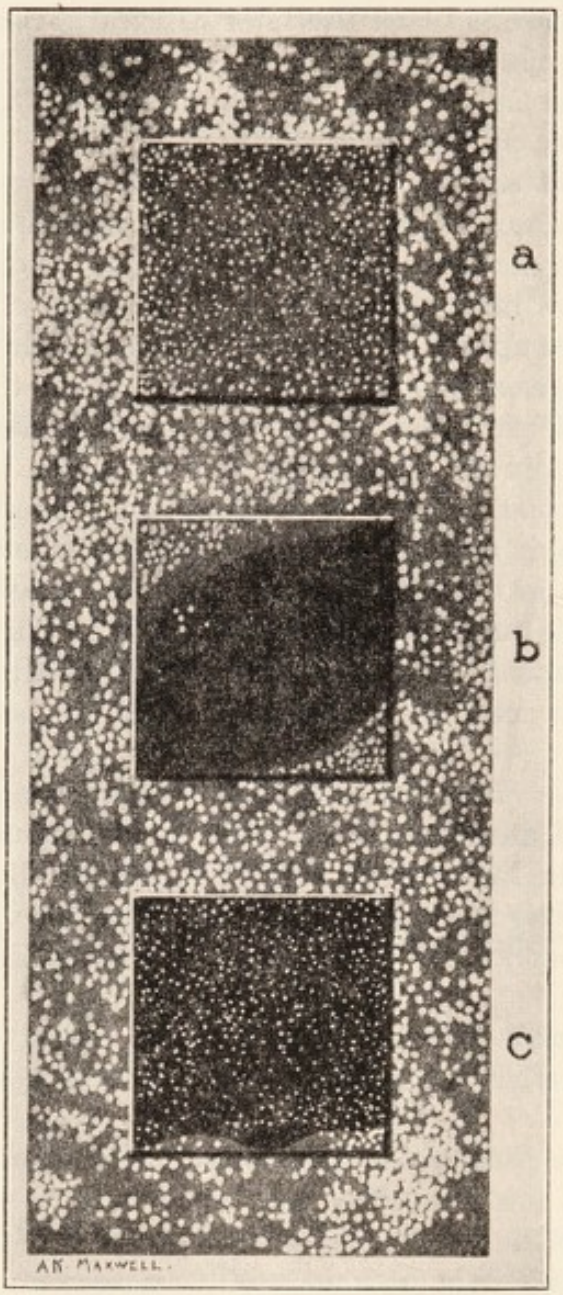


FIG. 1.

Drawing showing :

(A) The effect of imposing upon agar which has been implanted with staphylococcus, serum from the upper layer of centrifuged defibrinated blood.

(B) Effect of depositing on the same agar a drop of the leucocytic cream obtained from the defibrinated centrifuged blood.

(C) Effect of depositing upon the same agar a drop of blood from the lowest layer of red blood corpuscles of the centrifuged defibrinated blood.

all luxuriate. It must therefore be our great aim to prevent, or put an end to, the corruption of the discharges. We shall presently see all that that implies.

(3) *Neutralised or partially neutralised serum*—and we have such a serum in every

condition of collapse—is a medium in which not only the ordinary serophytes, but also all the microbes of gas-gangrene class, flourish. These gas-gangrene microbes—and this is important for treatment—are not genuine serophytes, but serophytes only of the acidosed blood-fluids. That means that a gas-gangrene infection in tissues, in the case where the circulation is uninterrupted, can be combated by draining away the acidosed lymph through incisions and replacing it by an alkaline lymph. Where the general blood-fluid is acidosed we must begin by remedying that.

(4) The *whole blood* constitutes a medium of essentially the same quality as the serum. In it, as in the serum, only serophytic microbes—and of the microbes usually found in wounds only the streptococcus and staphylococcus—will grow. And in whole blood, as in serum, the streptococcus in particular will grow from quite minimal implantations.

We must not misinterpret this. It is, as we have seen, difficult to believe that there should be microbes which can be killed neither by the blood-fluids nor by leucocytes. We must therefore scrutinise our experiment to see how the microbes can have escaped destruction. Here we must take note of the fact that the blood *in vitro* always separates itself into a corpuscular and a serum element. In defibrinated blood we have a layer of serum above and corpuscles below; in coagulated blood we have a cylinder of corpuscles surrounded with serum. If now a streptococcus escapes from the corpuscles into the serum it will, precisely as if originally inoculated into the serum, be quite out of reach of the phagocytes. Again, if a streptococcus remains lodged in the corpuscular layer or clot it will have to be discovered and killed by the phagocyte. And if not quickly discovered it will grow out into a colony, and then the phagocytes will be kept at bay. Reflection thus shows us that, even on the postulate that leucocytes can kill every species of microbe, it is only natural that streptococci should succeed in growing in whole blood.[1]

FIG. 2.

Glass laths in centrifuged blood, showing the red clot below, above this the leucocytic layer, and above this the white clot contracted round the laths.

With this we have obtained a clue as to what we must do and leave undone if we want to get ocular demonstration of bactericidal effects achieved by leucocytic agency. First, we must get rid of the serum which provides a culture medium; and, secondly, we must take steps to bring to bear upon the infection a maximum force of phagocytes. The simplest way will be to centrifuge defibrinated blood. By that we separate the blood into three layers. Above will be the serum; immediately below this is a layer of leucocytes admixed with a few red corpuscles; and below this again a deposit of red corpuscles with only a very small admixture of leucocytes. We now take an agar plate; implant it fairly heavily with

[1] *Vide supra*, p. 41.

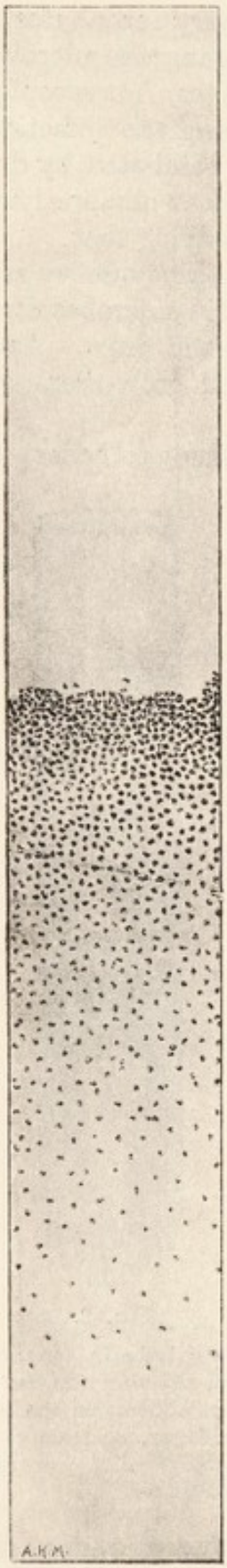


FIG. 3.—Emigrated leucocytes on a glass lath incubated in centrifuged blood for one hour.

streptococcus or staphylococcus ; and then transfer to it a drop of each of the three layers of our centrifuged blood, carefully siphoning off the last drop of serum before taking the sample of the leucocytic layer, and taking our sample of red blood corpuscles from the bottom of the tube. We then cover in each case with a cover-glass.

Here in the sample from the leucocytic layer are realised all the conditions required for the destruction of microbes by leucocytic agency. A considerable force of leucocytes has been brought together. A moist chamber is provided to keep them alive. Their locomotion is facilitated by their disposal between two closely apposed surfaces. And the excess of serum which provides a culture medium for the microbes, and conveys them out of reach of the phagocytes, has been removed.

The results obtained on cultivating the three specimens are shown in Fig. 1.

In the serum specimen we have just the same number of colonies as upon the surrounding agar.

Under the cover-glass which covers the specimen from the leucocytic layer almost no colonies make their appearance.

And in the specimen where we have practically only red corpuscles again a great number of colonies come up.

The concentration of the leucocytes and the elimination of the excess of serum here shown to be requisite for the achievement of conspicuous bactericidal effects can be obtained also in another way—that is to say, by emigration. Just as in the body leucocytes will come out from the capillary blood, so outside the body they will come out from a blood clot. They will attach themselves to glass, and we can then apply this to an agar surface implanted with microbes.[1]

Where we want to operate with denser masses of leucocytes than simple imposition of blood upon glass will furnish, we can—and this will be analogous to emigration from capillaries crowded with leucocytes—concentrate our leucocytes by centrifugalisation before we set them to emigrate.

The technique is quite simple. We prick the finger

[1] Wright, "New Methods for the Study of Emigration, etc.", *The Lancet*, 26th Jan., 1918.

and fill our blood into a tube about 8 mm. in diameter and 3 to 5 cm. in length. We now centrifuge, having first inserted into the blood a glass lath cut from a thin microscope slide—or, better, as shown in Fig. 2, a couple of such laths placed back-to-back. We now incubate for an hour.

During this time the leucocytes attach themselves in ever-increasing numbers to the laths (Fig. 3), giving us across the middle a band some 3 to 5 mm. in breadth in which the leucocytes lie absolutely edge to edge, and below this band a certain number of scattered leucocytes.

We now with forceps gently disengage our laths from the clot, draining off superfluous serum ; turn the leucocyte-covered face down and apply it to an agar surface thickly implanted with staphyloccus, streptococcus, or, if we like, any other organism.

We then incubate and take note of what happens. Under the upper part of the lath—that part which is quite free from leucocytes—the streptococcal or staphylococcal colonies come up just as thickly as on the surrounding agar—the staphylococcal colonies, however (because of the anaerobic conditions), less luxuriantly. Across the middle of the lath where the leucocytes are densest we have a clear band

TABLE II.—*Showing the Bactericidal Effect exerted by emigrated Leucocytes operating in their own Serum upon Streptococcus Pyogenes and Staphylococcus*

From whom obtained	Nature of microbe with which tested	No. of colonies which developed upon 1 sq. cm. of implanted agar incubated under glass carpeted with emigrated leucocytes	No. of colonies [1] which developed upon same area of same implanted agar incubated under clean glass	Proportion of implanted microbes killed
		Normal Bloods		Per cent.
A. E. W. -	Streptococcus	16	210	92·4
W. D. T. -	,,	8	210	96·2
N. M. K. -	,,	15	210	93
A. F. -	,,	12	100	88
A. F. -	,,	{31 40 / 42 26} average 35	4,900	99
L. C. -	,,	3	5,000	Over 99·9
		Bloods from Patients whose Wounds were Infected with Streptococcus		
Pte. C. -	Streptococcus	0	50,000	100
Pte. F. -	,,	0	50,000	100
Sgt. S. -	,,	0	50,000	100
Pte. H. -	,,	20	5,000	99·6
		Normal Bloods		
J. F. -	Staphylococcus	9	80	88
L. C. -	,,	20	202	90
A. F. -	,,	{0 / 2} duplicate tests	250	{100 / 99}

[1] Where these were too numerous for direct numeration their number was arrived at by counting the number of colonies which developed on agar implanted with a 100- or 1000-fold dilution of the original bacterial suspension.

entirely free from colonies. And on the lower part of the lath we have only scattered colonies. (Fig. 4.)

Control experiments with laths dried before they were imposed upon implanted agar show that it is the living leucocytes that are here the sterilising agents.

And again control experiments with laths washed off with physiological salt

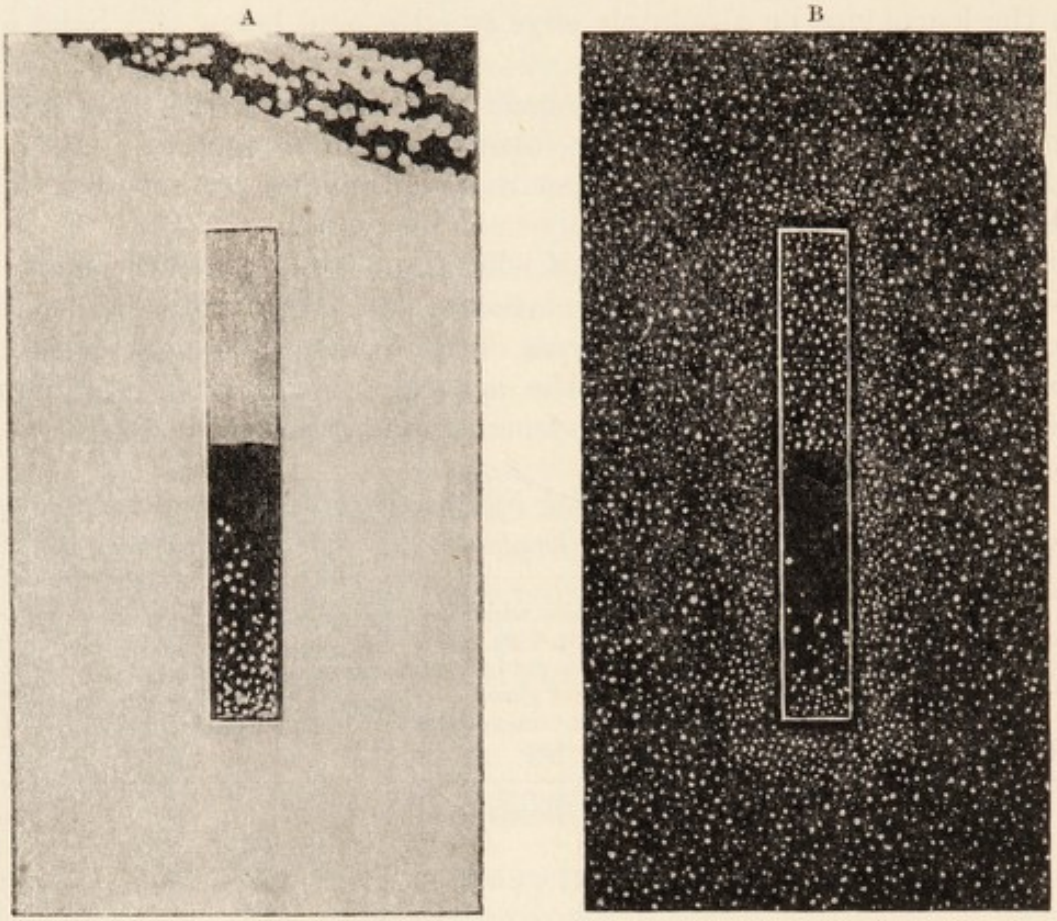


FIG. 4.

Glass laths, such as are shown in Fig. 3, imposed on agar surfaces implanted (A) with staphylococcus, (B) with a haemolytic streptococcus pyogenes.

solution or heated serum show that the opsonic properties of the serum are not essential to the achievement of bactericidal effects.

With these and the foregoing experiments the problem of killing serophytic microbes by leucocytic agency has at last found its solution.

An idea of the magnitude of the bactericidal effects achieved can be obtained from Table II. The films of leucocytes here employed were derived in each case from clots imposed upon a glass surface.

We pass now to consider the application of this to wounds. It will have an application—not to foul wounds with corrupted exudate and a sero-saprophytic infection, for in such wounds phagocytosis is abolished—but to clean wounds, that is, wounds with uncorrupted exudate and purely serophytic infection.

If we take from such a clean wound a drop of thick pus, place it upon an agar

plate, and put down upon it a cover-glass—let us call this a *bio-pyo-culture*—we shall have there substantially the same conditions as when we imposed our leucocyte-

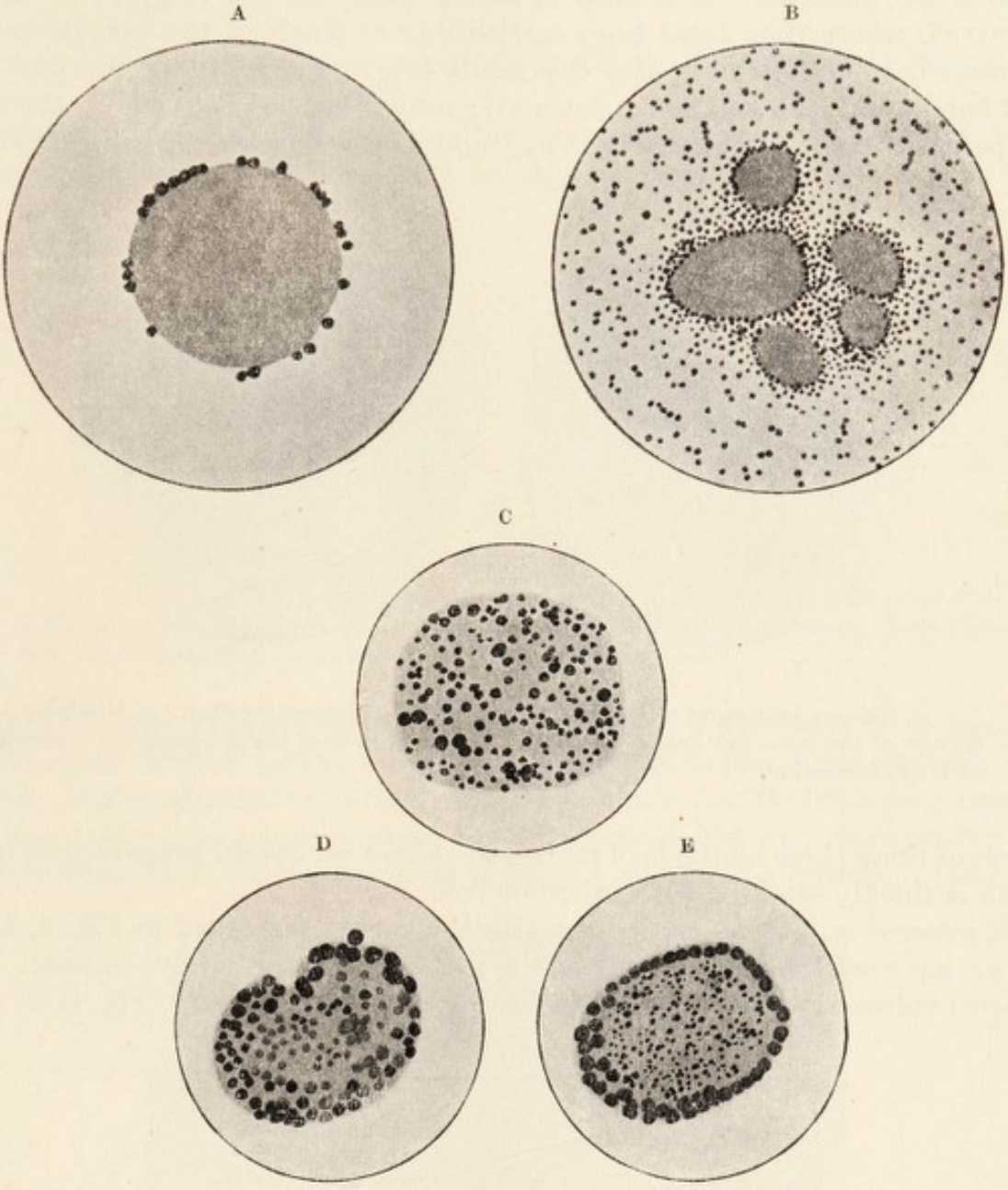


FIG. 5.

A, Pus from a clean wound spread out on a sterile agar surface under a cover-glass and incubated. Streptococcus colonies develop only in the narrow ring of serum beyond the edge of the pus. B, The same pus stirred up with serum, but in other respects treated in exactly the same way. Streptococcus colonies develop in the serum everywhere round the pus. C, The same pus dried on to the cover-glass before it was imposed upon the agar. D, The same pus heated to 46° C. There are here less numerous colonies than in C and E. E, The same pus frozen and thawed.

covered laths or cover-glasses on an implanted agar surface; and Fig. 5 shows that we obtain an essentially similar result.

In A, where the leucocytes form a continuous sheet, the central area of the

specimen remains sterile. On the margin of the pus a certain number of colonies—here they are colonies of streptococcus—come up. With this result we may contrast that obtained when we mix a drop of serum with the pus (Fig. 5 B). Here the streptococci, where they have been carried out of reach of the phagocytes, grow unrestrained. We may note also the result (Fig. 5 C) of drying the pus (it was merely spread out thin and left uncovered); and of heating it to 48° C., the thermal death-point of the leucocytes (Fig. 5 D); and of freezing and thawing it (Fig. 5 E).

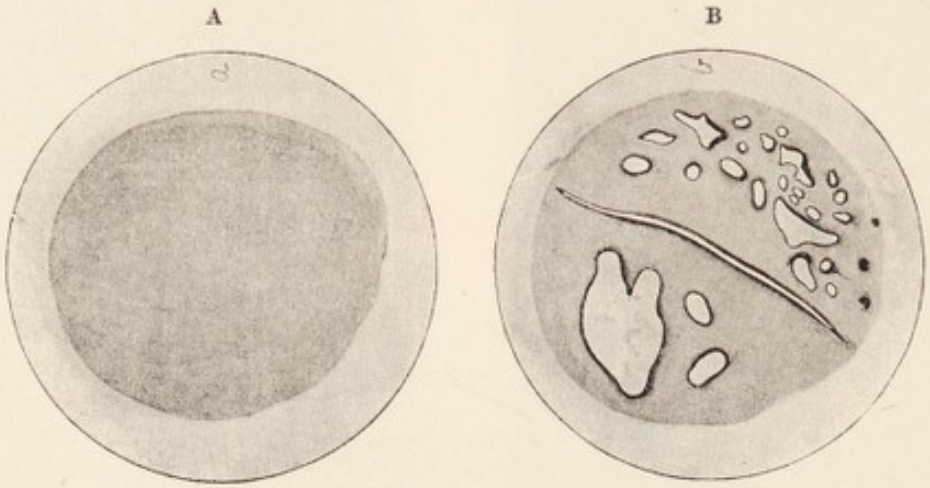


FIG. 6.

A, Bio-pyo-culture of a pus containing the gas-gangrene bacillus. B, Necro-pyo-culture of the same pus heated to 46° C. showing growth of the gas-gangrene bacillus with gas formation.

By each of these three methods of *necro-pyo-culture* we obtain preparations in which the pus is thickly studded with microbic colonies.

Of interest in this connexion are also the results displayed in Fig. 6, A and B. In A we have with the unheated pus a perfectly sterile bio-pyo-culture. In the necro-pyo-culture made with the pus heated to 46° C. we have (Fig. 6, B) colonies

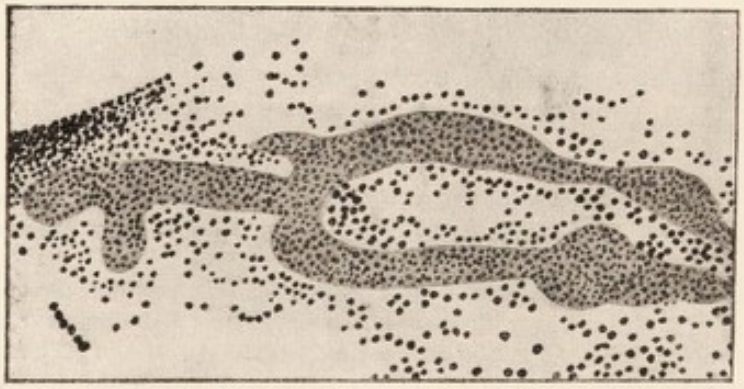


FIG. 7.—BIO-PYO-CULTURE.

Pus from a furuncle spread out on agar under a cover-glass and incubated. Innumerable staphylococcus colonies have developed in the pus and in the surrounding liquor puris.

of the bacillus of Welch with gas formation. The reader will appreciate that these cover-glass preparations give us anaerobic conditions.

The next figures bring before the eye a point of quite cardinal importance—that of the quality of the leucocytes in pus.

We have in Fig. 7 a bio-pyo-culture from a boil. The leucocytes here are quite ineffective.

In Fig. 8 A we have a bio-pyo-culture from a clean wound which has been left to itself for 24 hours. The pus here is very far from ineffective, but it fails to

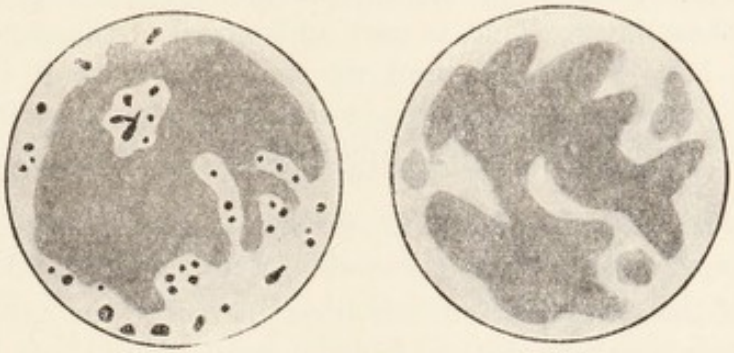


FIG. 8.—BIO-PYO-CULTURES.

A, From a clean wound in which pus had collected overnight (a certain number of colonies are seen in and around the pus); B, from a clean wound which had been carefully washed out four hours before. The pus sterilises itself.

sterilise itself, and so falls short of standard. In Fig. 8 B we have a bio-pyo-culture from the same kind of wound which had four hours before been carefully washed out with physiological salt solution. We have here a pus that sterilises itself.

A pus such as this has in point of fact a bactericidal power incomparably greater than manifests itself when we impose it upon a sterile agar surface. How large a

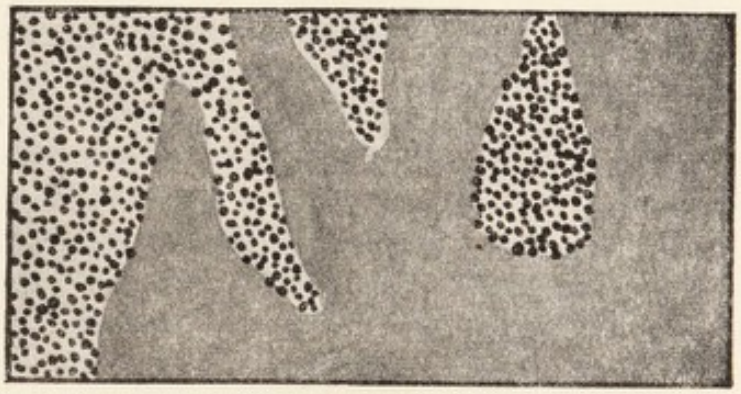


FIG. 9.

Pus spread out under a cover-glass upon an agar surface heavily implanted with staphylococcus. Here the agar surface which is covered by pus is sterile, while the portions of the surface which are not covered by pus have grown innumerable colonies.

surplus of bactericidal power it possesses is made manifest when we impose it upon an agar surface thickly sown with staphylococcus or streptococcus, or, probably,

any other microbe. Fig. 9 will convey to the eye some notion of the magnitude of the bactericidal effect then exerted.

We thus see that the results obtained with leucocytes from a clean wound surface are precisely the same as those with leucocytes which emigrate from our blood-clots. In each case what is essential to the achievement of bactericidal effects is the employment of freshly emigrated leucocytes, the keeping of these alive and active, and the removal of the excess of serum which would carry the microbes out of reach.

It will be obvious that the problem of sterilising the actual wound surface must be soluble along these lines. That is part and parcel of the general problem of the treatment of the infected wound, and we shall deal with it in its place. First, however, let us see whether it is possible to sterilise a wound surface by an antiseptic applied directly, and by an antiseptic applied after washing with saline solution.

Effect of Direct Applications of an Antiseptic to Flat Wound Surfaces, and of Applications preceded by thorough washing with Physiological Salt Solution

The results of these applications are brought before the eye in Fig. 10.

In A we have a bio-pyo-culture from a clean wound left to itself overnight. There are here only a few streptococcal colonies—in other words, only a few streptococci have here escaped destruction. In B and C we have cover-glass specimens taken and cultured in exactly the same way after the one half of the surface (B) had been washed with eusol and the other half (C) with physiological salt solution. What calls for notice is, first, that while we have in A only a few bacterial colonies, and a background of pus, we have in B and C very numerous colonies and a quite bare background.

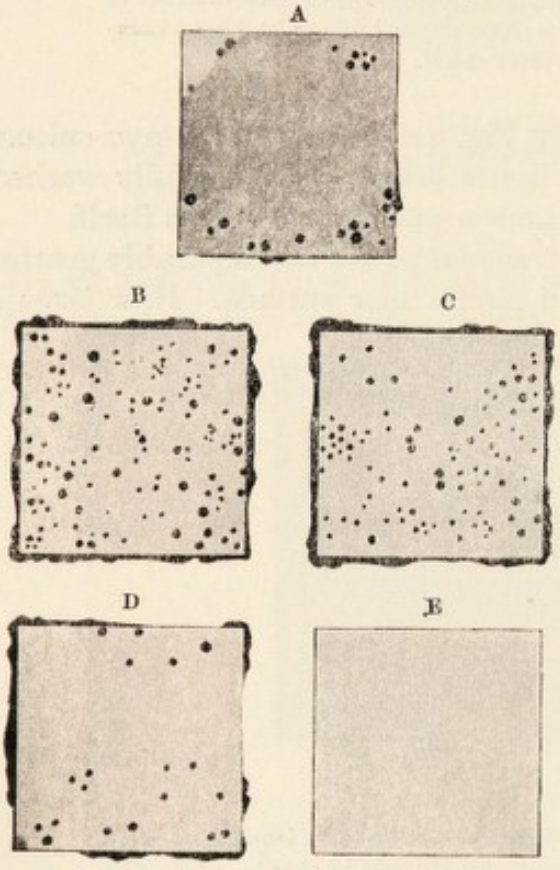


FIG. 10.

Bio-pyo-culture from clean wound and cultures made from it after washing with eusol and physiological salt solution. Description in text.

That teaches that the mechanical effect of washing is much more important than the chemical effect of the washing fluid.

We wash away the leucocytes and leave behind the microbes ; and these, now escaping destruction by the leucocytes, grow out into colonies. That the microbes on the wound-surface are after eusol just as numerous as after physiological salt solution is, no doubt, due to the antiseptic expending all its strength upon the overlying pus. The microbes which remain are presumably those which were hidden away under leucocytes.

In D and E we have again cultures made by the same method from the wound-surface after further treatment with eusol. In D—i.e.

in the preparation made from the half of the wound which has been twice treated with eusol—sterilisation is, as we see, incomplete. On the other hand, in E, the preparation made from the half of the wound which was washed first with physiological salt solution and afterwards with eusol, we have complete sterilisation. In D the microbes were no doubt buried under coagulated albumin ; in E the washing off of the albuminous discharges must have left the microbes without protection.

The experimental data just set out make it clear—and, indeed, it never could have been doubted—that it is possible to sterilise out of hand the superficies of a wound by the agency of antiseptics, *provided that that surface has been washed perfectly clean from albuminous substances.*

Practical Application of the Physiological and Biological Lessons we have learned to the Treatment of Wound Infections

It will be obvious to all who have not the bandages of tradition over their eyes that our treatment of wounds will be successful or unsuccessful according as it falls in with or disregards physiological and biological facts such as those we have been dealing with. And it is clear that whenever new facts of this kind are brought to light we are bound to review the whole of our treatment, and see whether any of our treatment runs counter to the facts we have learned ; and whether each of these is turned to full account. Let us carry this out, asking ourselves in connexion with each successive phase of the wound what would be the proper treatment to follow. We may—though loth to waste time in discussing treatment which is obviously right and widely accepted—say first a word on the subject of early primary suture.

Early Primary Suture

This procedure, recently taken over by us from the Belgians and French, stands on precisely the same footing as primary suture of wounds as carried out after ordinary surgical operations. In wounds which have received early surgical treatment—that is to say, in wounds which have been fully opened up and mechanically cleansed and resected—the conditions encountered are, one may say, identical with those in most civil operations. In both cases we are bringing together healthy tissues on which there is at most a minimal microbic implantation. And in both cases—except when we leave dead spaces and allow these to fill up with lymph, and have in these a streptococcus implantation—the body can very safely be trusted to deal with the few scattered microbes. The limitation here enunciated is one which every intelligent man, who had studied the first column of the first experiment in this paper, would have anticipated.

From early primary suture we turn to the infected wound. There are two categories of infected wounds.

The first is that of *foul wounds*. These will be (*a*) wounds which have never been opened up and cleansed and resected. With these may be grouped (*b*) wounds that have been sutured, but have, by reason of imperfect cleansing and resection, afterwards broken down ; and (*c*) wounds originally clean which have been long untended.

The second category is that of *clean wounds*. These may be (*a*) unsutured wounds which have at the outset been properly cleansed and resected and have afterwards received due attention ; and (*b*) wounds originally foul which have been cleansed. In the class of clean wounds we may perhaps also place properly resected sutured wounds with a streptococcus infection which have at the first sign of trouble been reopened.

All wounds which fall into the category of *foul wounds*—i.e. all those with unwholesome slough-covered walls, tryptic discharges, and a sero-saprophytic infection—ought to be treated in one way.

All *clean wounds*—i.e. all those with wholesome walls, uncorrupted (i.e. anti-tryptic) discharges, and a purely serophytic infection—in another.

Treatment of Foul Wounds

The first step here must be to clean off all the sloughs which, by continuously corrupting the exudation, favour the pullulation of every species of microbe in the wound. Then, having rendered our wound-surface wholesome, we must get rid of all the sero-saprophytic bacteria.

The first object can be achieved by tryptic digestion. When it has done its work the second can be achieved by an inpouring of wholesome lymph into the wound.

If the wound is simply left to itself, Nature herself slowly takes in hand the digestive cleansing of the wound, making use of the trypsin set free from leucocytes which are broken down by microbic agency.

But infinitely faster digestive cleansing can be obtained if we ourselves rapidly break down the leucocytes in the sloughs and in the pus. We can do so by soaking the slough-covered walls with 5 per cent. salt, afterwards permitting this to dilute itself by diffusing out into the exudation which the hypertonic salt draws into the wound cavity. Cleansing digestion completed, the hypertonic salt continues to act as a lymphagogue, and the inpouring of antitryptic serum makes an end to the sero-saprophytic infection. The serophytic infection also is held in check so long as the concentration of salt in the discharges is maintained at a high level.[1]

Immediately related with the treatment of foul wounds is that of gas-gangrene infection of the tissues. Here we have, as in the foul wound : (*a*) necrotic tissues which must be removed—in this case by the knife ; (*b*) altered lymph to be got rid of and be replaced by wholesome lymph ; and (*c*) a saprophytic microbe (the bacillus of Welch) which can subsist only in degenerated—i.e. acidosed or trypsinised—blood-fluids.

The point of treatment which is every day overlooked, and therefore requires to be emphasised, relates to the necessity of replacing, when extirpation has to be left incomplete, the degenerated by wholesome lymph. The proper agency for doing this is a local lymphagogue such as is available in hypertonic salt solution.

Neither in foul slough-covered wounds nor in gas-gangrene infection are antiseptics of any service whatever. For these cannot penetrate sloughs, or pockets of

[1] To this point we shall recur when we come to deal with the question of a phylactic dressing for use where the wound cannot be at the time surgically cleansed and resected.

pus, or infected tissues. Nor do they influence that corruption of the discharges which favours the pullulation of every species of microbe.

Nor again can closure of the wound—a procedure which is, as we shall realise, applicable to clean wounds with serophytic infection—be resorted to where we have corrupted discharges and a sero-saprophytic infection.

Treatment of Clean Wounds

We have seen that treatment in the case of foul wounds resolves itself into a cleansing digestion of the wound cavity, followed by an elimination of the sero-saprophytes by local auto-sero-therapy. In the case of clean wounds we have to complete the sterilisation by the destruction of the serophytic bacteria. We can, as we have seen, have recourse to the patient's leucocytes or to chemical antiseptics —i.e. to auto-leucocyto-therapy or chemotherapy.

By both methods sterilising effects can be obtained. But the difficulty is to obtain a sterilisation which shall be topographically complete.

In our bio-pyo-cultures we had colonies of streptococcus coming up around the margin of the preparation whenever there was in the pus any trace of superfluous fluid. Exactly the same must happen on the face of the wound. There will often be lacunae in the leucocytic covering, and in these there will be septic fluid.

In the case where we go to work with an antiseptic we must, as we have seen, as a preliminary, wash off every albuminous element which might quench that antiseptic or prevent it penetrating.

This—it is not necessary to insist—will often be difficult of attainment. If we have upon the face of our wound pits or sulci, or islands of inspissated pus, we shall inevitably, by reason of the incomplete washing, have unsterilised patches. From such foci, from the septic lacunae in pus already spoken of, from bacterial niduses below the surface, and from the skin margin and the exterior, the sterilised tracts of the wound will continually be subject to reinvasion.

From this we see that that method of sterilisation will be the method of choice which, leaving the fewest septic foci, most efficiently protects the sterilised tracts against reinfection.

In relation to this it is evident that a tract which has been washed quite clear of leucocytes, and then sterilised by antiseptics, is a tract left quite without protection against bacterial invasion. As soon as ever a drop of fluid from a septic focus reaches it, infection will be restarted, and the sterile area will remain in such unprotected condition until, sooner or later—that will depend upon the antiseptic—the leucocytic guard returns.

Quite different are the conditions upon a clean wound-surface which is being sterilised by leucocytic agency. Pus from such a surface possesses—we saw this in our experiments—a quite astonishing phylactic power. With that the superiority of sterilisation by leucocytes over sterilisation by antiseptics is, as it seems to us, quite settled.

But it is of interest and importance to inquire how long the protection afforded by the leucocytes will last. The data of a typical experiment are brought before the eye in Fig. 11. We have here a series of bio-pyo-cultures from a clean wound.

A is a specimen taken from the wound after it had been left to itself for a night. A few colonies of streptococcus are in evidence. They suffice to show that this pus can no longer give effective protection.

In B we have an impression-preparation of the wound taken immediately after washing with physiological salt solution and implanted on agar. It will be seen

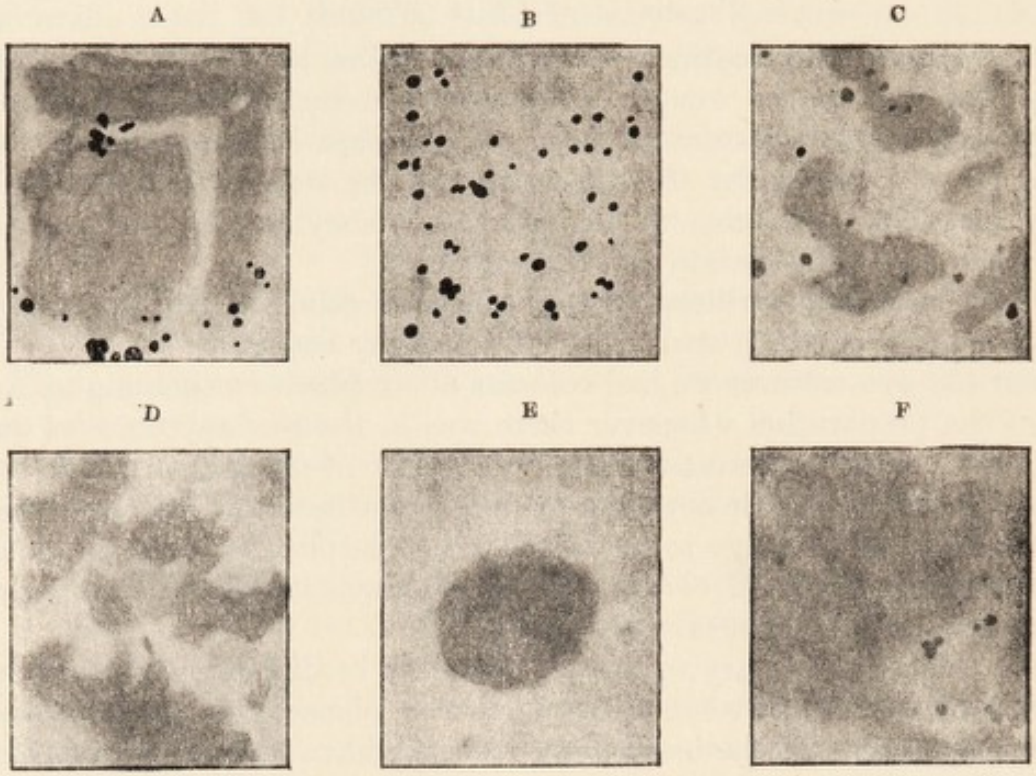


FIG. 11.—The description will be found in the text.

that the cultural result is exactly the same as in a similar washing experiment already figured (Fig. 10). In C, D and E we have bio-pyo-cultures taken respectively 2, 4 and 8 hours after washing. The first of these is almost and the other two are quite sterile. And finally we have in F a bio-pyo-culture taken the next morning. Here the original conditions have returned—that is to say, we have again a pus which can no longer give effective protection.

Question as to whether and in what respects the Closure of the Wound furnishes more favourable Conditions for Sterilisation

We have learned in our experiments conducted with blood the conditions which are requisite for sterilisation by leucocytic agency.

We have seen that we must employ freshly emigrated leucocytes, employ them if possible in serried masses, that we must keep them in good condition, provide them with ready access to the microbes, and must, when combating serophytic microbes, drain off every drop of superfluous serum so as to prevent proliferation out of reach of the phagocytes.

And in our experiments conducted with pus there has been brought out that while our bio-pyo-cultures are not unfrequently, our necro-pyo-cultures are only

very rarely sterile. That teaches that the leucocytes from a clean wound surface are competent to do much more effective sterilising work than they are actually doing in the open wound. It follows as a corollary that if conditions more like those which our experiments have shown to be requisite can be obtained by suturing, we shall by suture assist sterilisation.

Let us therefore ask ourselves in what way suturing would change the conditions in the wound. It will, of course, keep off external infection. This is not worth spending any words on.

Let us see what we do for the leucocytes. By bringing together the two faces of our wound we double the leucocytic forces available at any point, filling in the lacunae arising from irregular distribution of the leucocytes, and dispersing the serum which has collected in those lacunae. Further, we protect the leucocytes from desiccation, and by the fact that we dispose them between two apposed sur-

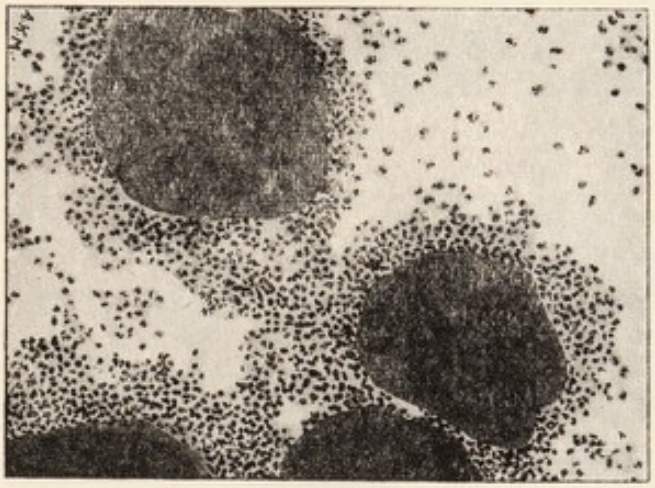


Fig. 12.

Leucocytes of pus aggregating themselves in dense rings round colonies of staphylococcus.

faces we enable them to move about more freely and to congregate to infected points. In illustration of this we subjoin Fig. 12. Here a bio-pyo-culture was made by disposing pus in a thin layer between an agar surface and a cover-glass. The prominent objects in the illustration are colonies of staphylococcus encircled by leucocytes. These, of course, are leucocytes which have rallied to the focus of infection.

But when we suture the wound we affect also elements other than the leucocytes. In particular we influence the lymph exudation. If our operative procedure is really successful we give effective support to the walls, and, by the pressure thus brought to bear, restrict the exudation. If, on the other hand, we leave behind in the wound hollow spaces, then suture simply confines the fluid. And then if streptococci find access to that fluid all the good we have done is undone. For the streptococcus is provided with the means of multiplying out of reach of the phagocytes.

Question of Policy as between (a) suturing the Wound and (b) leaving it open and applying 'Physiological' Treatment

The question of policy is here that of balancing the advantages of closing the wound, bound up as these are with the risk of occasional failure, against the disadvantage of leaving the wound open. We have seen that if hollow spaces are left and these fill up and become infected the wound will have to be reopened. There

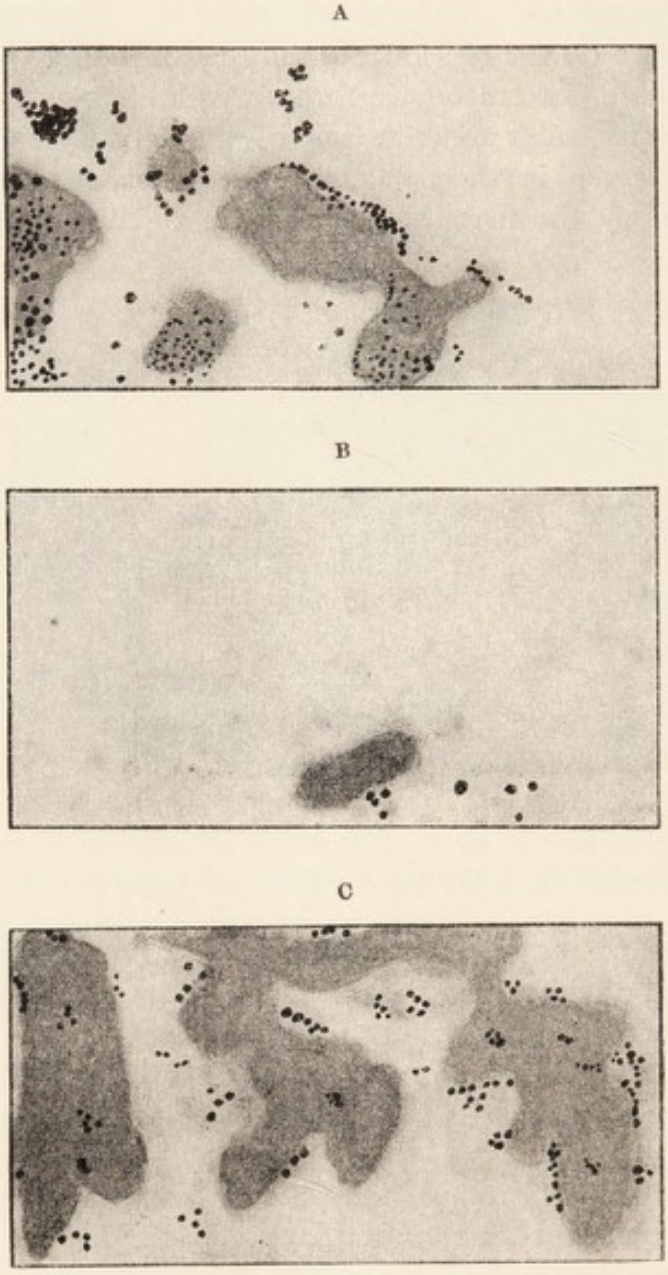


FIG. 13.—The description will be found in the text.

will be two ways of reducing this risk. Precautions can by applying pressure be taken against leaving dead spaces. This is a question of surgical technique and also a question of choosing for the operation a time when some of the hollows have filled up, and the tissues are not yet too much indurated by scar formation.

And again the microbic infection can in the open wound be restricted. This is a question of making our sterilising operations as effective as is possible. The important point to emphasise here is that to promote exudation—as, for instance, by the application of hypertonic saline solution—is to promote the serophytic infection ; to leave the discharges to take care of themselves under impermeable protective is generally to leave the infection unaltered ; and that to remove all superfluous fluid, while keeping the wound surface moist, is the way to diminish the infection.

We bring before the reader's eyes in Fig. 13 the result of a comparative experiment undertaken upon a clean wound. In A is depicted a bio-pyo-culture made from the wound merely covered in with impervious protective. We note that a certain number of colonies of streptococcus have come up. That was to be expected from a procedure which confines the serum and so provides a culture medium for the streptococcus. In B we have a bio-pyo-culture made from the same wound after it had been left for 24 hours under a dressing of dry gauze. Our culture is here almost sterile. And we can learn from this that by merely absorbing the excess of serum we can carry the sterilisation of a clean wound up to a point where we get a sterile bio-pyo-culture. In C we have another bio-pyo-culture from the same wound after return to simple protective covering. Here, again, we have a growth of streptococcus.

Question as to whether it is possible to obtain a pansement d'attente*—i.e. a Phylactic Dressing for use where the Wound cannot at the time be surgically cleansed and resected.*

Among the problems of treatment there is one which up to this has been omitted from consideration. This is the question as to whether anything can be done to restrain the bacterial infection in the case of patients brought in off the field who have large open wounds and cannot for the time being receive full operative attention.

A word may be devoted to this. We believe that hypertonic salt solution fulfils all the requirements of a phylactic dressing and *pansement d'attente*.

In the first place, by inhibiting leucocytic emigration, it prevents that corruption of the discharges which prepares the way for sero-saprophytic infections, and above all for gas-gangrene infection. Again hypertonic saline solution, by virtue of its lymphagogic properties, prevents that drying up of the wound and shutting down of the surface capillary circulation which must, more than any other factor, produce sloughing of the wound surface. And, lastly, by direct action of the salt the hypertonic saline solution will, so long as it remains sufficiently concentrated, inhibit the growth of serophytic microbes in the exudation. All that would be necessary would be to cover over the whole wound surface with several layers of gauze soaked in 5 per cent. salt (i.e. saturated salt solution seven times diluted) ; to back this with a plugging of gauze steeped in saturated salt solution, and then to cover with a layer of impervious protective.

What we have to unlearn

It is a very penetrating observation—made by Professor William James—that we never fully grasp the import of any true statement until the opposite untrue statement is clearly set over against it in our minds. To this end, we may now, in concluding, set over against what has been ascertained to be true that which is erroneous.

1. It has been erroneously inculcated that every wound should be sterilised before closure ; and that, therefore, *primary suture* should be avoided and *secondary suture* undertaken only after a course of antiseptics.

There is now no question, *with respect to primary suture*, that the wound taken after early surgical cleansing and resection is as good as sterile ; and, *with regard to secondary suture*, undertaken with a wound in good condition and a purely sero-phytic infection, that suture, provided it leaves behind no infected dead spaces, directly contributes to sterilisation.

2. It has been taught that we should judge of the fitness of the wound for closure by necro-pyo-cultures and direct microscopic examination of the pus.

We have learned that it would be infinitely more reasonable to base our judgments upon the results of bio-pyo-culture.

3. It has been taught that suture cannot be successful in a wound containing a haemolytic *Streptococcus pyogenes*.

We have seen that leucocytes can, given proper conditions, successfully combat this, and of course all other streptococci ; and that these conditions can be realised in connexion with the suture of wounds.

4. It has been taught that for the removal of sloughs from foul wounds chemical solvents such as hypochlorites are required.

We have learned that sloughs can be removed by tryptic ferment set free from disintegrated leucocytes, and that the liberation of this ferment can be greatly accelerated by breaking down the leucocytes in the discharges with hypertonic saline solution.

5. Lastly, it has been taught in connexion with antiseptics that sterilisation is obtainable only by continuous or very frequently repeated application.

We have learned that there is nothing to prevent any part of a wound surface which has been washed quite clear of albuminous matter being sterilised by a single application of antiseptics.

In concluding we wish to express to Sergeant A. K. Maxwell, our illustrator, our thanks for his care and skill.

A LECTURE ON THE LESSONS OF THE WAR AND ON SOME NEW PROSPECTS IN THE FIELD OF THERAPEUTIC IMMUNISATION[1]

(Delivered before the Royal Society of Medicine, 25th February, 1919)

(Embodying Research Work done in conjunction with Dr. Leonard Colebrook)

Gentlemen,—The war has taught two great lessons in immunisation. It has taught the surgeon that if he provides the requisite conditions—and he does provide them when he excises all devitalised and heavily infected tissues and brings together the walls of the wound—the protective mechanism of the body can, without any antiseptics, deal successfully with every kind of infection. I say advisedly every kind of infection. For the experiments with leucocytes—which I shall presently show you—and experience with retarded suture (where we can count on emigration into the wound) have conclusively shown that leucocytes can kill streptococci, and that one can successfully close upon streptococcic infections.

The second great lesson of the war has been learned in connexion with antityphoid inoculation. The signal success of that procedure has made it manifest to everybody that the natural powers of resistance of the human body can be powerfully reinforced by inoculation.

I propose here to take as my text those two teachings of experience; and I shall try to show you that when we have arrived at a proper comprehension of these, we shall have realised the principles upon which therapeutic immunisation, and, I would urge, all treatment of bacterial disease, must proceed.

First Principles.

Let me start quite at the beginning. Long after the principle of prophylactic inoculation had established itself in medicine, it was believed that to inoculate microbes into the already infected system would be as illogical as to instil further poison into an already poisoned system. Pasteur was the first to teach us here a distinction. He pointed out, in connexion with immunisation against rabies, that a vaccine might legitimately come into application in the incubation period. That was the beginning of therapeutic immunisation; and from that time forth it was recognised that you may legitimately inoculate in the incubation stage, and try to get in advance of the infection. But it was in everybody's mind that immunisation took ten days to establish itself. When I showed in connexion with antityphoid inoculation that bactericidal substances were very rapidly elaborated, it became plain that this involved shifting the old landmarks and taking in further territory for therapeutic immunisation, and one had to put to oneself all sorts of penetrating questions. One had to ask oneself in connexion with 'generalised infections' at what particular stage of the infection one was to regard the body as overmastered

[1] Reprinted from *The Lancet*, 29th March, 1919.

by the bacterial poison, and incapable of further immunising response. Again, in connexion with ' localised infections ' one had to inquire whether they should not be envisaged as general infections indefinitely arrested in their incubation stage, and whether they might not, in consonance with that, be brought within the sphere of inoculation.

Further consideration suggested that the problem of therapeutic inoculation can be approached also from a point of view different from that taken up by Pasteur. With respect to immunising response, the body had been visualised as a single and undivided unit. That is clearly erroneous. One region of the body may be making immunising response while the other is inactive. For instance, in the stage of incubation it is presumably only the region which is actually harbouring the microbe, and in the stage of generalised infection it is presumably the entire body which is incited to respond. And again, in localised infections we may—making here some reserves—assume that we have only localised response.

Placing ourselves at this point of outlook, therapeutic immunisation will, it is clear, be theoretically admissible so long as there remains in the body any part which is not already making its maximum immunising response. And the programme of therapeutic inoculation would accordingly consist in exploiting in the interest of the infected regions of the body the immunising responses of the regions which are uninfected.

Results of Vaccine Therapy.

Keeping that now in view, let me try, very briefly, to tell you what are, in my view, the results which have been achieved by applying this therapeutic method. I can do that in a very few words.

In every form of infection a certain quota of unequivocal successes may be credited to the method, and especially successful results have been obtained in furunculosis and acute inflammatory sycosis ; in ' poisoned wounds '—meaning by that localised cellulitis set up by a streptococcus infection ; in streptococcal infections taking the form of lymphangitis, in erysipelas ; in tubercular adenitis, tubercular joint infections, tubercular dactylitis, tubercular orchitis, and tubercular affections of the eye, especially in phlyctenules of the conjunctiva ; again in bronchitis, in coli cystitis, and gonorrhoeal rheumatism. The most dramatic and convincing—convincing because here no other therapeutic measures are employed as adjuncts—are the successes obtained in streptococcal lymphangitis, in streptococcal cellulitis—I am thinking of those cases which have already been incised without striking benefit—and in conjunctival phlyctenules.

When we analyse the successes and failures [1] of vaccine therapy the following points come out quite clearly :

[1] I here, as clear thinking exacts, exclude from the failures of vaccine therapy the failures of that preventive inoculation against individual infections to which vaccine therapy is the usual precursor. The efficacy of such prophylactic procedure is a question apart. But I may usefully point out to you that the superior credit which attaches to antityphoid inoculation, and preventive inoculation against infective diseases generally, as compared with preventive inoculation against what I may call *individual infections*, is probably attributable to the fact that, in the case where we are dealing with an infective

(1) Vaccine therapy is generally unsuccessful where the infection—as in phthisis—is producing constitutional disturbance and recurring pyrexia.

(2) Vaccine therapy is also generally unsuccessful where we have to deal with unopened abscesses, or sloughing wounds with corrupt discharges.

(3) In long-standing infections vaccine therapy is much less successful than in recent infections.

To see what auxiliary measures should be applied in these cases, I must take you back for a moment to the region of general principles. And here I want you to allow me the use of some new technical terms.

A Few Words on Technical Terms.

May I preface the bringing forward of these by a few words of disculpation? I am not blind to the fact that the natural man has an acute disrelish for new technical terms. He feels when he meets with them the same sort of ennui as when asked to learn a string of surnames before he has any interest in the persons who bear them. But let me ask you to look also on the other side, and to reflect how unsatisfactory an experience it is to have had intellectual traffic with an interesting man and to have been left in ignorance of his name. We then experience a definite want. We want a labelled pigeon-hole in our minds into which to put away for safe keeping our new mental record, and we are conscious that we shall have difficulty in remembering and turning up that record unless we have it properly registered under a name. I would further have you reflect that if any one of us were this moment invited to give an account of the people we had met in the course of the day we should find that we remembered practically only those few who happened to be known to us by name. Now, with ideas it is exactly the same as with men. Only those which have been fitted out with names occupy any place in our thoughts. All unnamed concepts, even though they may have formulated themselves quite clearly in our minds, immediately go out of our thoughts and get lost. So no new concept can be helpful until there has been devised for it a technical name.

---

disease, the external circumstances are as favourable to success as they are in the case of inoculation against ' individual infections ' unfavourable.

Let us reflect that in the case of inoculation against an infective disease it is not usually a requirement that the patient should come into his immunity immediately, or that a negative phase should be avoided. That will be essential only when inoculation is undertaken in the actual presence of infection. On the other hand, in inoculation against an ' individual infection ', since here the pathogenic microbe is always knocking at the door, the avoidance of a negative phase and immediate immunisation are always indispensable and every failure will straightway notify itself. Again, in preventive inoculation against infective disease we administer inoculations to all and sundry—to the susceptible and the unsusceptible. In preventive immunisation against individual infections we apply inoculation only to the susceptible. For example, preventive inoculation against furunculosis is applied only to the susceptible—to those who have suffered from boils. Lastly, where we inoculate a community against an epidemic disease *pari passu* with the number of men successfully inoculated, the chances of infection are for the others reduced. In other words, the successfully inoculated give protection to the unsuccessfully inoculated ; and we obtain the benefits of what I have, in contrast with a *circulus vitiosus*, called a *circulus felix*. Nothing of that kind comes to our aid in immunisation against an individual infection—for here we inoculate the patient against a microbe which he constantly bears about with him.

Especially will that name be required for introducing the concept to others. The new technical term is the missionary of the idea.

One more point I want you to consider. Technical terms are distasteful not only because they are unfamiliar, but because they are foreign and difficult. We should, however, bear it in mind that the store of short and simple and native words has long since been exhausted, and very nearly every Latin word has already been incorporated into our language, and also nearly all the simpler Greek words have been taken into service. So there remains over only the longer composite Greek words—the terms that are so distasteful. But if we refuse to accept these, it will become impossible to put into currency any new ideas. When you want to specify a particular man or concept you cannot get on without the use of a label. For, in default of a label, you have every time to resort to a full specification.

Let me now return to my exposition asking you to let me, in connexion with it, introduce to you the new technical terms which I have prepared for you—hoping that they will be helpful.

The Defensive Mechanism of the Body.

To combat bacterial infection the organism must have defensive powers. That power of guarding itself against infection we may—the suggestion is Lord Moulton's—call *phylactic power*. The leucocytes and the bacteriotropic substances in the blood-fluids we may call phylactic agents. But phylactic power in the blood will not be all that is required. Military similes become stale; but let me here just indicate that the requirements for the defence of a State are not limited to the possession of a standing army. There is required also efficient staff work to bring your defensive force to the point attacked. The self-same thing applies to the body. You must have, not only phylactic power in the blood, but also provision for the transport of your leucocytes and bacteriotropic blood-fluids to the site of infection. Let me call this transport of phylactic agents to the site of infection *kata-phylaxis*.[1] (You have a similar use of the prefix *kata* in cataplasm and kataphoresis.) And let me term any condition which interferes with the transport an *anti-kata-phylactic influence*.

Now in the body, when in sound physiological condition, we have efficient kataphylactic arrangements—blood-fluids and leucocytes have ready access to practically every part of the body. But when anti-kataphylactic influences are brought to bear; when the arterial supply is interrupted, or is closed down by collapse, or the body is petrified by cold, and the alkalinity of the lymph is blunted off by acid metabolites derived from the muscles; then the emigration of leucocytes is arrested, and the transport of blood-fluids into the tissues comes to a standstill. And with that all pathogenetic microbes which may find entrance—even microbes like gas-

[1] While this paper was under revision for the press I discovered that the term 'kataphylaxis' had already been employed by Bullock and Cramer in a paper which had already appeared in the form of an abstract. With a graceful courtesy, for which I am very grateful, these authors are now replacing the term *kataphylactic* in their paper by the term *aphylactic*, thus generously ceding to me their rights of prior user, and leaving the field free for the employment of the former term with the signification which is here assigned to it.

gangrene bacilli which (*vide supra*, p. 94) grow with immense difficulty in the healthy blood-fluids—flourish unopposed.

Phylaxis and kata-phylaxis—these are the normal defences of the body. But there are also resources in reserve. By a process comparable to a mobilisation for the reinforcement of a standing army, the phylactic powers of the blood-fluids can be increased. We may call that *epi-phylactic reinforcement*, or *epi-phylactic response*. Such epiphylactic response manifests itself, as you know, in connexion with, we may say, all infections that give rise to constitutional disturbance. And such response follows, as you know also, upon bacterial inoculations when conducted with appropriate doses. But, as I pointed [1] out already in connexion with one of my first batches of experimental antityphoid inoculations, there follows directly upon the inoculation of a large dose always a phase of diminished blood resistance —I called it a *negative phase*. It would be more conformable to the system of terminology I am advocating to employ here the term *apo-phylactic phase*.

Ec-phylaxis

We now come to something which is much less familiar—less familiar, but, I think, even more important.

I have in view here conditions which I drew attention to twenty years ago [2] in connexion with typhoid and Malta fevers, coining for my propagandist purposes the terms ' regions of diminished bacteriotropic pressure ', ' non-bacteriotropic niduses ', and ' non-bacteriotropic envelopes '. These terms may perhaps have been unsuccessfully coined ; they have, at any rate, not proved effective missionaries of the idea, and I would propose now to try to put into currency instead the terms *ec-phylaxis*, *ec-phylactic region*, and *ec-phylactic envelope*. When I speak of an ec-phylactic region you will understand me to mean a region in which the guardian elements of the blood have been rendered impotent or, as the case may be, have been excluded. A moment ago, in describing the effects produced by the abolition or suspension of the circulation by injury to the blood-vessels or exposure to cold, I was picturing to you an ec-phylactic region. Much more commonly—and these, of course, are the conditions I described in typhoid and Malta fever—the ec-phylactic region has been fabricated by a bacterial colony. You will appreciate that every living bacterial colony must become the centre of an ec-phylactic sphere. It will become so (*a*) by radiating out toxins which will (when of sufficient strength) repel leucocytes ; (*b*) by absorbing bacteriotropic substances from the blood-fluids ; and, probably (*c*), by abstracting anti-tryptic power from the blood-fluids and so converting these into a congenial culture medium.

Types of Ec-phylactic Foci

In the diagrams I here show you, I have depicted three different types of ec-phylactic foci. In Diagram 1—reproduced here as Fig. 1—we are dealing with serum which is tinted with litmus implanted with gas-gangrene bacilli in moderate

[1] *The Lancet*, 14th Sept., 1901.
[2] *The Lancet*, 23rd Dec., 1899 ; and Wright, *Studies on Immunisation*, Constable, London.

numbers. On looking at Tube A, where by occasional shaking the microbes have been kept dispersed, you will see no indications of a change in the medium, or growth. In the companion tube, B, where the microbes were carried down and compacted by centrifugalisation, the chemical action of the microbes has at the bottom of the tube produced the ec-phylactic region, which is indicated upon the figure by lighter shading. In this region, by the diminution of its anti-tryptic power

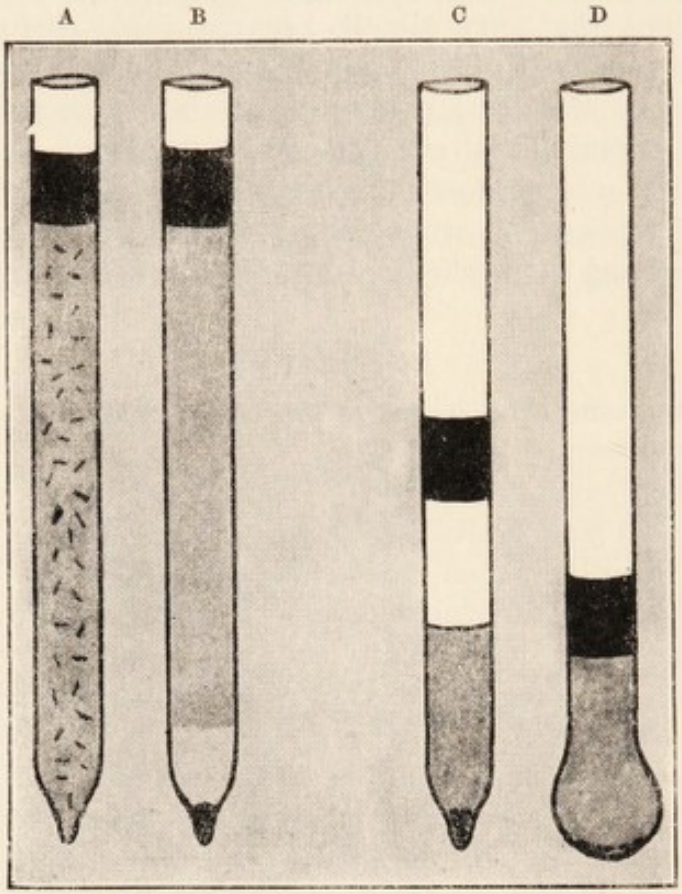


FIG. 1.

Diagram showing, in connexion with the bacillus of Welch, that the compacting of infection produces, as in B, ec-phylactic changes in the neighbouring serum, and afterwards, as in C, a general infection of the medium with gas formation. In A, where the microbes are kept dispersed by shaking, and in D, where their close aggregation is prevented by the shape of the tube, there are no ec-phylactic changes and no growth.

and a blunting off of its alkalinity, the serum has been converted into a congenial culture medium for the gas-gangrene bacilli, and if incubation had been continued longer we should have had after this preparatory process massive growth with gas-formation.

Tubes C and D represent another pair of companion tubes that have been kept longer in the incubator. In Tube D, where to prevent conglomeration of the microbes the test-tube has, as suggested by Dr. Fleming, been blown out into a bulb ; there are, as you see, no indications of growth. In C, owing to the circumstance that the microbes could here collect together by gravitation, opportunity

was afforded for the development of an ec-phylactic focus ; and here as an after result we have a massive culture with abundant production of gas.

Diagram 2 [1] (not reproduced here) shows the second type of ec-phylactic focus —that produced by negative chemotaxis. You have represented what happens when we take (*a*) a clean surface, (*b*) a surface thinly coated with microbes, and (*c*) a surface thickly coated with microbes ; impose on each a drop of blood ; and then incubate in a moist chamber. Upon the *first* surface we get a moderate emigration of leucocytes ; upon the *second* an augmented emigration ; and upon the *third*—and it is to this that I want to direct your attention—absolutely no emigration. In other words, here by condensing the bacterial infection there has been fabricated an ec-phylactic region.

In the next diagram (*vide*, p. 47) we have the third type of ec-phylactic focus—that produced by exudation of fluid. Where that occurs the leucocytes are —so far as any phagocytic activity is concerned—put out of office, and the infecting microbes are—so far as phagocytic attack is concerned—safe. That is the justification of the surgeon's solicitude about infections in artificial or natural ' dead spaces '. You will appreciate that leucocytes, though, of course, they will emigrate into, cannot swim or transport themselves from place to place in, a fluid medium. They can only crawl along surfaces and creep along the trellis work of the tissues.

Contrast between Preventive and Therapeutic Inoculation.

I have now introduced you to my new technical terms. And I propose now to show you that the concepts which I have designated by the terms *phylaxis*, *kata-phylaxis*, *anti-kataphylaxis*, *epi-* and *apo-phylaxis*, and *ec-phylaxis* provide us with a key to the understanding of the difficulties which are encountered in vaccine therapy, and, indeed, in all treatment of bacterial disease. Further, I want to try to show you that these concepts teach us how these difficulties may be in many cases surmounted.

Let me begin by drawing your attention to the fundamental contrast between the conditions in preventive and therapeutic inoculation. In preventive inoculation we start from the platform of normal resistance, with normal phylactic power, and to that we superadd the reinforcement contributed by the epi-phylactic response ; and we can count upon the kata-phylactic arrangements being maintained upon a normal and perhaps (for emigrational response may be more active) on an improved footing. It is as if we had started with a well-equipped standing army, had reinforced it by mobilisation, and had maintained or improved the organisation for the transport of a military force to any point of attack. With all this, we should be in a position to repel assault. And similarly, it should be possible to make a success of preventive inoculation.

In the nature of things therapeutic inoculation should be infinitely more precarious. The important point to grasp is that should epi-phylactic response or kata-phylactic reaction or either of these make default, therapeutic inoculation is almost bound to miscarry. You will remember my telling you in connexion with the

[1] *Vide* ' New Methods for the Study of Emigration and of the Bactericidal Effects exerted in the Wound by Leucocytes,' *The Lancet*, 26th Jan., 1918, Fig. 1.

results of vaccine-therapy that cases of continuous or frequently recurring pyrexia, and cases of unopened abscess, were intractable. You now appreciate that in the first class of cases the epi-phylactic, and in the second class of cases the kata-phylactic, reaction makes default.

Causes of Failure in Vaccine Therapy.

Let me say a word or two about each kind of failure.

Epi-phylactic response will be interfered with when the patient is suffering from continuous or frequently recurring conveyance of bacterial toxins into the blood. So long as the patient is thus tormented by auto-inoculation, we can effect nothing by vaccine therapy.

In such a case the proper remedial measure is to abolish the auto-inoculations. The best procedure is to incise and evacuate the contents of the focus of infection. Where this is inapplicable we must have recourse to immobilisation. In the case of a limited local infection, local immobilisation will suffice ; where the focus is of large dimensions, rest in bed will be indicated ; and in the case of a more extensive infection, the programme of ' absolute rest ', as laid down by Dr. Marcus Paterson,[1] for pyrexia in phthisis is imperative. You will appreciate, of course, that when we try to abolish the auto-inoculations, what we are trying to do is to obtain a free field for the employment of properly graduated doses of vaccine, or, as the case may be, for properly controlled auto-inoculations.

Vaccine-therapy will less frequently make shipwreck through default of epi-phylaxis than through shortcomings in kata-phylaxis. Frustrated kata-phylaxis accounts for almost all failure in the treatment of bacterial disease. The situation we have to deal with is as follows : Microbes can establish themselves in the organism only in two circumstances. First, when they find access to a region rendered ec-phylactic by interference with the circulation or other anti-kataphylactic agency ; and, secondly, when they succeed in fabricating for themselves an ec-phylactic environment. An ec-phylactic area once established, special measures will be required to bring the leucocytes and protective substances of the blood-fluids into application.

Kata-phylactic Measures.

Three different types of kata-phylactic measures may be resorted to : (1) The contents of the ec-phylactic focus may be evacuated. Then by the emigration of fresh leucocytes and the transudation of fresh serum physiological conditions will spontaneously establish themselves in the focus of infection. (2) Normal conditions may be restored by augmenting the transudation of lymph into the focus of infection, and displacing and expelling by this agency the ec-phylactic lymph. (3) Physiological conditions may be restored by processes of simple diffusion.

You will want to have before your mind a clear picture of what procedures come under these headings.

[1] *Auto-inoculation in the Treatment of Phthisis*, Nisbet, London.

1. *Procedures for Evacuating the Ec-phylactic Fluid into the Exterior.*

(1) *Incision.*—The first among such procedures is incision into the focus of infection. It is clear that incision will evacuate any collection of ec-phylactic fluid ; but only rarely will the fluid which flows away comprise the whole of the ec-phylactic fluid. In the case of an abscess we evacuate only the contents of the cavity and only a very small amount of lymph will spontaneously follow. Where tissues are incised only the fluid which is standing under pressure will flow out, and even this may be prematurely arrested by its coagulating upon the walls of the incision. But even under the happiest conditions incision will give us only an incomplete draining away of the ec-phylactic fluid. The same holds, of course, of aspiration.

(2) *Incision and cupping.*—This procedure, which was brought forward by Klapp, might at first sight appear to be calculated to draw off all the ec-phylactic lymph from the focus of infection. In actual practice the method fails, when, as in carbuncle, we have to deal with lymph spaces blocked with leucocytes and coagulated exudate. And in any case, in extracting lymph by Klapp's method the same difficulties will confront us as when we employ negative pressure to draw a coagulable fluid through a paper filter. The filter very soon becomes obstructed—and then it is very likely to tear—and we never can get much fluid through.

(3) *Application of hypertonic salt solution to a naked tissue surface.*—We have here instead of a local lymphagogue, which acts by direct mechanical pressure, one which functions by what I may call ' diffusion pressure '. In other words, we have here an agent into which fluids of lower salt content will be drawn in. By virtue of this power it will suck out ec-phylactic lymph from infected tissues.

(4) *Application of irritant solutions to naked tissue surfaces.*—My fellow-worker, Dr. Alexander Fleming, has shown that an outpouring of lymph—which is very clearly differentiated from that produced by hypertonic salt in the respect that it is delayed instead of immediate—is obtained from a wound also by the application of solutions of the hypochlorites—such as Dakin's fluid. No doubt this lymph outflow is attributable to the hyperaemic reaction produced. A massive transudation —of, I think, similar derivation—supervenes upon the application of concentrated carbolic acid and also of certain other antiseptics to the wound.

2. *Procedures for restoring Normal Conditions by augmenting Transudation from the Blood and displacing and driving out the Ec-phylactic Fluid from the Focus of Infection.*

Under this heading may be enumerated three procedures : the *application of hot fomentations*, the *application of a Bier's bandage*, and *massage*. In the first two we make use of increased transudation—obtaining that increased transudation in the one case by active and in the other by passive congestion. In massage we use mechanical propulsion. It will generally be inapplicable to an active focus of infection.

3. *Procedures for restoring Physiological Conditions in the Focus of Infection by Spontaneous Diffusion of Protective Substances from the Blood*

If we had under Socratic cross-examination the man who expects benefit indiscriminately from every therapeutic inoculation it would be elicited that he

had a confused expectation that the protective substances obtained by inoculation would diffuse into and do effective work in every focus of infection. In the case of a focus which has attained a certain magnitude that cannot by any possibility happen. For the infecting microbes are incessantly obstructing the kata-phylaxis. They are continuously paralysing and repelling the leucocytes and depraving the blood-fluid to their advantage, and thus they neutralise and more than neutralise the in-streaming protective substances. Added to that, when infection induces effusion, and the effusion gathers bulk, and the infecting microbes transform it, that transudation fluid is less and less affected by diffusion from the surrounding blood-vessels. We have here assuredly the explanation of the fact that we get as good as no success from therapeutic inoculations when dealing with large and unopened foci of infection ; that we get much better results when the infective foci have attained only moderate dimensions ; that we get very good results when dealing with very small foci ; and our very best when, as in prophylactic inoculation, we are dealing with infecting microbes before they have had time to fabricate round themselves any ec-phylactic focus.

Of such dominating importance is efficient kata-phylaxis in the conflict with bacterial disease that I do not hesitate to assert—and these are views with which every surgeon will fall in—that if we were to put our election, on the one hand, between efficient epi-phylaxis without kata-phylaxis ; and, on the other hand, efficient kata-phylaxis without epi-phylaxis, we ought every time to choose the latter.

Septic War Wounds.

Up to the point to which I have now carried you, we had arrived already years before this war, and I had in a succession of papers reprinted in my *Studies in Immunisation*,[1] explained the broad therapeutical principles which I have here been laying before you. But these—it was perhaps for lack of the right words to serve as missionaries of the ideas—had not won for themselves any general recognition when on a sudden, with the outbreak of this war, there was thrust upon the whole medical profession the task of combating bacterial infections in wounds.

You know only too well the situation which confronted us in the early days of the war. Every wound was indescribably septic. We were back again—as Sir Alfred Keogh told me as he sent me out—to the gross septic infections of the Middle Ages. Where the projectile had left only small external openings the wound by the time it arrived at the base had been converted into a putrid unopened abscess. When the projectile had made a large opening tearing away the tissues, the entire surface was covered with foul sloughs. And when amputations had been sewn up at the front, and everything was sealed up tight, the sepsis was even more acute and the conditions more deplorable.

Such conditions required—as we now all of us have learned—not the exhibition of antiseptics, nor yet epi-phylactic treatment by vaccines, but instead efficient kata-phylaxis. The wound with a putrid abscess and the sutured amputation stood

[1] Constable, London, 1909.

in need of free opening and efficient drainage—drainage both of pus from the wound cavity, and of ec-phylactic lymph from the surrounding infected tissues. And the putrid slough-covered wound required digestive cleansing, followed again by extraction of ec-phylactic lymph from the subjacent tissues. It was for the attainment of these objects that I recommended applications of hypertonic salt solution ; and it is not, I believe, open to question that applied for these specific objects [1] the hypertonic treatment is quite eminently efficacious.

I will not, however, here take up your time with discussing details of treatment ; what I want you to realise is that we have in the putrid wound an ec-phylactic focus which lies open to study. Figs. 2 and 3 bring before us the essential important facts relating to the characters of the fluid in such a focus.

In Fig. 2 is represented a foul suppurating wound with a pool of pus in its dependent portion. In this pus—as you see represented in the inset in No. 1—the

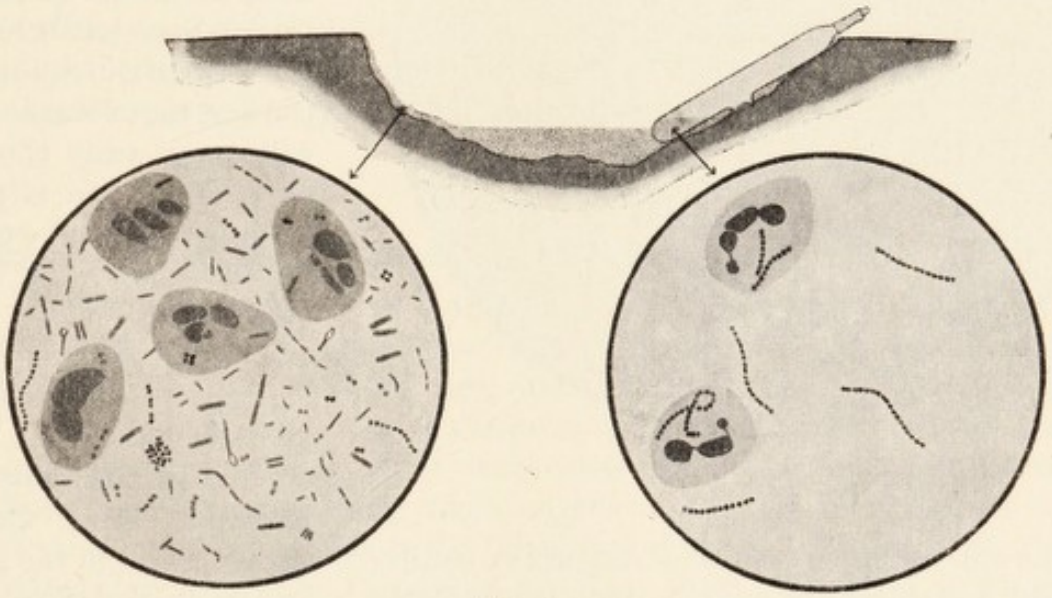


FIG. 2.

microscope shows broken-down leucocytes and a collection of every conceivable species of microbe—streptococci, staphylococci, coliform organisms, and, despite this being an open wound, all sorts of anaerobic microbes, including gas gangrene and tetanus bacilli.

In the main diagram we have further represented what I call a *lymph-leech*. In its essence this is a small cupping apparatus which, as soon as a negative pressure is established in its interior, fixes itself tightly to the walls of the wound and then sucks in fluid.

[1] I need not here come back upon the fact that strong salt solution draws out lymph from the tissues, nor upon the fact that it liberates the trypsin required for digesting off the sloughs. These points I have, I feel, established (vide *The Lancet*, 23rd June, 1917, sections entitled Drawing Action of, and Setting Free of Trypsin by, Hypertonic Salt-Solution).

In inset No. 2 we see a sample of the fluid taken from the lymph-leech after it has been left in position overnight. Here, as you see, the leucocytes are sparingly present, but they are in good condition, and in the fluid—though it of course exuded from a wound surface soiled with every kind of microbe—we have, as you see, a pure or practically pure culture of streptococci.

Another type of experiment which is, as you will recognise in a moment, essentially similar to this is represented in Fig. 3. Here we take a corrupted pus from a wound, draw one unit volume into a capillary pipette, and then follow on with a series of unit volumes of normal serum, separating these off by air-bubbles. I call that a pyo-sero-culture made by the wash and after-wash method. Of the trail of infected pus left behind upon the walls of the capillary stem the first unit volume of serum will carry away the greater part, and there is progressively less pus left behind for the after following unit volumes of serum.

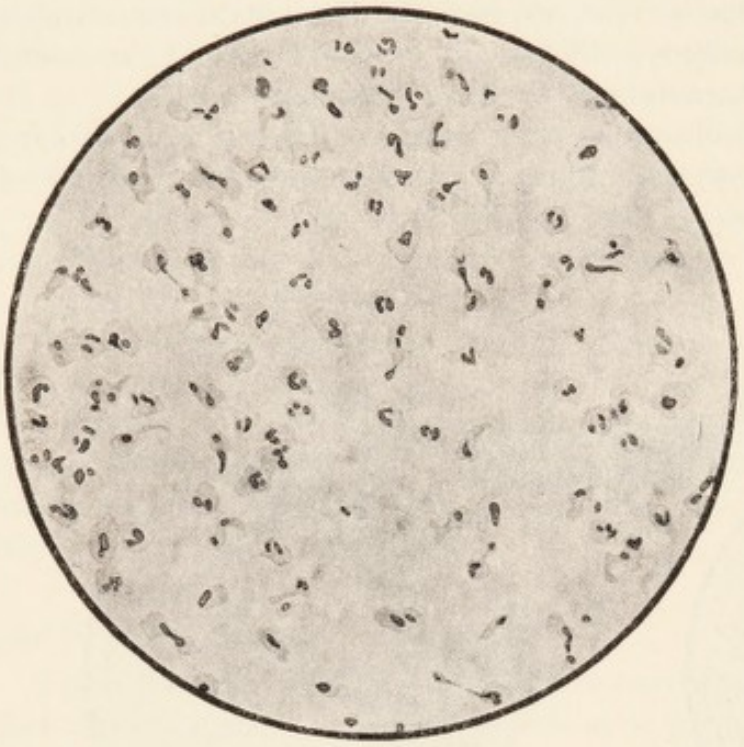


Fig. 3.

When we now incubate our pipette and blow out the volumes one after another, we find in the most heavily implanted and most corrupted serum volume, conditions essentially similar to those shown in the pus from the putrid open wound ; and, in the progressively less heavily implanted and less corrupted serum volumes, conditions identical with those in the exudate taken from the belly of the lymph-leech.

Types of Infection.

We have here a fundamental fact relating to microbic infections. Of the infinitely numerous varieties of microbes which exist in nature it would seem that nearly all can grow in the blood-fluids when their anti-tryptic power has been sufficiently reduced by an addition of trypsin ; and the gas-gangrene bacilli in particular can grow not only in the blood-fluids which have been, as I call it, ' corrupted ' by trypsin, but also in blood-fluids whose alkalinity has been blunted off. Only a few species of microbes, and of these the streptococcus and the staphylococcus are the most important, can grow also (but grow, of course, less freely) in the unaltered

blood-fluids. I have suggested that we should call the microbes which can grow upon unaltered serum *serophytes* and those which can grow only on corrupted serum *sero-saprophytes*.

All this has brought home to you that we have two distinct types of exudates in wounds, and two distinct types of infection. In a ' foul wound ' we have an exudate with reduced anti-tryptic power and a multiform sero-saprophytic infection. In a ' clean wound ' we have an exudate with undiminished anti-tryptic power and a purely serophytic (i.e. generally a strepto- or staphylo-coccic and occasionally a diphtheroid) infection.

We come therefore here to a broad therapeutic principle. A ' foul ' wound can be rendered ' clean ', and a sero-saprophytic can be converted into a purely serophytic infection, by bringing into the wound wholesome blood-fluids. But there is also a corollary to this. When we have converted a primitively ' foul ' into a ' clean ' wound, we can gain nothing from further flooding the wound with blood-fluids. We shall, in fact, by such treatment only be supplying fresh culture medium for serophytes.

How, then, does the body combat serophytic infections? Manifestly it must do so by the aid of the leucocytes. The series of illustrations which have figured and have been explained on pp. 96–103 *supra* furnish proof of that.

Destruction of Microbes by Leucocytes.

The experiments here in question are full of instruction. They teach us that we must when we want to extinguish a serophytic infection in wounds bring into application active leucocytes, and they further teach us that leucocytes can kill microbes not only *intra-cellularly*, but also *extra-cellularly*, and that without any aid from serum. That leucocytes can kill microbes extra-cellularly can be shown also by implanting microbes into a drop of blood taken from the finger and then centrifuging this in flat ' emigration tubes ' (*vide* author's *Technique of the Test and Capillary Tube*, Constable, London, 1921). We then, if we have hit off the appropriate microbial implantation, find just above the leucocyte layer a band of clot which is perfectly bare of colonies, and which reminds one of the bare bands of agar in Fig. 4, p. 100.

Further Experiments on the Killing of Serophytic Microbes by Leucocytes.

Bactericidal experiments which yield results exactly similar to those already considered can be made with freshly emigrated leucocytes procured from a ' clean wound ' previously cleansed with physiological salt solution. These experiments were devised by my fellow-worker, Dr. A. Fleming.

My next figure (Fig. 4) furnishes you with a précis of what is important to know about microbic destruction by pus. A drop of pus obtained from a clean wound recently washed out is taken and spread out on the surface of nutrient

agar by the pressure of a cover-glass. In A, B and C the pus was imposed upon a sterile surface, in D and E upon a surface heavily implanted with staphylococcus. In A, B and D we have what I have called *necro-pyo-cultures* or *necro-cyto-cultures*—that is, cultures made from a pus whose cells are dead. In A and D the cells were killed by heating to 48° C., which is the thermal death-point of leucocytes ; in B the pus cells were killed by simple desiccation. In C and E we have *bio-pyo* or *bio-cyto-cultures*—i.e. cultures made from a pus whose cells are alive and active.

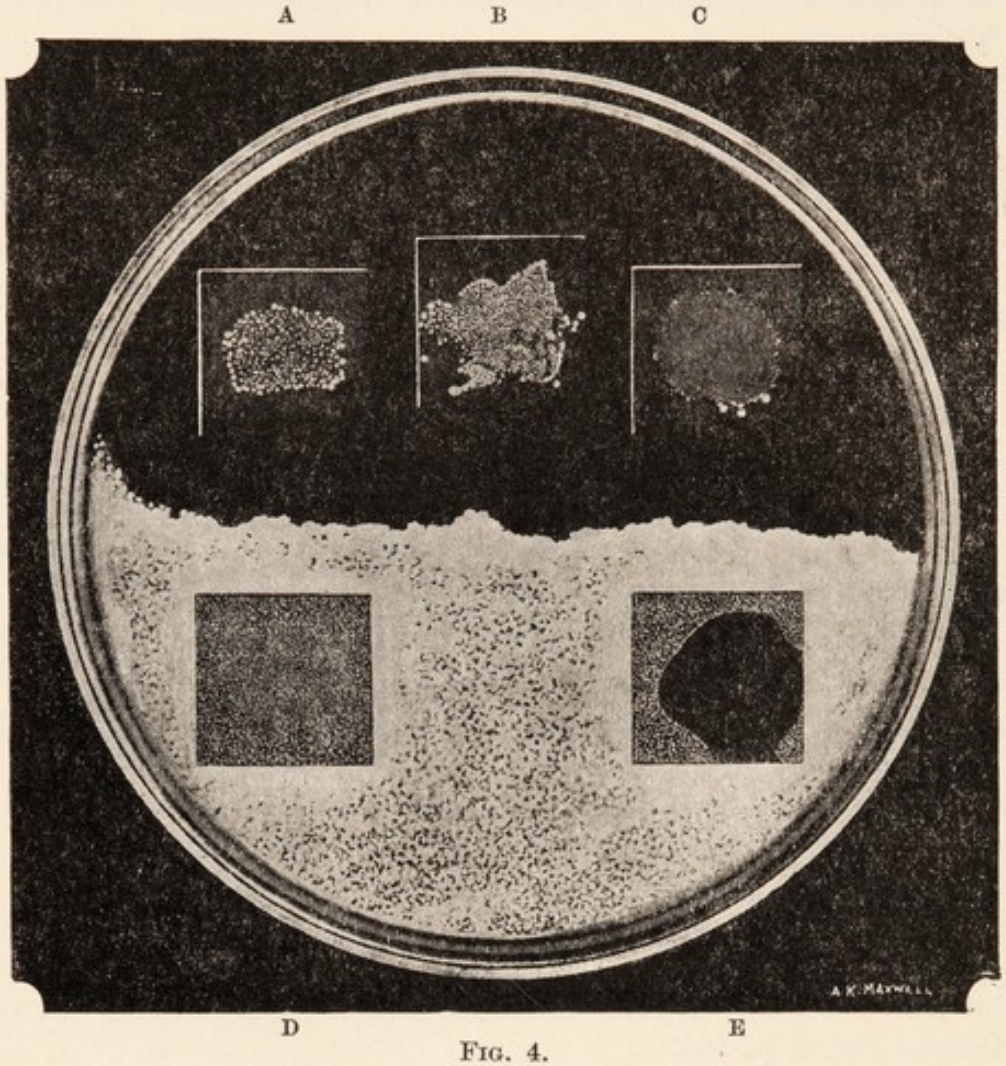


FIG. 4.

Drawing made after 24 hours of specimens of pus from a clean wound (recently washed out with normal salt solution) imposed under cover-glasses on sterile agar and agar implanted with staphylococcus. A, pus heated to 48° C. B, dried pus. C, living pus. D, pus heated to 48° C. E, living pus.

You will see at a glance that in necro-cultures A and B the microbes of the pus have grown out into very numerous colonies. In sharp contrast with this is the event in the bio-culture C. Here the living pus cells have killed all the microbes with the exception of a few upon the circumference which have grown out in a marginal ring of serum expressed from the pus by the weight of the cover-glass. In D—which is again a necro-culture—we have a dense growth consisting of the microbes originally contained in the pus with, in addition, those from the implanted

agar surface. And finally in E—which, again, is a bio-culture—the pus has killed off not only its contained microbes but, in addition, those with which the agar surface was implanted.

Let me now call your attention to the next figure (Fig. 5), and you have then, I think, the full story of the growth and destruction of serophytes in pus from a clean wound recently washed out. In A, which serves as the control, you have, as you see, only the customary few colonies round the margin of the bio-pyo-culture. In

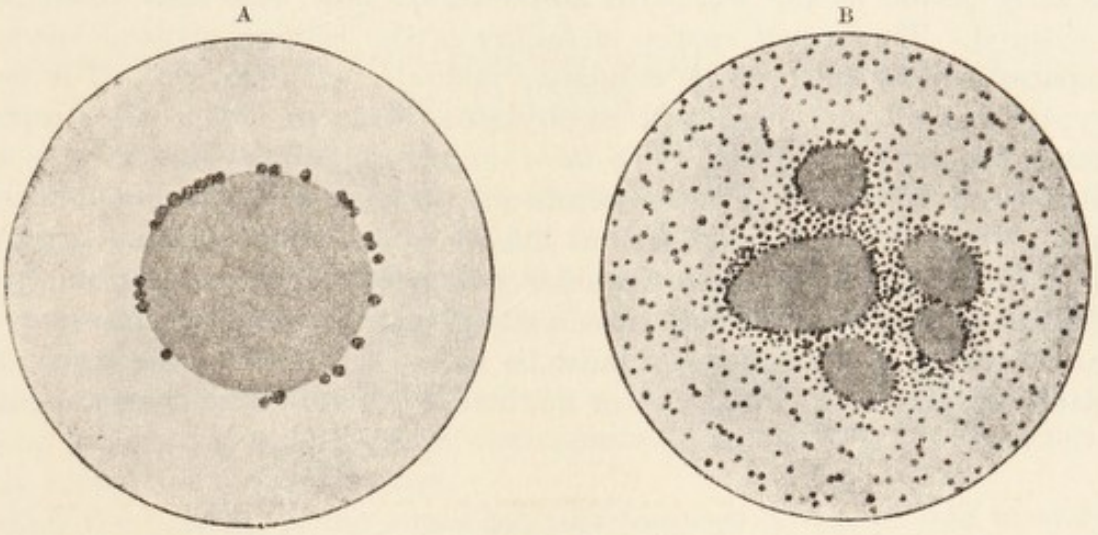


FIG. 5

Specimens of pus from a clean wound imposed on sterile agar under cover-glasses and cultivated 24 hours. A, living pus. B, ditto which has been stirred up with a little sterile serum.

B a pellet of pus has been stirred up with the serum. Here you have a voluminous growth of micro-organisms in the serum surrounding the islands of pus. And once things have gone so far as they have gone here, it will not be long before all the cells are poisoned off and microbes reinvade the substance of the pus.

Suture of Wounds.

As I have been telling you these things your minds have no doubt been running ahead, and you have been thinking of the bearing of all this upon the suture of wounds. It has, of course, obvious applications. It shows you in the first place that if the surface of the wound is not sterile, that is no reason for deferring suture. The pus with which we operated in these experiments was, when taken from the wound, full of living microbes ; and none the less it turned out that this pus was, when we provided proper conditions for the leucocytes, competent to kill not only the contained microbes, but also that large number more that we added. Now when we bring together two surfaces of a wound each furnished with active leucocytes fresh from the blood-vessels, we are providing for those leucocytes far more favourable conditions than when we impose them in nutrient agar and cover them in with a cover-glass ; and, moreover, when we operate *in vivo*, we can count upon the continuous new arrival of leucocytes from the blood-stream.

Successful suture of an infected wound is therefore not a thing to be wondered at. Failure is what stands in need of explanation. There are three main sources of failure. The *first* is the leaving behind of corrupted pus. This, if a sufficient exudation of wholesome lymph does not intervene, will little by little corrupt the local exudate ; and there will then come into existence in the depth of the wound an ec-phylactic focus in which not only serophytic, but also all manner of sero-saprophytic micro-organisms will grow unrestrained. This was wont to happen in the early period of the war with amputations that were sent down from the front sutured. The *second* source of failure is the leaving of dead spaces. For dead spaces rapidly fill up with exudate ; and such exudate, even if it be of full antitryptic power, will create an ec-phylactic focus in which the streptococcus and staphylococcus will grow. The *third* source of failure—and to this and the last mentioned is to be traced the erroneous doctrine of the impossibility of successfully suturing over a streptococcal infection—is default of leucocytic emigration into the wound. When we consider the success of retarded primary suture, and the failure of early primary suture in streptococcic wound infections, we cannot, I think, doubt that the difference must lie in the fact that in the former case an abundance of, and in the latter few or no, leucocytes are brought into operation.

THE PHYSIOLOGY OF WOUNDS

REPRINTED FROM THE OFFICIAL MEDICAL HISTORY OF THE 1914–1918 WAR.

In any complete dissertation on the physiology of wounds the physiology and histology of trauma and wound repair, the physiology and chemistry of shock, and above all the reaction of the wound to bacterial infections and to the therapeutic methods employed in combating those infections, would have to be considered.

This chapter deals almost exclusively with the last of these subjects, but it may none the less be useful to note what points under the first two headings would properly come up for consideration.

Under the heading of the *physiology and histology of trauma and wound repair*, the histological responses to trauma, the production of granulation tissue and callus, the formation of new bone and connective tissue, and, finally, the growth of new epithelium and the healing over of the wound should come under consideration. And there should also come under discussion not only the histology of the aseptic, but also that of the septic wound. No important contribution to these questions would appear, however, to have been made in the course of the war, and they need not be considered here.

Further, in connection with the physiology of repair there would appropriately come up for consideration the procedures of skin and bone grafting and the suture of the wound. These subjects, involving as they do questions of surgical technique, have already been dealt with in the volumes on the Surgery of the War. Suture of the wound must, however, in view of its bearing on the treatment of bacterial infection, come under consideration here.

Under the heading of the *physiology of shock* there would have to be discussed that instantaneous collapse which follows in quite exceptional cases upon the traumatic ictus ; and, again, that delayed form of collapse which almost regularly supervenes when the severely wounded man is exposed to cold ; when the circulation in a limb is cut off by a tourniquet ; when, instead of being immobilised, a fractured limb is subjected to succussions during transport ; and when the patient is placed under an anaesthetic which sends down his blood-pressure. This so-called secondary shock—which killed in the course of the war perhaps as many of the wounded as sepsis, and which kills practically all who die of operations in times of peace and in civil practice—is almost certainly a chemical as distinguished from a nerve shock, the poisons which come into operation here being almost certainly acid

metabolic products, elaborated in exaemic muscle.[1] The general physiology and treatment of shock has already been dealt with in the volumes on the Surgery of the War.

It is therefore not specially considered here, except in so far as it is linked up with the development of gas gangrene. In connexion with this it may be premised that the chemical conditions which are provided by exaemia of muscle exactly satisfy the requirements and consequently favour the development of the gas-gangrene bacillus.

That wound sepsis and saprogenous infections—by which are meant septicaemia, tetanus, gas gangrene and such-like—were going to constitute the great medical tragedy of the war was appreciated quite at the beginning by those who carefully pondered the condition of the wounded arriving at the base. The Director-General, Sir Alfred Keogh, in October 1914, concisely summed up the medical situation thus : ' We have in this war gone straight back into all the septic infections of the Middle Ages.'

It may here be useful to describe succinctly the state of things that prevailed in the hospitals at the base in the early months of the war.

Every wound—one may say every wound, for there was hardly an exception —was very heavily infected, and presented, each according to its type, the features summarised below :

(1) *Avulsing wounds*, i.e. wounds produced by the avulsing of great pieces of flesh.—In these the originally naked surface of the wound was coated with black and stinking sloughs, while the trough was occupied by a putrid and almost faecal-looking discharge in which every kind and variety of microbe was pullulating.

(2) *Perforating and fracturing wounds*, i.e. wounds in which the projectile had in its passage encountered bone and broken this to pieces.—Of these wounds there were two varieties. In the one the fragmented bone had been blown clean out, leaving an irregularly crateriform wound of exit, at the bottom of which were pockets between the muscles and extensive fissures in the fractured bone. In the other the explosive impact had hollowed out in the interior of the limb a cavity of quite irregular contour with blind passages running in between the muscles, the cavity being cut off, or to all intents and purposes cut off, from the exterior by hernia of muscle, supplemented in some cases by a valvular closing over of the skin. Such valvular closure was the result of the limb being at the moment of wounding in the flexed position, and being afterwards in bed brought into the extended position.

In both varieties of the perforating and fracturing wound the cavity contained fragments of bone, pieces of projectile, portions of clothing, frayed ends of muscle and such-like, all these lying embedded in a corrupted pus in which every conceivable microbe was luxuriantly growing.

(3) *Sutured amputation wounds.*—In these the dead spaces left by the bringing together of the flaps were filled with a putrid discharge in which there was a luxuriant mixed bacterial growth.

[1] Wright and Colebrook, ' On the Acidosis of Shock and Suspended Circulation ' (*Lancet*, 1st June, 1918) ; also *Technique of the Teat and Capillary Glass Tube* (Constable, London, 1921), chap. vii, ' Clinical Appendix on Acidosis and Acidaemia '.

(4) Lastly, there were what may be described as *implunging wounds*, i.e. wounds produced by nearly spent pieces of shell or shrapnel. The projectile, together with the clothing it carried in, was here implunged into the soft parts, and these had closed round the foreign body, leaving no encompassing cavity or communication with the exterior.

In all these different types of wound the infection had in practically every instance extended beyond its focus of origin. Streptococcal invasions of the encasing tissues were all but universal, and diffuse cellulitis was specially frequent in unopened implunging wounds, this being no doubt due to the microbes being here implanted directly into connective tissue or muscle instead of, as in other types of wounds, into a cavity extraneous to the tissues.

Not infrequently these streptococcal infections of the tissues had led on to septicaemia.

Tetanus, also, was a frequent occurrence, and it occurred in connexion with all the different types of wound.

Even more ghastly were the numerous cases of gas gangrene. The form of gas gangrene which in the early days of the war came most conspicuously under observation was that in which the infection spread up the limb in the subcutaneous tissue, manifesting itself first in a rusty or dull purplish mottling, then in oedema with fine gaseous crepitation. This ended in a leaden blue discoloration of the skin ; and on this livid background were large sagging bullae filled with a black haemorrhagic fluid peopled with gas-gangrene bacilli. In these bullae there was often a production of gas, and this floated and moved about in the fluid after the fashion of a bubble in a spirit level.

The other form of gas gangrene, that in which the infection is deep-seated and travels up in muscles, had at this time not yet been recognised. But cases of that form of invasion often presented themselves—the injured limb becoming hard, glistening white, and cold as marble, and death always followed. Frequently the gas-gangrene infection had its focus of origin in heavily infected perforating and fracturing wounds, or amputation wounds that had been sutured. But injuries which cut off the arterial supply of the muscles of the calf of the leg, and bruises which disorganised the capillary circulation in large areas of muscle, and implunging wounds which, of course, would produce similar interference with the circulation, were those that gave most frequent occasion to gas-gangrene infection.

What was intellectually distressing in connexion with all this septic disaster was that the edifice built up by Lister and his successors and by the confident dogmata of surgeons seemed here to lie in ruins. It is indubitable that if before the outbreak of the war a concensus of surgical opinion had been taken on the question as to whether grave and universal infection of wounds was in prospect, it would, in view of the experience gained in the South African War and in the accident wards of civil hospitals, have been confidently asserted that such sepsis was a thing that belonged to the past. It is not, therefore, a matter for surprise that when septic infection became rampant the idea occurred that some sinister unknown agency must with the outbreak of the war have come into operation.

It took time to surmount that illusion ; but little by little it became clear that what was presenting itself in war wounds was only what regularly presents itself in cases of accident in the wilds ; and of course not only there, but wherever lacerated wounds are abandoned to themselves. What was actually occurring was only what was bound to happen in the medical situation then existing. The military position in the first months of the war was such that only the most urgent operative procedures, such as the amputation of shattered limbs, could be undertaken at the front. Practically all the wounds—and it must be remembered that war wounds are from their very nature bound to be grossly infected wounds—had to be sent down unoperated upon to the base.

That this postponement of operation was the direct cause of the sepsis was established beyond doubt as soon as it became possible to make different medical dispositions. A new era began when, following the example of the French army, the casualty clearing stations, whose appointed function it had been to evacuate the wounded, were fully equipped as surgical hospitals. From that time on, except in times of great pressure, all wounds which required operative treatment were operated upon as soon as the patient was brought in from the field. The wound was laid open and was cleansed and resected. That is to say, the foreign matter was turned out, the devascularised tissues which would have necrosed and formed sloughs were excised, and drainage-tubes were inserted. In fact the wound was, so far as operative procedures can achieve this, placed in a satisfactory physiological condition. After the adoption of these measures putrid wound infections became, relatively speaking, rare and the incidence of saprogenous diseases, such as gangrene and tetanus, was greatly reduced.

Preliminary Research into the Physiology of Wounds.

This general survey may serve as an introduction to an account of the research work on septic infection of wounds undertaken during the war in the Research Laboratory at Boulogne. To arrive at an understanding of the procession of events in infected wounds not only those initial and terminal events which come to the cognisance of the senses and impress themselves on clinical observation, but also all those intermediate events which escape clinical observation, and are therefore commonly ignored, must be brought into the field of view. To obtain information with respect to these intermediate events special laboratory methods have to be devised and exploited.

In setting down what has been learned by these methods with respect to bacterial infections of wounds, it will be well to commence with the simplest kind of wound and then go on to septic infections of greater complication.

A certain preliminary physiological foundation must first be laid down. Part of that foundation will consist of facts which are of common knowledge ; part of new fundamental facts discovered in the course of the war and not yet familiar.

The facts of common knowledge are first that microbes are destroyed by phagocytosis and intracellular digestion in leucocytes ; and secondly, that the blood-fluids, although the current conceptions here are very nebulous, possess a certain bactericidal power.

New Data concerning the Blood-fluids.

Of the new facts which are essential for the understanding of the processes of septic infection the most important is that the microbes found in wounds can be distributed into two classes—a class of *serophytes* and a class of *sero-saprophytes*. Serophytes can grow and multiply in the unaltered blood-fluids. Sero-saprophytes can support life and multiply only in what may provisionally be called ' corrupted ' blood-fluids.

The evidence on this question is clear and simple. Any mixture of microbes is taken, such, for example, as is obtainable from a putrid septic wound, or from the intestinal contents. One unit volume of this is then aspirated into the distal

FIG. 1.

portion of a capillary tube ; then (making in this way a ' wash and after-wash ' culture) a series of separate unit volumes of normal serum is drawn into the capillary stem, and the tube is then placed in the incubator. In the first and heaviest implanted volumes of serum there will be obtained a mixed culture of serophytic and non-serophytic microbes ; in the intermediate and more highly implanted volumes, as a rule only a culture of staphylococcus and streptococcus with occasionally a diphtheroid microbe ; and in the distal unit volumes, a pure cultivation of streptococcus. This quite invariable result shows that the staphylococcus and streptococcus grow better than any other microbes in the blood-fluids and lymph. Further proof of this is obtained by attaching a small cupping apparatus —' lymph leech '—to the non-disinfected walls of a putrid septic wound. There will—despite the fact that there will here have been implanted all manner of microbes—then be obtained in the fluid drawn into the belly of this lymph leech (*vide* Fig. 2, *supra*, p. 123), a culture consisting entirely of serophytes, and often a pure cultivation of streptococcus.

Leaving out of regard for the moment what further can be learned from this experiment, attention may be focused on two great general principles : *first*, on the principle that serophytic microbes, and only serophytic microbes, will be capable of growing in the clean and wholesome wound ; *secondly*, on the principle that of all the organisms found in the putrid wound only the serophytic organisms, and in particular the streptococcus, will be capable of invading the blood-stream. That

none of the saprophytic organisms can invade the blood-stream, will, of course, hold good only so long as the blood-fluids remain ' uncorrupted '.

For the explanation of these facts that only serophytes can grow in the wholesome wound, and that only these can invade the blood-stream, one must look primarily to the antitryptic power of the blood-fluids. It has long been known, but it has not, in connexion with resistance to bacterial infection, been appreciated, that the blood-fluids have the power of neutralising digestive ferments ; that, put more briefly, they have an antitryptic power.

In the course of the researches summarised in this chapter it suggested itself with respect to this antitryptic power that it must constitute an important element of antibacterial defence, for reflection showed that microbes in the blood would, for their nutriment, be bound to depend on such digestive action as they might be able to exert upon the food-elements around them ; and that with that power abolished they must starve, just as starvation would follow if a man were deprived of his digestive enzymes. The obvious way of putting the inference that the antitryptic power of the blood inhibited microbic growth to the proof was to make graduated additions of trypsin (using inactivated trypsin in the control experiments) to the serum. When the experiment in question is made it comes out quite clearly that additions of trypsin favour the growth of streptococcus in the serum. For example, with complete neutralisation of the antitryptic power of the serum, a 6,000-fold increased growth of streptococcus [1] has been obtained. Further, it comes out clearly that *pari passu* with the blunting off of the antitryptic power the serum becomes an eminently favourable medium for all the different varieties of serosaprophytic organisms. To this must be added that the bactericidal and also the opsonic power of the serum are, as increasing doses of trypsin are introduced into the serum, first reduced and then completely abolished.

The application of these facts to the physiology of the wound appears when they are related to the facts that leucocytes furnish a tryptic ferment, and that leucocytes which have injested microbes furnish this in greater abundance, and that this ferment is discharged when the leucocytes disintegrate or are artificially broken down. The view that antitryptic power of the blood-fluids is an important element in the mechanism of defence wins support also from the fact that when this power is increased, as it regularly is in the wounded,[2] the growth of serophytic organisms in the serum is correspondingly restricted.

Further experiments showed how it is that serophytes manage, in spite of the antitryptic power of the serum, to grow out in it into colonies. When staphylococci or streptococci are implanted into ordinary blood-plasma obtained by simple centrifugalisation of the blood, or into recalcified citrated plasma, and such implanted plasma is, before it clots, filled into a capillary tube, or into such a ' slide cell ' as is

[1] In the case of staphylococcus implantations no increased growth is achieved by adding trypsin to the serum. This, no doubt, stands in relation with the fact that the staphylococcus secretes a very potent tryptic ferment.

[2] In the case of the severely wounded (*vide supra*, p. 64 *et seq.*) the antitryptic power may be as much as fourfold the normal, this increase being already well marked within twenty-four hours after wounding. A similar increase of antitryptic power comes under observation also after inoculations of bacterial vaccines.

shown in Fig. 2, then each colony (those shown in the figure are colonies of staphylococcus) digests the fibrin which is in immediate contact with it, hollowing out for itself in this way a cavity in the clot. And as the colony grows, the clear halo around it grows bigger and bigger.

It is thus shown that serophytic microbes can, by a secretion of trypsin, overcome the antitryptic power of the serum and obtain for themselves nutriment by

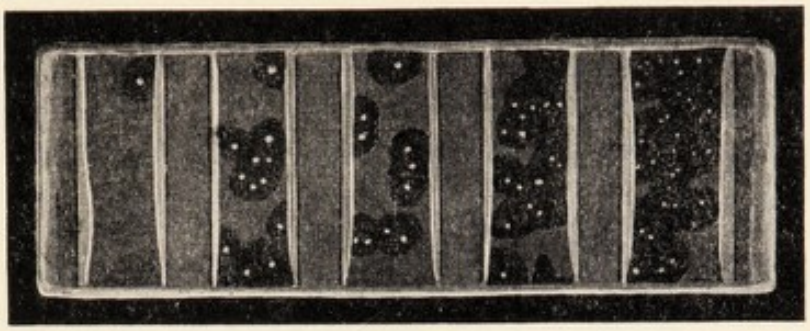


FIG. 2.

the digestion of the proteins of the blood-fluids. With this the question as to how serophytic microbes succeed in growing out in the blood would appear to be solved.

There are, however, certain other points remaining; and it will facilitate the discussion of these and also of a number of others which will come up in connexion with the pathology and treatment of bacterial infections to make use of an apparatus of new technical terms. It will be convenient to speak of the normal blood, and also of the normal blood-fluids (for these, as has been seen, have a certain power of protecting themselves against bacterial invasion), as possessing *phylactic* power. When the blood or blood-fluids have been deprived of that power, they may be termed *apo-phylactic*. When they have by immunisation received an access of phylactic power, they may be called *epi-phylactic*. Finally when phylactic elements are transported into an ecphylactic focus, the term *kata-phylaxis* may be employed or the agent may be termed a *kataphylactic agent*. Now making use of these terms it will be appreciated that when trypsin is introduced into and mixed with serum the entire fluid is rendered *pro tanto* apophylactic. Where, as in experiments such as that figured above, the staphylococcus is implanted sparsely into the plasma, the whole medium is not rendered apophylactic; but instead a certain number of *ecphylactic faci*—foci in which the microbes can henceforward grow unrestrained—are established.

The rôle played in pathology by the ecphylactic focus and the necessity of taking this into account in the treatment of all bacterial infection will gradually become clear. It will be sufficient here to bring out two points.

If after the microbes had been implanted the blood-fluid had been kept in continual motion instead of being allowed to come to rest, the tryptic ferment of the microbes would have been dispersed through the medium and so frittered away, and the ecphylactic conditions required for free growth of the microbes would not have been realised. And, again, in the circumstances, the implanted microbes, instead of being exposed to the antibacterial action of only that fraction of serum

which immediately encompasses them, would have been exposed to that of the entire volume of blood-fluids.

It is thus seen that stagnant, as distinguished from actively streaming blood-fluids must be more liable to become infected.

The next point has application to kataphylactic treatment. Consideration will show that if after growth had already started perpetually renewed supplies of anti-tryptic serum could be transported into the foci of bacterial growth the ecphylactic conditions there initially established would, little by little, be abolished and microbic growth would have been arrested.

All that has been said above with regard to the rôle of the blood-fluids in hindering or favouring infection may be summarised in the form of two general physiological principles :

(1) The natural uncorrupted blood-fluids are competent to keep saprophytic microbes at bay and to preserve the wound against putrid infections, but these uncorrupted blood-fluids will, when they collect in the wound, furnish a favourable nutrient medium for serophytic bacteria.

(2) Additions of trypsin, such as are furnished by the disintegration of leucocytes, corrupt the wound discharges and convert these into an ideal cultivation medium for serophytic and sero-saprophytic organisms indiscriminately.

From these physiological generalisations emerge two broad therapeutical principles for the treatment of wounds :

(1) Where there is a putrid and unwholesome wound—in other words, a wound with sero-saprophytic infection—the proper treatment will be to flush it with fresh wholesome blood-fluids.

(2) Where there is an infected but non-putrid wound—in other words, a wound with a purely serophytic infection—fresh and active leucocytes must be brought into the wound, and these must be provided with the conditions which are essential to their efficient functioning. To that end the physiology of the leucocyte must be carefully studied.

New Data relating to the Physiology of the Leucocyte.

The most important of the physiological properties of the leucocyte, and in particular of the polyneuclear leucocyte, are : (*a*) its very active spontaneous motility ; (*b*) its power of emigrating from the capillaries ; (*c*) its stereotropism ; (*d*) its chemotactic attractions and repulsions ; (*e*) its power of ingesting and destroying by intracellular digestion microbes that have been prepared for phagocytosis and digestion by the opsonic and protryptic [1] action of the serum ; and (*f*) its power of excreting under appropriate stimuli bactericidal substances which kill particular classes of microbes. Further, there comes into consideration, in connection with the leucocyte, the fact that it sets free trypsin when it disintegrates.

The bald proposition that the leucocyte is motile fails to bring before the mind any adequate conception of its activity. How far the current conception falls below actuality can be realised by proceeding as follows : A drop of blood is placed on a

[1] S. R. Douglas, *Proc. Roy. Soc.* B., 1916, vol. lxxxix.

glass slide, is allowed to clot, and is then incubated in a moist chamber at blood temperature for twenty to thirty minutes. The clot is now shaken off, the loose red corpuscles are washed off under a tap, and the drop fixed and stained. It will now be seen, on examination under the microscope, that the area of the slide upon which the blood was deposited is occupied by an almost continuous sheet of leucocytes which have emigrated from the clot and have flattened themselves upon the glass in every condition of active movement (Fig. 3).

As this emigration takes place upon almost every kind of surface, the influence of chemotactic stimuli cannot here come into operation ; and the obvious inference is that in this experiment nothing more has been done than to provide the leucocytes with what they require for locomotion—fixed points to which they can make fast

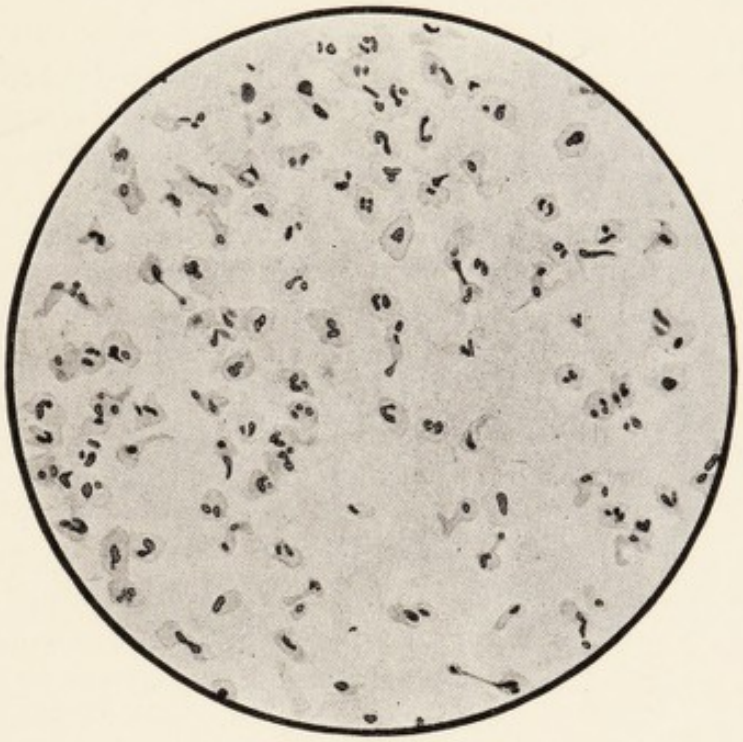


Fig. 3.

and then haul upon. Such points of attachment are provided by the strands of fibrin in the blood clot. To these fibrin strands the leucocytes will, in obedience to their stereotropism, attach themselves and along these they will find their way to the surface of the slide. Arrived there, they will flatten themselves out so as to come in contact with a maximum area of solid surface ; and then, finding at their disposition everywhere on the slide and the under-face of the clot firm points of attachment, they will in the exercise of their propensity for spontaneous movement haul themselves about from place to place.

There are two other points which should be appreciated. The less important may, as directly linking itself on here, be taken first. Inspection shows that practically all the leucocytes found in these emigration films are polynuclear. The polynuclear leucocyte has in the matter of locomotion two advantages over the mononuclear. It can, owing to the subdivision of its nucleus, make its way out

through the capillary wall. And, again—and it is this that comes into consideration here—it can travel much faster. Proof of this is obtained by the following procedure : Blood is filled into an emigration tube [1] and is then centrifugalised. The red corpuscles are thus carried to the bottom ; there are ranged upon the top of these the polynuclear leucocytes, and over these again the large and small mononuclear leucocytes, while the upper half of the tube is occupied by a clear plasma which presently sets into a clot. When an emigration tube containing such centrifuged blood is placed in the incubator the leucocytes immediately begin to transport themselves into the vacant clot, crawling up the trellis of fibrin. In the first half-hour the mononuclear leucocytes, which being disposed at the top have the advantage of the start, are in advance ; but soon the polynuclears, coming forward through the ranks of the mononuclears, take the lead. After that they forge steadily ahead, leaving the mononuclears further and further behind (Fig. 4).

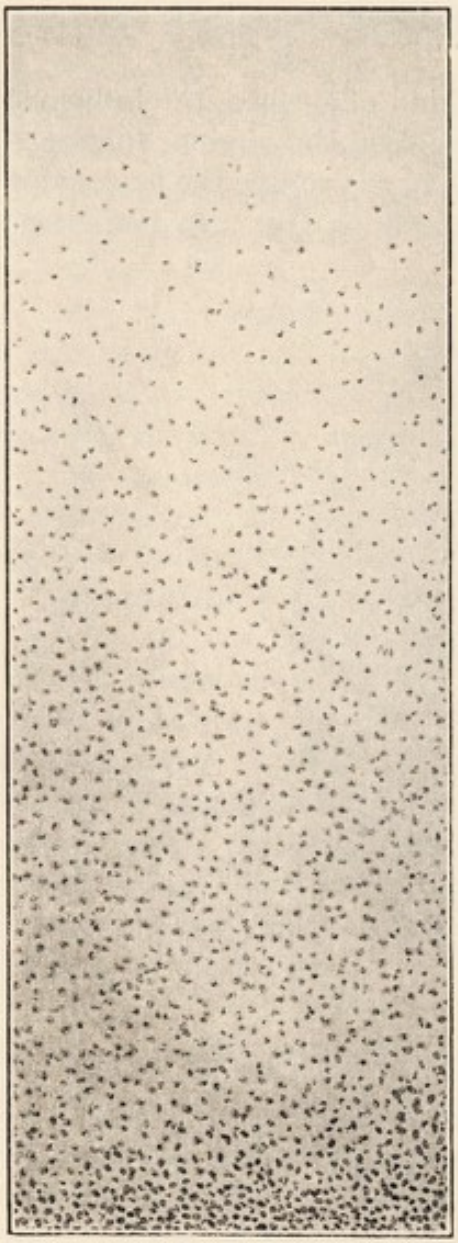


Fig. 4.

The second and most important point relates to the behaviour of leucocytes freely suspended in fluid These, because they have no fixed points to anchor themselves to and haul upon, cannot transport themselves from place to place. In a moving fluid they are swept along by the current ; in a quiescent fluid they sink to the bottom.

That leucocytes cannot transport themselves in pursuit of microbes through a fluid medium is of vital importance in the treatment of wounds, for it teaches that a wound which contains any appreciable amount of effusion is a wound which cannot be sterilised by leucocytic agency. Given an effusion of serum, serophytic microbes will always find opportunity for cultivating themselves out of reach of the leucocytes.

The fact that leucocytic movements can be influenced and directed by *chemotactic stimuli* must next be taken into consideration.

When comparative experiments are made, imposing blood on the one hand on a clean glass surface and on the other on surfaces which have been coated with progressively stronger dilutions of Na_2CO_3 or of streptococcal cultures, it is found that leucocytes emigrate in larger numbers on to surfaces which are lightly coated with alkalies or bacteria, and that they are repelled from heavily coated surfaces. Illustration of this is furnished in Fig. 5 (A, B and C).

Coming now to the consideration of the *bactericidal effect* exerted by leucocytes,

[1] This is a broad flat capillary tube. The method of drawing out such tubes is described in *The Technique of the Teat and Capillary Glass Tube* (Wright and Colebrook. Constable, London, 1921).

perhaps the most instructive single experiment is the following. For it the following articles are required : (*a*) a piece of glass tubing about $2\frac{1}{2}$ in. in length and $\frac{1}{2}$ in. internal diameter, and sealed off and rounded at the end ; (*b*) a glass lath (i.e. a rectangular slat of cover-glass or microscopic slide) cut to such dimensions as to fit loosely into the tube ; and (*c*) an agar plate whose surface has been evenly im-

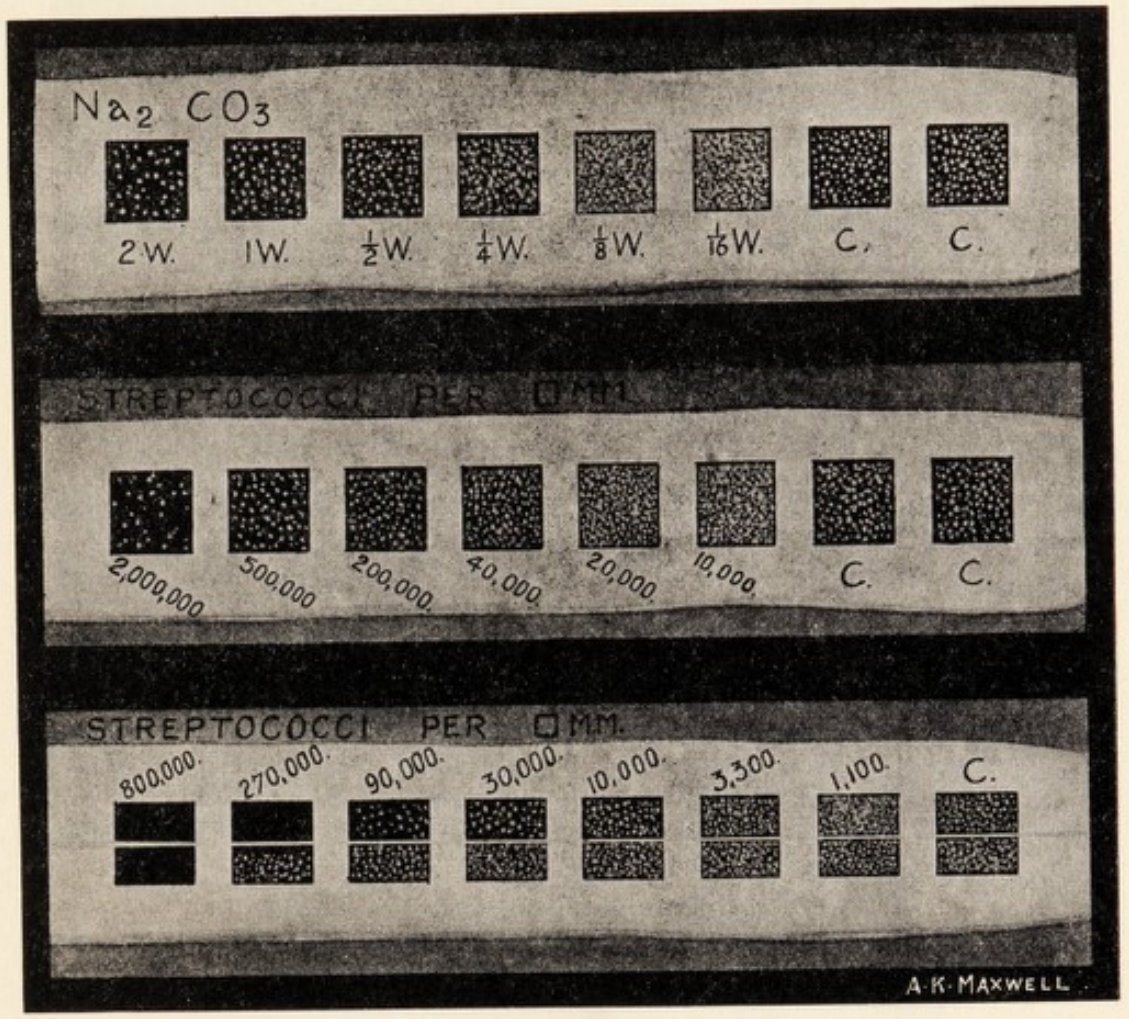


FIG. 5.

In A the white dots which stand out against a black background represent emigrated leucocytes. The sodium carbonate solutions (of which just enough was imposed to cover the bare glass) varied between a 2-wash to a $\frac{1}{16}$-wash dilution of a 570 Na_2CO_3 solution.

In B and C the white dots again represent emigrated leucocytes ; and the figures show the number of streptococci imposed on each square mm. of surface. The microbes were in B imposed upon the whole, in C only upon the upper half of each square.

planted with a culture of staphylococcus or streptococcus. The lath is introduced into the tube, blood is then filled in, and this is immediately centrifugalised so as to carry down the red corpuscles, and to give a stratified layer of leucocytes at the top of this and plasma above. (*Vide supra*, p. 97, Fig. 2). With the lath left in position, the tube is now incubated for half an hour or more. On removing the lath from the clot and washing off the red blood corpuscles with serum, a dense

band of leucocytes will be found on each face, firmly attached in the form of a belt upon the glass (*supra*, p. 98, Fig. 3). One face of the lath is now wiped clean, and the other is now imposed on the implanted surface of agar and pressed down

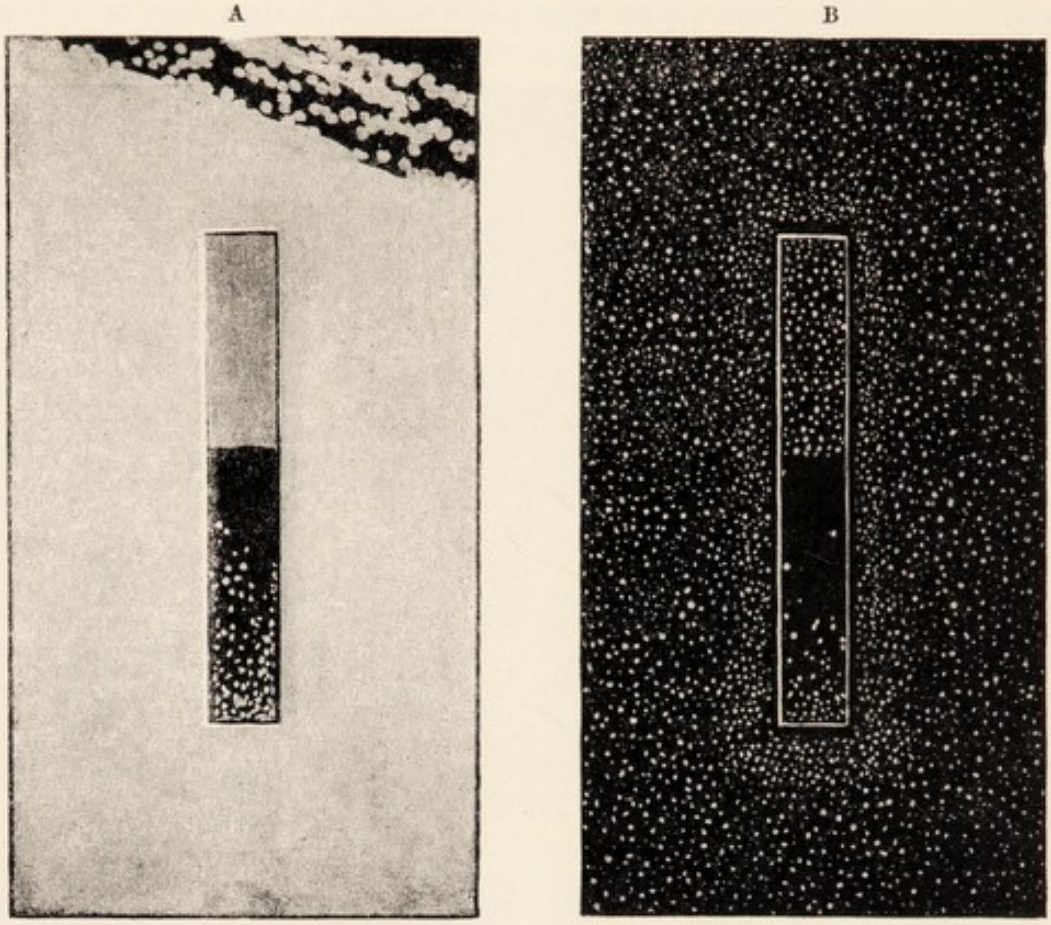


FIG. 6.

Glass laths imposed on agar surfaces implanted (A) with staphylococcus, (B) with a haemolytic streptococcus pyogenes.

gently so as to get rid of superfluous serum. The plate is now incubated, and the result is then as shown in Fig. 6 (reintroduced here from p. 100). It will be seen that the entire surface of the agar is covered with a continuous sheet of microbes, except only where the leucocytes have come into operation. There the agar remains bare, and if the lath is now removed from the agar and the leucocytes fixed and stained, they will be found, if the leucocytes were operating in serum, full of ingested microbes.

On the other hand, if the lath had been washed free from serum the microbes are just as effectively destroyed, but they are here (for microscopic examination shows that there is in this case no phagocytes) bactericidins excreted by the leucocytes.

The difference between the mechanism of bacterial destruction which comes into operation in these different cases is well shown in Fig. 6. A and B.

The fact that leucocytes can in two several ways bring about the destruction of microbes has in connection with the treatment of bacterial disease generally far-

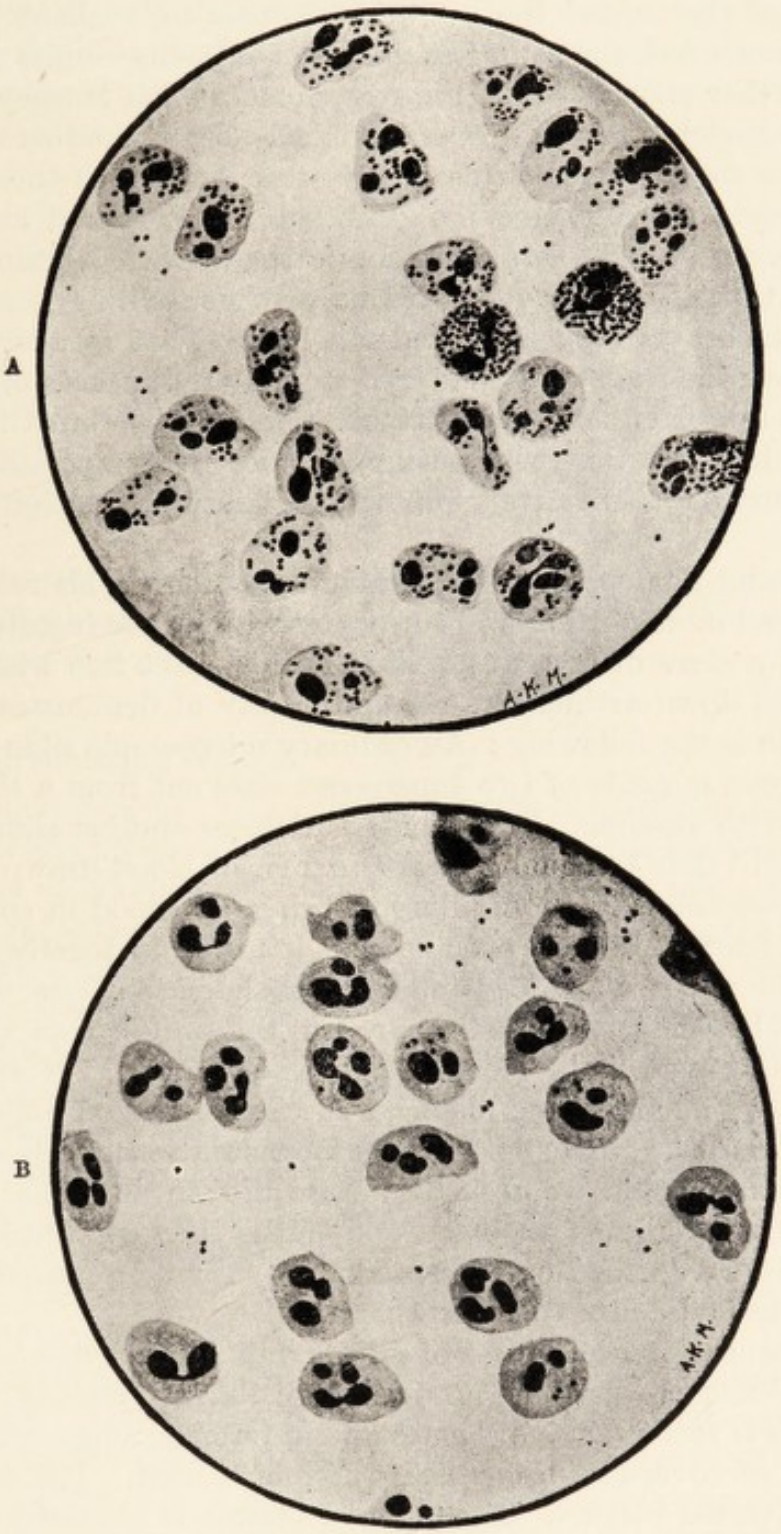


FIG. 7.

In A leucocytes operating in serum—phagocytic destruction of microbes. In B leucocytes operating in physiological salt solution—extra-cellular destruction of microbes.

reaching importance, but the fact of chief concern here is that the imposition of a leucocyte-covered lath on an infected surface is in its essence the same procedure as the suture of an infected wound. In other words, what is of concern here is that if in the suture of the wound the conditions which are realised in these *in vitro* experiments are achieved, the same satisfactory sterilising results will be obtained. Consideration further shows that if the experiments with leucocyte-covered laths are to serve as a model in suturing operations it is clear that there must come into application in the wound blood-fluids of the same quality as those of the normal blood, and leucocytes in the same proportionate numbers and as freshly derived from the blood as are brought into operation in the *in vitro* experiments. Again, it will be essential that the leucocytes shall be provided with the same facilities of access to the microbes as they have under a lath. That means that there must not be left between the walls of the sutured wound any pockets of serum in which the microbes are safe from leucocytic attack. And lastly—but this is a condition which does not, in connexion with suture, require to be specially emphasised—the leucocytes must be as effectively protected against desiccation as in the above experiment.

One further and final point must receive attention. This relates to the fact that leucocytes, and more particularly leucocytes which have ingested bacteria, contain within them a store of trypsin ; and that this is set free when the leucocyte dies and is broken down artificially. A simple way of demonstrating the setting free of this trypsin is the following : An ordinary microscopic slide is taken, and at either end a buttress is made of two superposed slats cut from a thick microscopic slide and coated with vaseline. Upon these buttresses another slide is then placed. Into the ' slide-cell ' thus formed about 100 c.mm. of blood drawn from the finger are introduced, care being taken in filling to bring the blood in contact with both the roof and the floor of the slide cell so that it may run together into a column stretching from the upper to the lower slide. The slide cell is now placed in a moist chamber and incubated for about an hour. In this way a copious emigration of lucocytes from either end of the blood column is obtained. The cell is next pulled to pieces and the clot and loose red blood corpuscles washed off under a flowing tap, and the slides then dried. Next—and by this means the leucocytes which have been killed, but not disintegrated by desiccation, are broken down—a drop of physiological salt solution is imposed on them, and this is then concentrated and evaporated to dryness in the incubator. This operation may be repeated, adding a drop of water to the leucocytic film and re-evaporating.

The two slides, each with its area of disintegrated leucocytes, are now disposed so that the one leucocyte carpeted surface shall lie immediately over the other. Then the slide-cell is reconstructed, but this time for each supporting buttress only a single thin slat of cover-glass dipped in vaseline is used. The cell is then filled with recalcified citrated plasma. The citrated plasma is obtained by mixing with blood drawn from the finger one-tenth of a 5 per cent. solution of citrate of soda and then centrifuging. The plasma which is pipetted off is then, to restore its coagulability, recalcified by adding 0·25 per cent. of calcium chloride cryst. After filling in the plasma the ends and sides of the slide-cell are sealed with melted paraffin, and it

is then placed in the incubator for a number of hours. A digestion of the clot, commencing in the area occupied by the disintegrated leucocytes and spreading out from thence to the periphery, is now obtained.

The fact that the disintegrating leucocyte sets free trypsin—here rendered manifest by the digestive action exerted on the clot—is of general pathological significance. In relation to wounds, the setting free of trypsin from the leucocyte prepares the way for sero-saprophytic infections ; for it corrupts the discharges, and converts these into a favourable nutrient medium for all microbes without distinction. Again, the setting free of trypsin is responsible for the erosion which is seen at the mouth of every discharging sinus and on every wound surface which is not re-dressed at very frequent intervals. To the action of trypsin is due also that erosion in the depth of the wound which leads, when large vessels course in the neighbourhood, to secondary haemorrhage. Lastly, the separation of sloughs is in every case the work of trypsin set free from leucocytes, and it will be seen later that by employing a procedure essentially similar to that by which trypsin was set free in the experiment described above, the separation of sloughs can be very much accelerated.[1]

A certain scientific foundation has now been laid and this must serve as a basis to the study of the physiology of the infected wound. It will be convenient to take up first the study of the wholesome granulating wound.

The Wholesome Granulating Wound.

This is a wound in which there are antitryptic blood-fluids, and in consonance with this a purely serophytic infection. Further, upon the encasing walls there is a protective coating of granulation tissue, and superficial to this a film of leucocytes which is being constantly reinforced by fresh emigration from the capillaries in the vascular granulation tissue. The evolution of events which occur in this type of wound has been carefully studied by Dr. A. Fleming, employing a technique modelled upon that employed in the lath experiments already described.

In this case impression cultures were made by applying a cover-glass to the surface of the wound and then transferring this directly, or after desiccation, to an implanted or unimplanted surface of an agar plate. When transferred to the agar without delay the leucocytes of the discharge come into operation living, and the culture obtained may be designated a ' bio-pyo-culture '. When, before implantation on the agar, the leucocytes are allowed to desiccate, the culture obtained may be called a ' necro-pyo-culture '.

For the observations in question the point of departure selected was the moment after the wound had been thoroughly syringed out with physiological salt solution. The first fact brought to light was that syringing is a procedure which carries away from the surface of the wound all the larger formed elements, in other words, all the leucocytes ; but leaves behind many of the smaller elements—the microbes. When a cover-glass is applied to the surface of a syringed wound and is then fixed and stained, and examined by the microscope, leucocytes are found to be absent

[1] *Vide infra*, p. 162, Addendum to this discourse.

and only microbes are seen. And when a cover-glass is applied to a syringed wound, and is then imposed upon an agar plate and incubated, the implanted microbes grow out in full number into colonies.

A cover-glass applied to the surface of the wound three to eight hours afterwards gives a very different picture. Large numbers of freshly emigrated leucocytes are found and interspersed among these a few scattered microbes ; and when bio-pyo-cultures are made, in other words, when the leucocytes of the pus are placed in favourable external conditions, they attack and kill the microbes and complete sterilisation is effected.

Pyo-impressions made later show that the pus is, as it lies in the wound, gradually losing its antibacterial power ; and at the expiration of twenty-four hours there is on the surface of the wound a rapidly increasing population of microbes.

The whole cycle of events here described is made manifest to the eye. (*Vide supra*, p. 108, Fig. 11.)

Certain further material points were brought out by Dr. Fleming's researches.

(1) The first of these is that active leucocytes, such as are obtained from a wound which has been syringed out three hours before, are competent to destroy not only the microbes contained in the pus, but also extraneous microbes in large numbers. This is seen when leucocytes collected from the wound are imposed upon agar previously implanted with microbes. (*Vide supra*, p. 126, Fig. 4 (lower half).)

(2) Another practically important point has reference to the case where there is an excess of serum in the wound discharges. When a cover-glass is imposed on such a pus serum will be expressed and will dispose itself in the form of a ring round the leucocytic disc. Such serophytic microbes as have been carried beyond the reach of the leucocytes will grow out here, forming a ring of colonies. Fig. 5, A (p. 101), shows such a circlet of colonies. Where as was done in the case of the preparation in Fig. 5, B, a sample of pus is stirred up in a drop of serum, colonies of serophytic microbes come up all over the field except in the islands of pus.

(3) If before making a pyo-impression culture, the pus is allowed to dry, or is heated above 46° C., the thermal death-point of the leucocytes, its bactericidal power is abolished. This is shown by the fact that colonies of serophytic microbes now come up thickly in the substance of the pus (p. 101, Fig. 5, C, D and E).

The therapeutic lesson already learned from the lath experiments—the lesson that the proper way of sterilising an infected surface is to cover it in and turn leucocytes loose upon it—is by the data set forth above reinforced and supplemented.

The study of pyo-impression cultures brings out the subsidiary but very important facts that so long as the wound remains open the infection is never extinguished, and that washing and dressing impose only a temporary restriction upon bacterial growth, and that the infection begins again to make progress so soon as the leucocytes succumb to the unfavourable external conditions encountered in the wound.

This cycle of events here described is uninfluenced by any application of antiseptics. In point of fact the effect of antiseptics is in general pernicious. They may

by their negative chemotactic action hinder the emigration of leucocytes. They may coagulate the albumen of the tissue elements and of the discharges, forming a glaze over the walls of the wound which will mechanically confine the microbes and prevent also the emigration of leucocytes and the outflow of wholesome fluids into the wound. Again, antiseptics may by exerting an irritant action bring into the wound an excessive quantity of serum. Or again, they may induce the antitryptic power of the blood-fluids, and by so doing convert this into a more favourable nutrient medium for all kinds of microbes. Important illustration of all these points is furnished by Dr. A. Fleming in a paper on ' The Action of Chemical and Physiological Antiseptics in the Septic Wound '.[1]

Nor, again, can the cycle of events above described be influenced by the exhibition of vaccines. Vaccines cannot be of service when the leucocytes are unprovided with shelter and facilities for locomotion and the external conditions are such that the blood-fluids must, by the setting free of leucocytic trypsin very quickly be corrupted.

The proper principle when dealing with a wholesome wound is to *close in order to sterilise, instead of using antiseptics with a view to closing.* In connexion with this therapeutic principle the following points may be emphasised :

(1) The procedure here enjoined is that which Nature herself employs. She extinguishes the wound infection only by closing the wound.

(2) There is in the *modus operandi* of closure employed by Nature one outstanding defect. The epithelium grows in only very slowly from the edges of the wound. In consequence of this dilatory ingrowth the bacterial infection will in extensive wounds persist for indefinitely long periods, with the result that contracting scar tissue takes the place of the normal epithelial covering.

(3) By artificial closure, whether by actual suture, by drawing together of the edges by strapping, or by skin grafting, the wound is promptly sealed, with the result that the bacterial infection is rapidly extinguished and the formation of scar tissue is avoided.

The physiological technique of the suturing operation sums itself up in the case of the wholesome granulating wound in the following :

(*a*) The wound will be in the best condition for operation three or four hours after it has been washed out with physiological salt solution.

(*b*) An endeavour must be made to avoid leaving any pockets or dead spaces, and as far as possible to prevent any effusion into these. The best way of securing this will be to apply firm compression.

(*c*) The preparatory employment of antiseptic applications will, in view of what has been said above, be definitely contraindicated.

(*d*) Vaccines also may be ruled out as unnecessary if the operation can be properly conducted. But they may perhaps find useful application in those cases where it is difficult to secure accurate apposition of the walls of the wound. For by the agency of vaccines both the antitryptic and bactericidal power of the blood-fluids may be increased, and that being so, it should be possible to some extent to keep in check bacterial growth in pockets of serum.

[1] *Brit. Jl. of Surgery*, vol. vii, No. 25, 1919.

The Foul Wound with Putrid Infection.

There will, of course, be all kinds of differences in degree among the wounds that fall into the category of corrupt wounds. There will be (*a*) the lightest form, the neglected granulating wound where the discharges have by postponement of dressing been allowed to become tryptic, and a slight sero-saprophytic infection has supervened. There will be (*b*) such extravagantly putrid wounds as have been described at the beginning of this chapter. There will be (*c*) quite recent wounds where the infection is in the initial stage and which will, if they go untreated, develop into definitely putrid wounds.

It will be remembered that the special features of definitely putrid wounds are the following : The walls of the wound cavity are formed by naked tissues ; the cavity contains a putrid pus in which every kind of microbe is pullulating ; the infection has penetrated into the walls ; and these are covered with gangrenous sloughs. It will also be remembered that these wounds fall into two classes. Where the wound cavity has laid open to the air and where drying has closed the superficial capillaries the necrosis produced by bacterial infection will have been supplemented by that due to the shutting off of the blood supply. Where the cavity is cut off from the exterior there will be a profounder invasion of the surrounding tissues and a more aggravated bacterial intoxication of the system.

Surgical science as it existed before the war provided for the treatment of these cases only a very meagre armamentarium of therapeutic measures. For wounds leading into abscess cavities it prescribed only that they should be freely laid open, should be provided with drainage-tubes, and should be syringed out with antiseptics. For the slough-covered open putrid wound it prescribed only syringing with antiseptics.

That the free laying open of the wound achieved its main object cannot be doubted. It constantly staved off impending gangrene, and arrested to some extent that progressive invasion of the encasing tissues which ultimately leads to septicaemia. Over against this must be set the fact that all operative procedures upon infected tissues carry in their train risks from excessive auto-inoculation. In particular this applies to that preliminary routine which during the war was committed to the theatre orderly. Very vigorous ablutions and antiseptic applications and the careless casting loose of limbs from the splints under the anaesthetic must often have conveyed into the blood and lymph-stream formidable quanta of bacteria and bacterial products.

Passing to the therapeutic measures employed for holding in check the septic process in the wound, it is subject to no dispute that the syringings with antiseptics and the traditionary devices for draining which surgical science provides proved inefficacious as applied to the putrid septic wound. Day after day one saw the wounds so treated fill up with the same quantity of putrid pus, and this pus contained exactly the same pullulating population of microbes.

There was thus in connexion with putrid suppurating wounds a therapeutical problem urgently pressing for solution, a problem which was before the war, and is perhaps even now deliberately put out of sight. In that problem the following points stood out quite clearly : (*a*) the insertion of drainage-tubes is, as a device

for securing effective drainage, absolutely futile; (*b*) antiseptics applied in the wound are quite incapable of accomplishing what is demanded of them; (*c*) an extravagant pullulation of microbes such as occurs in the putrid wound is inexplicable except on the basis of some defect in the discharges.

(*a*) With regard to drainage, consideration shows that its true object and end should be (i) to drain away from the cavity of the wound and the surrounding infected tissues the corrupted fluid which provides a good nutrient medium for microbes, and (ii) to drain into the infected tissues and wound cavity uncorrupted fluids derived from the blood. In other words, the proper conception of drainage is arrived at when it is regarded as a kataphylactic operation whose object it is to abolish ecphylactic conditions, and bring the phylactic powers of the blood into action upon the infecting microbes. Now the drainage-tube itself does nothing beyond providing a channel of exit through which the discharges can escape when the cavity of the wound is full to overflowing, or when the outflow is favoured by gravity. But even when the wound opens downwards there will always remain behind on the walls of the cavity a slime of discharge, and that will prevent the infected surface of the cavity and the infected tissues below coming back to a wholesome condition.

It will appear later that effective drainage, which is in the treatment of putrid septic wounds absolutely essential, can in point of fact be quite simply achieved.

(*b*) Coming next to the consideration of the disappointing results of antiseptics applied in the wound, there is for these a very simple explanation. All antiseptics have, in addition to those chemical properties which have won them their title, and are published from the housetops, also other chemical properties about which the advocates of antiseptics say as little as possible. All antiseptics, not excluding those which are specially belauded as operative in serum, enter into chemical combination with proteins other than those contained in bacterial protoplasm. Those antiseptics which are dyestuffs also combine chemically with the fabrics which are used as dressings from the wound. In consequence of these vagrant chemical affinities antiseptics are efficacious only when brought into contact with microbes which are suspended in watery fluids or else lie high and dry, naked to chemical attack. Or, putting this in the inverse way, it may be said that antiseptics are quenched, in other words, they lose their power of entering into lethal chemical combination with microbes when they are introduced into or imposed upon albuminous fluids or applied to albuminous surfaces; and, as pointed out by Fleming, the same thing happens when antiseptics which are also dyestuffs are brought into contact with cotton or linen dressings.

The point specially important to appreciate is that antiseptic syringings can never extinguish an infection in pockets filled with pus or serous effusion. This is brought out very clearly by the instructive experiments of Fleming, made with 'artificial wounds', consisting of test-tubes drawn out at their inferior end into hollow spikes, in imitation of the diverticula of war wounds. These were filled with serum, implanted with faecal material, and then incubated. After twenty-four hours the contents were evacuated. The tube was then filled with antiseptic and re-emptied several times. It was then refilled with sterile serum and reincubated.

After twenty-four hours it was as heavily infected as before. In the next experiment the ' artificial wound ' was ' redressed ' in precisely the same fashion, except only that here the antiseptic was, on the first re-dressing, left in the wound for one hour ; on re-dressing the next day for three hours ; and on the subsequent day, at the third re-dressing, for twenty-four hours. In each case the sterile serum became heavily infected. And in comparative experiments, in which in one set of tubes physiological salt was employed for washing out the tube, and in other sets of tubes eusol, Dakin's solution, 2½ per cent. carbolic acid, brilliant green, and flavine respectively, the final results were precisely similar. And, again, precisely similar results were achieved when the conditions of the experiment were varied by employing for the serum culture, instead of a tube with recesses, a plain tube into which there had been introduced a pledget of asbestos wool to do duty as a foreign body.

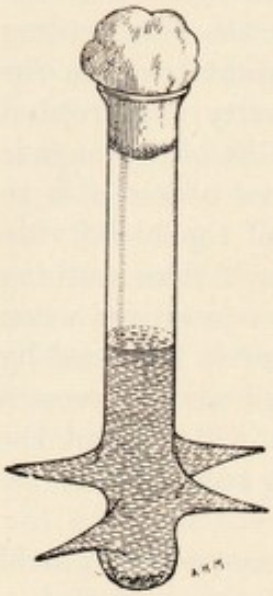


Fig. 8.

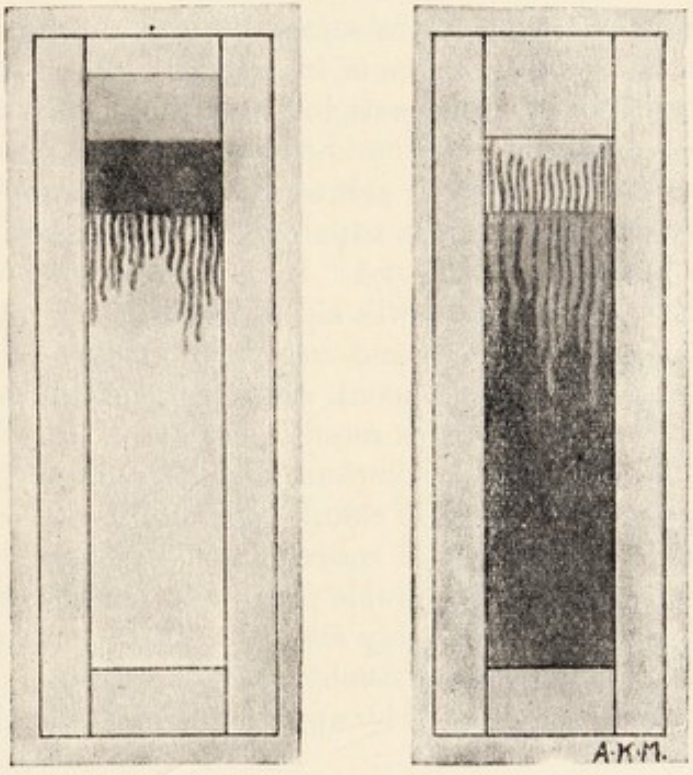
The lessons of these experiments are clearly that infected fluid can never, by ordinary mechanical means, be effectually evacuated from a recessed wound or a tissue or fibre, and that the microbes that lie in recesses or interspaces occupied by an albuminous fluid are by this completely sheltered from the attack of antiseptics. And these experiments further teach us that it is futile to hope for any effective washing out of a recessed wound or infected tissues, or for any sterilisation of recesses and interspaces by the agency of antiseptics unless we can find a solution which has the power of drawing into itself albuminous fluids, and which will at the same time itself be drawn into such fluids.

(*c*) The final point made in the criticism of the treatment applied to putrid wounds was that the rapid pullulation of microbes in these and the polymorphic character of the infection ought immediately to have made it clear that here the conditions are so favourable to the microbes that no application of antiseptics could by any possibility be effective. The moment this was appreciated it was seen to be essential to ascertain whether the patient's blood-fluids were vitiated in the source or whether they became vitiated only as they lay in the wound. An experiment already incidentally referred to, the experiment in which a ' lymph leech ' is applied to the walls of the wound, definitely resolved this question. The details of the experiment are as follows : An ordinary stout-walled test-tube is taken and a hole blown in the wall about half-way down to serve as a mouth, and the upper end is then drawn out into a convenient nozzle. A short length of rubber tubing sealed at one end with a little piece of glass rod is then fitted to this. The needle of a syringe is now passed through the wall of the rubber tubing and the mouth of the lymph leech is then applied to the wall of a putrid septic wound which has been emptied of pus. A vacuum is now created in the interior by drawing out the piston of the syringe. The needle is withdrawn, and the lymph leech is left clinging to the walls of the wound. (*Vide supra*, p. 5, Fig. 1 ; and p. 123, Fig. 2.) After a period of hours, when the cavity of the wound has filled up again with putrid discharge,

the belly of the lymph leech contains only a clear fluid. Specimens of the pus and of the fluid from the lymph leech are now taken and microscopic preparations made from each. The difference between the two will be seen on glancing at the insets to Fig. 2, p. 123. In the specimen of the discharge from the cavity of the wound there is a teeming population of microbes and disintegrated leucocytes. In the specimen from the belly of the lymph leech there is practically a pure cultivation of streptococcus. There are also wholesome leucocytes in small numbers.

The facts learnt from this experiment are : (*a*) that the lymph when tapped off from the walls of the wound is uncorrupted ; (*b*) that it is only after effusion and by the agency of corruptive influences operative in the wound that the lymph is converted into a nutrient medium in which every putrefactive microbe flourishes unrestrained ; and (*c*) that these corruptive influences can be overborne by providing a sufficient indraught of lymph into the wound cavity.

It will be seen that there is here the basis for an effective treatment of serosaprophytic infections of wounds. All that is required is to flush the wound with



A B

FIG. 9.

wholesome lymph. A variety of different agencies can effect this. (*a*) Direct negative pressure may be employed, as in the experiment with the lymph leech. (*b*) There can be applied to the walls of the wound any solution which induces active hyperaemia. (*c*) Recourse may be had to passive hyperaemia. And, lastly, (*d*) there can be applied in the wound any solution which has a power of drawing into itself an albuminous fluid. From the point of view of convenience and easy regulation this will be the easiest of all the methods.

Now salt solutions of appropriate strengths have in relation to albuminous

solutions very interesting and for the purpose here in view very important faculties.[1] They very energetically draw albuminous solutions into themselves, and are by reciprocal action drawn into albuminous fluids. This ' intertraction ' is very strikingly made manifest to the eye when there is introduced into a plane-wall cell [2] first a 5 to 7 per cent. solution of sodium chloride (Figs. 8 or 9). With this the cell is to be filled more than half full. Upon this heavier salt solution is to be superimposed a little serum coloured with watery eosin and upon the top of this a stratum of water. Then, directing attention to the dividing line between the serum and salt, one sees —appearing almost instantly—active mass movements of intertraction, with characteristic appearances which may be denoted ' pseudopodial interpenetration '. These are manifestations of a down-draught of the lighter supernatant serum into the heavier subjacent salt solution, and of updraught of salt solution into the serum, and by this process of mixture, which is subsequently reinforced and supplemented by ordinary diffusion, there is in a comparatively short time achieved, as shown by the uniform distribution of the eosin, a completely equable mixture of the stratified saline and albuminous solutions. While these active movements of indraught and mixture are in progress below where the serum and salt solution come together, the upper frontier, that where the serum is in contact with water, remains almost absolutely quiescent. Here there comes into operation only that very slow and quite familiar process of interpenetration known as diffusion.

The attractive power exercised by salt solution upon serum which is manifested to the eye in the above experiment is capable of being turned to good account in connexion with the putrid septic wound. Here is an agency which can establish genuine drainage. The salt solution will aid in ablution, inasmuch as it will draw out serum from the recesses of the wound and the interstices of infected tissues. It will also function as a kataphylactic agent, producing that indraught of wholesome serum into the wound cavity which is required for the abolition of the sero-saprophytic infection. The most suitable solutions of salt for employment in wounds will be solutions of $2\frac{1}{2}$ to 5 per cent. sodium chloride. Solutions weaker than $2\frac{1}{2}$ per cent. possess too little drawing power, and concentrated solutions act as escharotics—even 5 per cent. solutions give considerable pain when applied to tender new-formed skin at the edges of wounds. They may also, when kept long applied to unbroken skin, produce irritation and a pustular staphylococcic infection. But these incidental evil effects can all be guarded against by applying to the skin surfaces a protective covering of vaseline.

From the above it is apparent that by applying 5 per cent. salt solution a putrid infection lurking in the diverticula of wounds can be abolished. But in addition to this there is, as we have seen, another feature to be regarded. The surface of the putrid wound is coated with sloughs, and there is in these sloughs—just as there is infected foreign matter such as clothing or a sequestrum of dead bone—an ecphylactic focus which will prevent the re-establishment of wholesome condi-

[1] Wright, *Proc. Roy. Soc.* B, 1921, vol. xcii ; *Proc. Roy. Soc.* A, vols. cxii, 1926 : cxiv, 1927 : cxxv, 1929 ; and Schoneboom (a fellow-worker of the Author's), *Proc. Roy. Soc.* A, vol. ci, 1922. Two of the Author's papers are reproduced in an abridged form below, pp. 162–172 ; and to these is appended a postscript (*infra*, 172–173).

[2] The Slide Cell, described on p. 165 *infra*, is an ideally simple form of plane-wall cell.

tions and the healing of the wound. The next task must accordingly be to consider how to get rid of the sloughs.

The physiological agency Nature here employs is tryptic digestion, the trypsin for this purpose being provided by the disintegration of leucocytes. Upon this device therapeutics may profitably be modelled. Where there is a thin layer of desiccated slough, such as is formed when the skin only has been torn off and the subcutaneous tissue has been exposed to desiccation, an efficient method will be to apply strips of lint soaked in trypsin. But in the ordinary case where there is a thick necrotic layer a superficial application of trypsin will be quite inadequate, and the proper course will be to bring into application trypsin in the depth of the slough. In connexion with this it has been shown (*supra*, p. 135) that leucocytes set free trypsin when subjected to the action of strong salt solutions ; and also that when strong salt solutions are brought into application upon albuminous solutions the albumen is carried into the saline solution and the salt into the albuminous solution. If, therefore, a 5 per cent. salt solution is applied to a slough, albuminous fluids will pass out from the interstices, and salt solutions will pass in and will come into operation on the leucocytes held fast in its tissue. Trypsin will then be set free and the strands which hold together the necrotic material, and those also by which it is attached to the tissues beneath, will be eaten through and the entire slough will be disintegrated and cast loose.

Two quite simple experiments confirm these conclusions : (1) Two test-tubes are filled with white of egg leaving room in each above for a cotton-wool plug, and

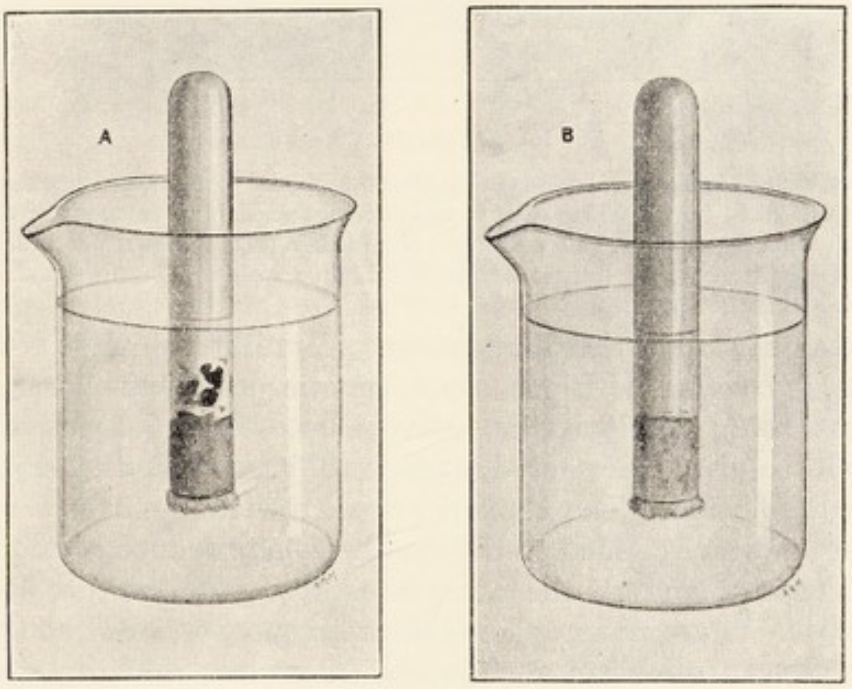


Fig. 10.

the albumen is then coagulated by immersion in boiling water. Two cotton-wool plugs, soaked in a non-tryptic pus, are then introduced into the test-tubes, and these are inverted into beakers, one B containing 0·85 per cent., and the other A 5 per

cent. salt solution. All this is now placed in the incubator and examined after twenty-four hours. The results will then be as shown in Fig. 10. It will be seen that while in the tube B very little has happened, in A tube the white of egg has been extensively tunnelled by digestion.

(2) In the second experiment an attempt is made to imitate more closely the conditions obtaining in a slough-covered wound. Two beakers are taken, filled to a depth of 2 or 3 cm. with egg albumen, and this is coagulated by immersion in boiling water. A little uncoagulated white of egg, left over for the purpose, is then poured on the surface. Two discs of lint which will lie comfortably in the beakers are now taken and, with the nap turned uppermost, imposed on the liquid white of egg. Then by again immersing the beakers in boiling water the discs of lint

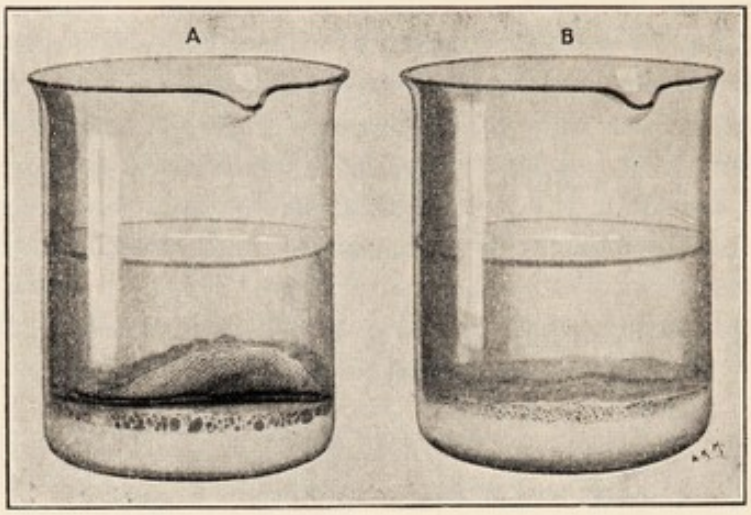


FIG. 11.

In beaker (A) is shown the loosening of the artificial slough, and the digestion of the subjacent hard-boiled white of egg, which is obtained by treatment of the superjacent pus with 5 per cent. salt solution. In beaker (B) is shown the much smaller amount of digestion obtained by treatment of the pus with 0·85 per cent. salt solution.

are luted down firmly upon this foundation. This lint, which is to do duty as an artificial slough, is covered with pus, a non-tryptic pus being chosen, and the same quantum of pus being employed in each beaker. Then into the beaker A some 5 per cent. salt solution is poured, and into beaker B the same quantity of physiological salt solution. The beakers are then incubated for an hour or more. After that enough water is added to the first beaker to reduce considerably the concentration of the salt, and to the other the same quantity of physiological salt solution. The beakers are now replaced in the incubator, and then the progress of events watched by examination at frequent intervals. It will then be seen that comparatively soon the artificial slough in the beaker with the 5 per cent. salt solution becomes loosened from its foundation, while the other remains for a long time firmly attached.

The results here obtained *in vitro* are in full concordance with those actually obtained in the wound. When 5 per cent. salt solution is applied the sloughs are

very rapidly cleaned off, and with this the conversion of the putrid wound into a clean and wholesome wound is completed. It must be clearly understood that with this the utility of the 5 per cent. salt solution treatment is exhausted. From this time forward, except only in the case of a recurrence of the sero-saprophytic infection, the wound must be treated in accordance with the therapeutic principles applicable to clean wounds.

We may pass now from the terribly putrid wound, that which has been left for days without surgical recision, to the less heavily infected wound. In dealing with this type of wound very signal successes, attracting general attention in the early middle period of the war, were obtained in the hospital at Compiègne under the direction of Alexis Carrel. As important questions of principle, and in particular the issue of the efficacy of antiseptics, are here in question, it will be well to consider carefully the treatment adopted by him.

The facts that have to be regarded are the following : (*a*) Owing to the propinquity of Compiègne to the firing line the patients were received for treatment before the infection of their wounds had made much progress ; (*b*) recision and surgical cleansing of the wounds was very carefully carried out ; (*c*) that done, the wounds were at frequent and regular intervals flushed with Dakin's fluid—this, which is a solution of hypochlorites, being carried down into the recesses of the wound by a system of tubes. To this flushing with Dakin's fluid the therapeutic successes achieved in the hospital were attributed. It was, in other words, assumed that the employment of a suitable bactericidal agent and its application in a suitable manner were the essential elements in the successful treatment of infected wounds.

One must here consider, *first*, whether the factor of proximity to the front and that of early and careful recision and cleansing did not, in connexion with the successes achieved, come heavily into account ; *secondly*, whether the mere mechanical lavage did not also count for much ; and, *lastly*, whether Dakin's fluid, though employed in the capacity of a bactericidal agent, does not really owe its therapeutic virtues to the physiological reaction it exerts on the wound.

With regard to the rôle played by early and careful recision and cleansing of the wound, it will suffice to hark back to the fact that as soon as surgical hospitals were established behind the firing line and emphasis was laid on early recision and surgical cleansing of the wound, putrid infections became rare. And it may perhaps be added that as soon as the influence of such early surgical intervention was fully appreciated the interest excited by Carrel's results and the vogue of his treatment quickly passed away.

With regard to the frequent and efficient lavage secured by Carrel's procedures it is obvious *a priori* that such lavage must in the treatment of wounds always be of great importance, and there is unanimity among those who have had to deal with wounds requiring frequent laborious and painful redressing that the methods of lavage elaborated by Carrel are extremely valuable.

Passing now to the vital issue as to whether Dakin's fluid, which is the essential element in Carrel's treatment, is therapeutically valuable by reason of its possessing bactericidal properties or by reason of its possessing other properties distinct from this but valuable in the wound, one's judgment must evidently be guided not by

the *a priori* views, but by the results of direct experimental enquiry. Such experimental enquiry into the bactericidal and physiological effects of applications of Dakin's fluid to wounds has been made by Fleming.[1] His investigations establish that Dakin's fluid loses all bactericidal potency within five minutes after its introduction into the wound, and further that applications made to the surface of a clean wound do not, even when repeated hourly for four hours, in any way diminish the population of microbes. To this may be added that the microbic population found on a clean wound treated with Dakin's fluid does not differ with respect to either character or number from that found on clean wounds treated only with salt solution. It is not without significance that under either treatment only sero-saprophytic microbes are eliminated, and only serophytic microbes are found to survive.

The experiments of Fleming have further shown that applications of Dakin's fluid induce increased effusion, this effusion manifesting itself not, as when 5 per cent. salt solution is applied, immediately; but only after the lapse of a certain latent period. The effusion here in question is accordingly produced not by the forces of ' intertraction ' but by the active congestion. That Dakin's fluid induces hyperaemia is, of course, familiar to those who have seen the bright coral-red granulations of wounds treated by hypochlorites, or have witnessed the troublesome irritation which develops on the circumjacent skin when hypochlorite solutions are employed in excessive strength.

The facts brought out here establish that it will, in every case where a beneficial result is attributed to antiseptic treatment, be logically necessary to show that the results cannot be ascribed to a beneficial physiological reaction produced in the wound. Thus, for example, in those oft-cited cases of Lister in which undiluted carbolic acid was successfully employed in the treatment of compound fractures, the possibility of successes of this kind being due to a kataphylactic pouring out of lymph must be taken into account. A profuse pouring out of lymph was in point of fact a very striking feature in connexion with those war wounds which were treated with undiluted carbolic acid, and such profuse outpouring is also specifically mentioned by Lister in connexion with his cases.

Gas-gangrene Infection.

The treatment of putrid infections leads by a natural transition to the consideration of gas gangrene and tetanus, for these are interlinked with the putrid wound infections by the fact that they develop only when ecphylactic conditions prevail in the wound and only, at any rate in the case of gas gangrene, when the fluids at the seat of implantation are profoundly altered.

Dealing first with gas gangrene, the key to its understanding lies in the study of the requirements and conditions of life of the microbe. In connexion with these the fact which has most impressed itself on the bacteriologist and the surgeon is that the microbes which produce gas gangrene—the *Bacillus Welchii* and its close congeners the *Bacillus Oedematiens* and the *Bacillus Fallax*—are anaerobic microbes. But exaggerated importance has been attached to this; and the erroneous assump-

[1] *Loc. cit.*

tion that the microbe could grow only under anaerobic conditions led at the outset of the war to quite futile methods of treatment. For example, oxygen was injected into the affected parts on the notion that infection might thus be prevented from spreading. That such practice lacked scientific foundation is clear when it is remembered that Tarozzi had already shown long before the war that, when pieces of animal tissue are added to bouillon, vigorous cultures of the gangrene bacillus can be obtained in open tubes. Confirmation of these findings of Tarozzi was obtained every day during the war, the bacillus of gas gangrene being often found growing luxuriantly in open wounds.

Instead of pursuing that theme let us turn our attention to a fundamental guiding principle in pathological and therapeutic research. In connexion with all infections, whether they are septicaemic infections or wound infections, or special saprogenous infections such as gas gangrene and tetanus, the facts which, above all other facts, require to be sought out are those which relate to the growth of these pathogenetic microbes in the blood-fluids.

In connexion with each species of pathogenetic microbe it should be determined first whether it can grow in the unaltered blood-fluids, and, if the microbes fail to grow in these, what are the influences which can convert the blood-fluids into a medium which will be favourable to its growth.

In the course of the researches undertaken during the war[1] it was ascertained that the bacillus of Welch will not grow in normal serum until enormous implantations, implantations of the order of 20,000,000 microbes per cubic centimetre, are arrived at; but it has to be appreciated, as having a general application, that if very much smaller numbers are implanted, and if the infection is subsequently concentrated by gravitation or centrifugalisation (*vide supra*, 48 and 49 and p. 118, Fig. 1), cultures are obtained with smaller implantations; and culture begins in each case in the lower end of the tubes. And, again, if as a preliminary to implanting into serum the gas-gangrene microbes are inserted into a fabric, they will develop in those interstitial pockets in which there is the required concentration of microbes in the unit volume of serum. This clearly accounts for the cases in which infection proceeds from a piece of infected clothing implanted into the tissues by the projectile.

Experiments of this kind undertaken with normal serum were, in view of what had been elicited with respect to sero-saprophytic infections generally, followed up by implantations of the gas-gangrene bacillus into serum of artificially reduced antitryptic power. In this medium, very luxuriant cultures were obtained from quite small implantations; and the gas-gangrene bacillus was found to grow also in aerobic conditions. Here, of course, is an explanation of the microbe of gas gangrene being very often found growing freely in open putrid wounds.

It was plain, however, that the faculty of growing freely in sera of reduced antitryptic power did not furnish the key to the explanation of the special features of gas-gangrene infection. And reflection after a time led to the finding of something that was special to the gas-gangrene bacillus. It suggested itself, on considering the fact that the microbe elaborates acid when it grows in serum or blood, or milk, and

[1] *Vide supra*, pp. 43-92.

on relating this with the 'avalanche growth' of the culture, that the blunting of the alkalinity of these media by the growing microbe might possibly be the factor which provided for the gas-gangrene bacillus favourable conditions of growth. Experiment showed that this is so, and that it is a matter of practical indifference whether the alkalinity of the serum is reduced by an addition of a mineral acid, or of lactic acid or by saturation with carbonic acid. The optimum addition of acid was found to be that which just neutralises or just falls short of neutralising the medium.[1]

Here, then, was perhaps a key to the problems of gas-gangrene infection. To take those problems in order :

(1) The first problem arises in connexion with the facts discovered by Welch. It was left an enigma by Welch why the gas-gangrene bacillus injected into the blood-stream produces no infection in the living rabbit, while, if the animal is killed immediately after injection and kept warm, there will be obtained in a very few hours a teeming blood culture which distends the whole corpse with gas and converts the liver into a foaming mass. This paradoxical result stands in relation to the fact that the alkalinity of the blood is, when the corpse is kept warm, rapidly reduced by an influx of lactic acid from the muscles. That here is the circumstance upon which the success of the bacterial implantation pivots is shown by the fact that the multiplication of the microbe in the corpse commences as soon as the alkalinity of the blood is sensibly reduced, and then gains speed like an avalanche, going faster and faster as the alkalinity of the blood is progressively reduced.

Proof that there is here a true nexus of cause and effect is obtained by varying the procedure.[1] If instead of giving first the intravenous injection and then killing and incubating the animal, the animal is first killed and successive samples of blood are now from time to time withdrawn from the corpse and implanted with the bacillus, the rate of growth and the luxuriance of the cultures increase with the reduction of blood alkalinity, while at the same time successful cultures are obtained from smaller and smaller implantations of the bacillus. Lastly, if the intravascular injection of Welch's bacillus is preceded or followed up by one of bicarbonate of soda the growth of the microbe in the dead animal is postponed.

(2) The key to the problem of the post-mortem invasion of the blood found, a whole series of clinical problems also are unlocked. There is *first* the problem as to why gas gangrene takes origin in connexion with muscle ; *secondly*, as to why it so often develops after the application of a tourniquet, and in the muscles of the calf after a lesion of the posterior tibial artery ; *thirdly*, why it is so frequently associated with trench foot, and implunging wounds, and wounds where there is extensive bruising by the agency of pebbles and grit driven in by explosions ; *fourthly*, why gas gangrene so often develops in the wounded who have lain out in the cold, in those who are affected with shock, and, if one can in such matters trust to impressions, in those suffering from exhaustion after extreme muscular effort.

Each and all of these problems find quite simple resolution when it is remembered that muscle elaborates and sets free lactic acid not only when it enters into

[1] *Vide supra*, p. 55 *et seq.*

rigor mortis, but also whenever its oxygen supply fails or becomes inadequate. Now this will happen under three different sets of conditions :

(1) It will happen, in the first place, when the blood supply to a muscle or set of muscles is interfered with. The interference may result from an arterial lesion—for example, a lesion to the principal artery of a limb, or to an artery which, like the posterior tibial, is the exclusive source of supply to a group of muscles ;—or from artificial compression of the vessels ; or from an extensive lesion of the capillary circulation such as results from bruising and implunging wounds ; or, lastly, from interference with the circulation such as results from long exposure to wet and cold.

(2) Again, the oxygen supply to the muscles will be interfered with when, as in shock, there is a general collapse of the circulation ; for when the blood-pressure sinks away the peripheral arteries carry no blood and the muscles are by consequence starved of oxygen.

(3) Lastly, when excessive demands are made upon the muscular system the supply of oxygen will, despite the fact that the blood-vessels are intact and the general blood-pressure is maintained, be unable to keep pace with the chemical requirements of the muscles.

Accordingly, under all these three different sets of conditions a local acidosis will be established in muscle, and where there is instead of a quite restricted myogenic acidosis a general muscular acidosis such as is associated with shock, there will inevitably, as soon as this excess of acid is conveyed into the blood-stream, supervene an acidaemia. This myogenous or shock acidaemia, as it may be termed, will prepare the way for the growth of the bacillus of Welch in the blood, in other words, for the development of a gas-gangrene septicaemia.

It has been seen in the above how the soil is, by the generation of acid in muscle, prepared first for the local invasion by the gas-gangrene bacillus, and afterwards for the secondary septicaemia. But the microbe can establish itself without assistance from myogenous acid. It can, when other circumstances are favourable, pave its own way. It has already been seen that the gangrene bacillus, when sufficiently heavily implanted, will furnish a culture even in normal serum, elaborating acid, and establishing by this conditions more favourable to its growth. In precisely the same way the gas-gangrene bacillus can, if sufficiently heavily implanted, establish itself in the subcutaneous tissues or elsewhere, and the local infection and production of acid in the lymph, when unchecked, without the help of any myogenous acid render the blood acidaemic and so prepare the way for a blood infection.[1]

But for the most part the events in gangrene are much more intricately interwoven than has as yet appeared, for the gas-gangrene bacillus, when it pullulates in the body, produces a characteristic toxaemia. Beginning quite abruptly with vomiting, this leads rapidly to a collapse of the circulation, which makes the undertaking of any operative procedures impossible. The pulse at the wrist becomes impalpable, the face turns an ashen grey, the hands, feet, and after these the entire limbs, tip of the nose, forehead and cheeks become cold as stone, while the mental faculties for the most part remain quite intact ; and then death—as is its wont in other acidaemias, and notably in scurvy—comes quietly and without warning given. For

[1] *Vide supra*, pp. 61–63, Charts I–VI.

example, one may look away from the patient for a moment and then, on turning round, find him dead. It will be clear that the toxaemic collapse and shock here in question will, like every other form of collapse and shock, cut off the oxygen supply from the muscles, thus engendering a myogenic acidaemia. After that if the circulation is brought back that will lead, as in other cases of shock, to an absorption of myogenous acid into the blood, and, if the focus of infection has not in the meantime been extirpated, in addition to a larger absorption of gas-gangrene toxins. With these points made clear, the treatment of gas gangrene may next be considered.

Nothing need be said here about the local surgical treatment except that, when extirpation has to be left incomplete—where, for example, it has proved impossible to resect the whole of the infected muscle, or where a limb has been amputated and the gangrene infection has already spread on to the trunk, or, again, where it has been impossible to get enough covering without including in a flap a doubtful patch of skin—it will be urgently necessary to supplement the treatment by efficient drainage, i.e. by drawing out the corrupt lymph from the infected tissues, and drawing into these tissues from the blood-vessels a lymph, in which the gas-gangrene bacillus cannot grow. In cases like the above-mentioned, and also wheresoever incisions are made with the idea of providing drainage, applications of a 5 per cent. salt solution will render useful service. They will in the case of incisions prevent these becoming lymph-bound, and will provide that copious kataphylactic flushing with wholesome lymph which is required.

With regard to general constitutional treatment of gas gangrene, this must clearly be contingent on the interpretation placed upon the symptoms. In other words, the treatment selected will depend upon whether the symptoms are ascribed predominantly to the acidaemic process, or predominantly to special toxins elaborated by the gas-gangrene bacillus, or to both these elements conjointly and to an approximately equal extent.

There is room here for frank differences of opinion, and the situation is as follows. When the train of reasoning set out above, and also inference from clinical observation, had led to the conclusion that there was an acidaemic factor in gas-gangrene toxaemia, and when it had been verified by titrations of the blood alkalinity that the patient's collapse and enfeeblement go hand in hand with the intensity of the acidaemia, the conclusion was inevitable that whatever else might be done or left undone, it was essential to combat the acidaemia. Accordingly, intravenous injections of 4 per cent. bicarbonate of soda were resorted to.[1] The benefit obtained by these injections is one of those things that are subject to no dispute ; and there is, in the domain of medicine, probably nothing more dramatic than what happens when a gas-gangrene patient who is in a state of complete collapse, and who may be panting in air-hunger, receives an injection of alkali. He will often within a very short time sit up in bed and smoke, read a newspaper, and call for food. The essential is that he is brought into a condition in which he is easily able to endure the administration of an anaesthetic and an extirpation operation. But—and this point cannot be too strongly insisted upon—the patient will, in default of proper treatment,

[1] *Vide* pp. 66–68, Table III and pp. 74–76, Table A.

after a time almost inevitably relapse, such relapse being due to the resorption of a fresh quantity of myogenic acid and (if in the meantime the focus of infection has not been extirpated) also of microbe-elaborated acid and toxins. Such relapse is best forestalled by the oral administration of lactate of soda, the lactate of soda being administered in doses of 8 grm. every three hours until such time as the body is saturated with alkali and the urine rendered alkaline.

The surprising therapeutic efficacy of bicarbonate of soda injections creates a doubt as to whether specific toxins, other than acids, come much into account in the causation of the collapse. The toxaemia of gas-gangrene infection has, however, by many investigators been envisaged from an entirely different point of view from that here maintained, and these observers see here a perspective in which acidaemia plays no part, and the toxins of the gas-gangrene bacillus attract to themselves all the attention. In their judgment the goal of endeavour in the treatment of gas gangrene must be to place at the disposal of the surgeon an antitoxic or antibacterial serum.

In connexion with this question it will suffice to note that the anti-gangrene sera which have been prepared by French scientists and employed in the French army have been very favourably reported upon. But it is not even certainly known with respect to these whether the action exerted upon the patient is antibacterial or antitoxic ; or whether—and this is in view of the large volume of serum employed and its insertion into the site of infection—the sera act simply as any kataphylactic introduction of wholesome blood-fluids would act. In the British army, the results obtained with anti-gas-gangrene sera were negative. Here, as in the French army, experiential and statistical methods were employed, instead of direct observation of the effects obtained on the patients' blood.

Tetanus.

While the special study of tetanus lay outside the sphere of research here summarised, it may not be unprofitable to indicate the important problems which here still await solution. Before all others it will be of import to determine, for this has a very important bearing on prophylaxis, whether the tetanus bacillus can grow in the unaltered or only in corrupted blood-fluids. For clearly, if, as the clinical facts suggest, the tetanus belongs, like the gas-gangrene bacillus and so many other microbes, to the class of the sero-saprophytic microbes, it will then be a denizen only of foul wounds and ecphylactic foci, and tetanus will occur only in such conditions as prevailed at the outset of the war ; and, if that is the case, it becomes a matter for consideration whether injections of antitetanic serum might not have been discarded with advantage in those cases where there was opportunity for the early and careful recision of wounds.

On the Forestalling of Infection in War Wounds and on the Physiological Principles which should here come into application.

The surgery of war wounds, that is to say, of wounds where there are mangled and devascularised tissues and an implantation of bacteria, may be summarised in three general principles :

(1) All devascularised parts must be resected, and this should be done with the least possible delay.

(2) When the devascularised parts have been resected steps must be taken to deal with the infection left in the wound and to prevent fresh infection.

(3) When the surgical cleansing and recision of the wound has to be postponed, steps must be taken to prevent, so far as possible, the development of infection in the devascularised tissues.

The rationale of these principles briefly is as follows :

(1) The amputation of lacerated limbs, and of limbs whose main artery has been severed, is of course dictated by the consideration that infected animal tissues when cut off from their blood supply fall a prey to gangrene and provide an ecphylactic region in which microbes can grow without restraint. And immediate amputation is required because microbic growth commences without any delay. In conformity with this, not even under the pressure of events at the outset of the war, were wounded limbs sent down to the base unamputated.

In the recision and surgical cleansing of wounds the very same principles come into application. The surgeon here resects all those tissues which the projectile has lacerated, and which, since they have been deprived of their anti-bacterial defence, will become infected sloughs. Here also, if putrid infection and gas gangrene are to be forestalled, there must be no delay. But at the same time, inasmuch as delay does not here as in the case of the mangled limb mean inevitable death, resection and surgical cleansing can, but of course only under penalty, be postponed or even omitted. As has already been seen at the outset of the war, the wounded were sent down to the base unoperated, and this was also the case afterwards, whenever after extensive military operations the medical units at the front were congested. The penalty that has to be paid for this is the development of gas gangrene in a certain proportion, and of putrid wound infections in nearly 100 per cent. of the severely wounded.

(2) When the devascularised parts have been resected there remain naked surfaces, and where the flaps have after amputation or after excision of tissues been loosely brought together there is also a wound cavity which fills up with effusion. On these naked tissues and in this effusion if proper measures are not taken microbes will establish themselves. To prevent this, steps must be taken to prevent desiccation—for desiccation closes down the capillary circulation and prevents the emigration and the functioning of leucocytes. Further, by bringing the walls of the wound everywhere in close contact, the leucocytes must be given free access to every part of the surface. Again, by bringing the walls of the wound in close contact, all dead spaces where serum might accumulate, must be obliterated. For accumulations of serum provide a nutrient medium for serophytes and a safe refuge from the leucocytes.

All this can be achieved by primary suture of the wound, but this procedure will not everywhere be applicable. For example, it may be impracticable to effect adequate cleansing of the wound ; or there may not be sufficient skin covering available ; or again the gap in the tissues may be of too large dimensions or too irregular to permit of its surfaces being accurately brought together.

Here it may parenthetically be observed that where the gap left by the resection

operation is of immoderate size, suture may in certain cases be made feasible by resort to some artificial filling. Fillings of fat have sometimes been employed ; and in the latter part of the war a filling of paraffin, bismuth and iodoform, proposed by Rutherford Morison as an antiseptic filling, was extensively employed. The faults of that particular filling were that the material though intended to operate as an antiseptic, was itself not sterile ; and that it contained in the bismuth and the iodoform definitely poisonous elements.

Where primary suture is impracticable, the resected and surgically cleansed wound should, pending resort to secondary suture, be treated on essentially the same principles as the clean granulating wound : that is to say, the wound should always, as soon as the emigrated leucocytes cease to operate effectively against the microbes, be cleansed with physiological salt solution, and if sero-saprophytic microbes should put in an appearance, these should be eliminated by short applications of a 5 per cent. salt solution.

(3) Where, owing to stress of circumstances, resection and surgical cleansing of the wound have to be postponed, treatment should aim at preventing, as far as possible, the development of putrid infection in the devascularised tissues. What the French call a *pansement d'attente*—a *retardative* or *inhibitory* dressing—is then required.

At the outset of the war the ordinary but not clearly formulated notion about a retardative dressing was that it might be any kind of antiseptic dressing. Afterwards, when in view of the condition of the wounded arriving at the base it had been realised that all the ordinary kinds of antiseptic dressing were useless as inhibitory dressings, the accepted idea for improving them was to employ more and more concentrated antiseptics, and when, again, these more concentrated antiseptics proved unavailing it was suggested that viscid and very slowly soluble antiseptic pastes should be filled into the wounds. Those who witnessed the outbreak of gas-gangrene cases which occurred in connexion with wounds choked with these pastes may claim to have seen something of the savage revenge that Nature can take when fundamental physiological principles are flouted.[1]

In reality, as suggested in a memorandum which was circulated in the war, what is really required is a *kataphylactic* dressing. Such a dressing would in the case of widely open wounds be gauze or lint soaked in 5 per cent. salt solution, backed with further dressings soaked in saturated 25 per cent. salt solution, and over these protective material. In the case of wounds with only small external openings, tubes might be introduced and through these 5 per cent. salt solution carried down repeatedly into the wound.

Such kataphylactic dressings might also with advantage be employed not only for the prevention of putrid infections in the devascularised tissues of the unresected wound, but also as a travelling dressing for wounds that have after resection and surgical cleansing to be transported from one hospital to another. They would prevent the desiccation of the wound and its invasion by sero-saprophytic microbes. In the words of an eminent French surgeon : [2] 'No method is more easy to carry

[1] The reply to Sir W. Watson Cheyne, which is reprinted by way of a codicil to this book, was inspired by personal acquaintance with these disastrous results.

[2] Policard, *Évolution de la Plaie de Guerre*, Masson, 1918.

out, and none so well adapted to the worst and most lamentable of the conditions encountered in war. It constitutes the routine method for those periods of ' surgical misery ' when the battle conditions, the pouring in of the wounded, the difficulties of transport, and the insufficiency of staff prohibit the employment of more purely surgical methods.'

In conclusion, it may be pointed out that this question of retardative and travelling dressings, which has suffered from much neglect by reason of the fact that in this war surgical hospitals were established close behind the lines, is bound in future wars to make good its claim to attention. In wars of movement, and even in stationary wars in all times of pressure, there will only be one way of staving off putrid wound infections and gas gangrene and tetanus, and that will be by using an efficient retardative dressing.

ADDENDUM ON SECONDARY HAEMORRHAGE FROM WOUNDS[1]

Secondary haemorrhage, which is perhaps the most distressing sequela of suppuration occurring in wounds that pass near arteries (and the same, of course, applies to haemoptysis in the consumptive), results when the pus which is in contact with an artery has become tryptic and has digested through the wall of the vessel.

The risk of such haemorrhage occurring in badly drained narrow penetrating wounds can never be left out of sight. The danger can, however, always be warded off by keeping the wound syringed with 5 per cent. salt solution. And warning of eventual danger can always be obtained by testing a sample of pus obtained by passing a swab down to the bottom of the wound.

The method of testing for trypsin is perfectly simple. All that is necessary is to keep at hand tubes of sterilised milk to which there has been added 1 per 1,000 of calcium chloride cyst ;[2] to introduce into this a pledget of cotton wool soaked in pus and to incubate the pus-implanted milk in a water bath standing at 50° C. Tryptic pus coagulates the milk. In the later years of the 1914–1918 European War the surgeons attached to the No. 13 General Hospital were regularly supplied with such tubes.

[1] This section, which should properly have appeared in the chapter on the ' Physiology of Wounds ' as originally published, has here been added.

[2] The calcium chloride converts the milk into a more sensitive trypsin indicator ; and in the case of boiled or autoclaved milk the calcium chloride added serves to replace the calcium salts thrown out of solution by the application of heat. (*Vide* Author's *Technique of the Teat and Capillary Tube*, 2nd Edition, Constable, London, 1921), pp. 123–129.

ON 'INTERTRACTION' BETWEEN ALBUMINOUS SUBSTANCES AND SALINE SOLUTIONS[1]

In 1906 I pointed out that hypertonic salt solutions applied to wounds, sinuses and foci of infection increased the discharge from these, supplementing the ordinary mechanical drainage by drawing out from the tissues infected and corrupted lymph.

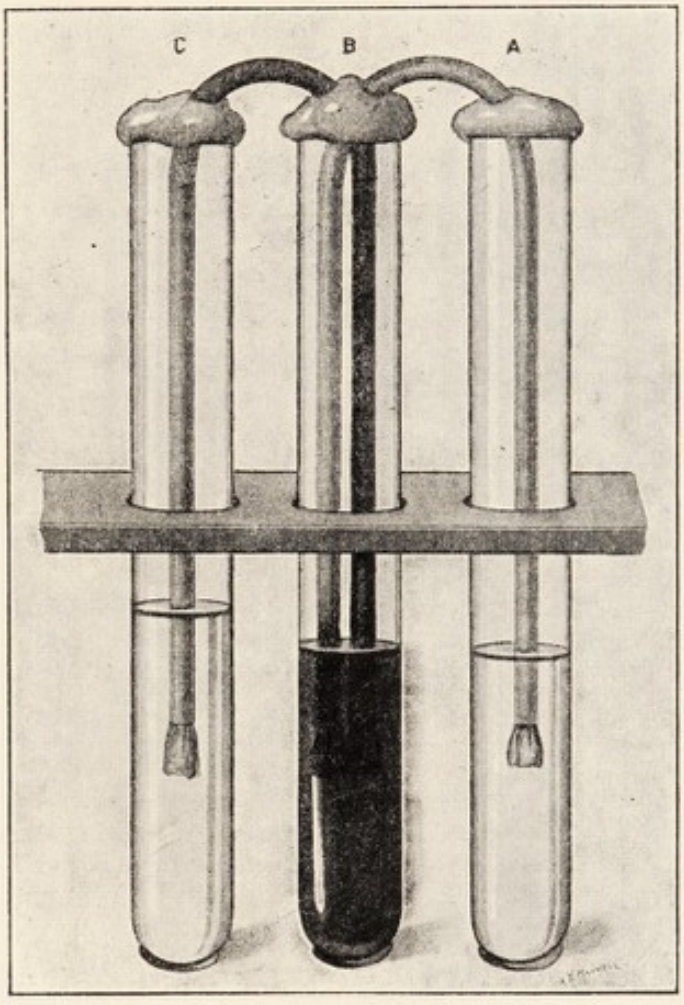


FIG. 1.

Tube A contains uncoloured water; Tube B, water coloured with methylene blue; and Tube C, saturated salt solution. The fluids stood originally at the same height in each tube.

[1] Reprinted with some introductory matter from the *Proceedings of the Royal Society*, B, vol. 92.

In the war, and especially in its earlier period when every form of sepsis and gangrene was rife and almost every wound was foul, I again advocated treatment by hypertonic salt solutions. The method was then employed extensively and with good results.[1]

Hereupon followed a detailed study of the action of hypertonic salt solutions upon the wound, and also an examination of their action *in vitro*.[2] It was in the course of this latter found that when a receptacle containing strong salt solution

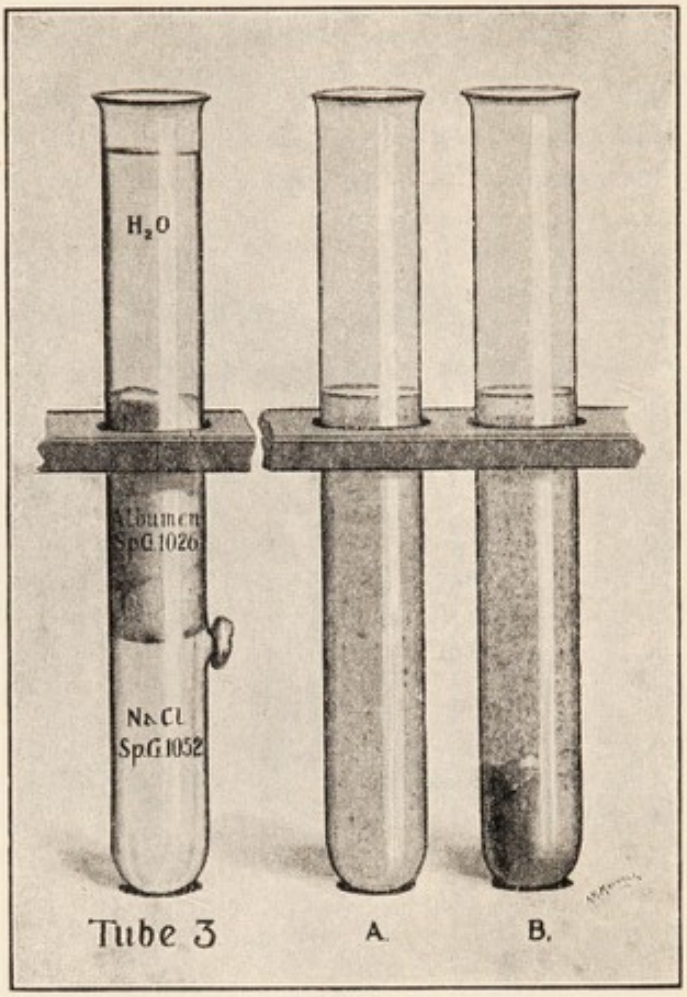


FIG. 2.

Tube 3 is flanked with test-tubes labelled A and B showing the result of boiling the fluid from the upper (A) and the lower (B) compartments of this tube.

is connected up with a receptacle containing water by a siphon tube threaded with a wick or filled with water and armed (at the end which dips into the salt solution) with a tight cottonwool plug, water is slowly drawn into the salt solution—the level of this rising and that of the water falling (Fig. 1).

A much more rapid and abundant drawing effect—in the form of a down

[1] The lay reader may here be referred to the citation from the distinguished French surgeon cited on p. 161 *supra*.

[2] *Proceedings Royal Institution*, March 9, 1917; and *Lancet*, June 23, 1917.

draught of supernatant fluid into a heavier salt solution [1] was obtained by taking a test-tube, dividing it up into an upper and lower compartment by a plug of cotton-wool soaked in a solution of white of egg possessing a specific gravity of 1026, and then filling the lower compartment (through a lateral opening) with a saline solution possessing a specific gravity of 1052, and the upper chamber (which here provides a control) with water. It was found that the egg albumen was under these conditions carried down rapidly and in large quantity into the subjacent heavier salt solution while none found its way into the superjacent water (Fig. 2).

That experiment would seem to suggest that the forces of diffusion are at any rate in the case where albuminous substances and saline solutions are brought into conjunction, supplemented by what I should like to call '*forces of intertraction*'.

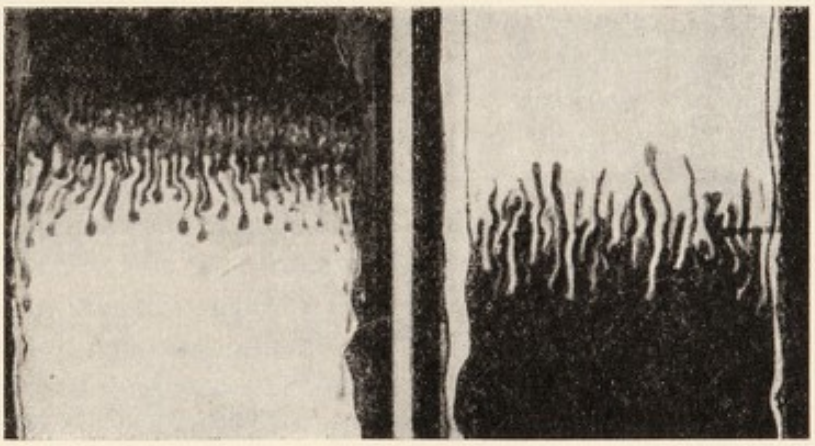
In the following that hypothesis is subjected to certain further examination.

The method of investigation adopted was to superimpose serum or other albuminous fluids directly upon heavier saline solutions, or upon occasion lighter salt solutions upon heavier albuminous fluids—adding generally to one or other fluid a trace of colouring matter (eosin) in order to render the course of events more manifest to the eye.

The experiments are most conveniently conducted in 'slide cells'. These are made by laying down five strips of paper which have been soaked in melted vaseline transversely at equal distances on a microscopic slide, and then bringing down another microscopic slide upon the vaselined strips; the slide-cell being, after the lower half has been filled in by capillarity, made staunch by sealing its lower edge with melted paraffin.

When in such a cell serum coloured with eosin, or containing in suspension red corpuscles or Indian ink is allowed to run down gently from a pipette on to the surface of a heavier (e.g. 6 per cent.) saline solution, the following train of events occurs.

As a first effect the serum indents the surface of the salt solution, but it immediately by hydrostatic resilience takes up a position on its surface and is delimited



A B

FIG. 3.

[1] Figs. 1 and 2 and Fig. 3 which is reproduced from photographs did not appear in this Royal Society publication. I have taken 1 and 2 from my *Technique of the Teat and Capillary Tube*, 2nd Edition, Constable, 1921.

below by a somewhat wavy outline. Then within a very few seconds—seemingly as a result of whirlpool movements sucking in downwards the protruding wave summits—this specifically lighter serum is drawn down into the heavier salt solution below. The appearance is then as if pseudopodia or tentacles were being let down into the depths. Simultaneously with this, as can be seen when we employ uncoloured serum and a coloured salt solution or salt solution containing Indian ink in suspension, this last is carried up into the serum, forming there a system of ascending streams (Fig. 3, A and B).

This down- and up-streaming progresses apace and gives, as an intermediate result : a stratum of transported serum upon the floor of the cell ; and a layer of transported salt solution ranged at the top of the cell superficially to the original stratum of serum. As a terminal result, we have complete interfusion, manifested to the eye, when a diffusable colouring substance like eosin has been employed, as a fluid of quite uniform coloration.

It will be seen that we have here two arresting features : the singular fashion in which the lighter and heavier fluids interpenetrate (we may perhaps speak of this as 'pseudopodial invagination'), and the rapidity in which complete interfusion is achieved.

A further point is brought out in Fig. 4, which is a diagrammatic drawing of a plane-walled cell, in which we have three superposed strata of fluid 5 per cent. salt solution below, coloured serum in the middle, and water on the top of the serum. It will be seen here that while the lower boundary line is in commotion the upper boundary line is absolutely quiet.

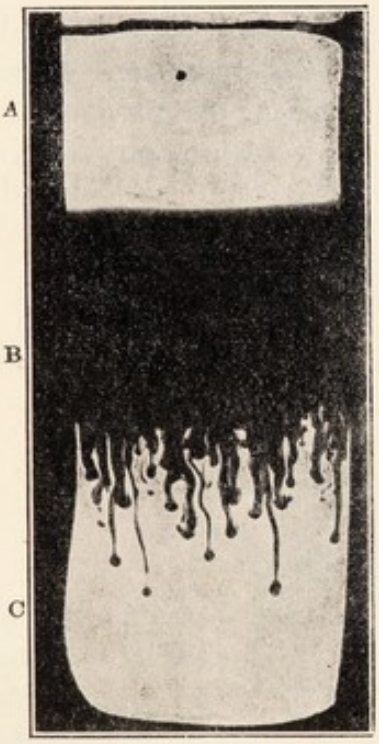


FIG. 4.

Comment

The body of observations set out above would appear to invite a re-examination of the doctrine that in *diffusion*—or as it would seem more proper to call it *interfusion*—we are dealing in every case with a perfectly passive recipient fluid and with a disbursing fluid which has a monopoly of activity. In other words, the data here obtained would seem to invite some review of the doctrine that when a solute passes out from its menstruum into an adjoining fluid territory; or a diluting fluid is carried into a concentrated solution, dispersive forces resident in the solute are the only forces which come into operation.

While that doctrine ostensibly holds the field there is to be noted that in German text-books the term *Adhäsion*, and in French text-books the term *appel* are still employed in explanation of the passage of water through a dialysing membrane into salt solution. In view of the observations here set out it may perhaps be legitimate to put forward for consideration whether the term *Adhäsion* (which

would have as its English equivalent ' binding or conjoining force ') and the term *appel* (which might perhaps be translated into the invocation ' come hither ') are simply figures of speech, figures behind which there lurks nothing substantial and objective.

And if it be permissible to generalise from the case of what happens when albuminous substances and saline solutions are brought into conjunction, it may be suggested that it would be appropriate explicitly to recognise the existence of *tractor* or *drawing forces*, and more generally of *intertraction*, as an agency which may co-operate with diffusion and assist in bringing about interfusion.

A FURTHER CONTRIBUTION TO THE STUDY OF THE PHENOMENA OF INTERTRACTION

REPRINTED FROM THE ' PROCEEDINGS OF THE ROYAL SOCIETY ', A, VOL. 114, 1927

Seeing that a phenomenon of lateral streaming which I recently described and figured [1] as convincing evidence of *horizontal intertraction* is construed otherwise by N. K. Adam,[2] I have, with a view to testing his interpretation of the phenomenon, made some further quite simple experiments.

It will not be amiss, as a preliminary to detailing these, to place the real issue in debate—the issue as to whether there is such a *vis operans* as intertraction—before us in proper perspective. I would propose to do this by recounting what led up to the investigation of intertraction.

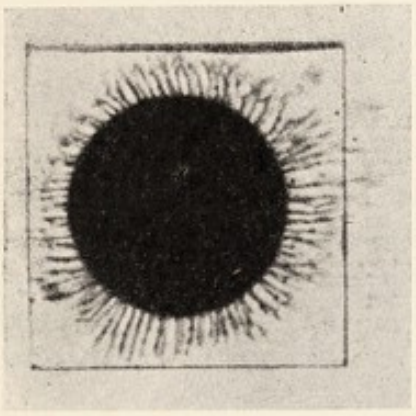


FIG. 5.

The study of this *vis operans* began with observations on the effect of applying to furuncles requiring evacuation a plaster consisting of soap and sugar which is used in folk-medicine for ' drawing ' such boils. It was found that soap and sugar applied to open boils did, in point of fact, keep the orifice through which pus had discharged itself open and did at the same time induce a copious welling-up of lymph from the subjacent tissues. In pondering this effect it suggested itself that the soap constituent might by decalcifying and preventing the coagulation of the out-flowing lymph be staving off the sealing of the wound by scab ; and that the sugar constituent of the plaster might be attracting, or to use the household word, ' drawing ', fluid from the open lymph spaces.

Acting upon this idea—and, of course, mindful of the fact that Heidenhain had

[1] *Roy. Soc. Proc.*, A, vol. 112, 1926 : *vide* Fig. 5.

[2] *Roy. Soc. Proc.*, A, vol. 113, 1926.

found that sodium chloride and other crystalline substances introduced into the blood call forth an increased lymph flow—I substituted sodium chloride for the sugar, and citrate of soda for the soap; and proceeded to treat wounds which required 'drawing' with a 5 per cent. solution of sodium chloride combined with 0·5 per cent. of citrate of soda. This was found to be a very effective 'drawing agent'.

Later when I realised how voluminous was the outflow of lymph achieved, and recognised that this of itself would prevent the wound becoming '*lymph-bound*', I omitted the citrate of soda, and employed as a 'drawing agent', or if the term is preferred, as a 'local lymphagogue', a simple hypertonic (2·5 to 5 per cent.) sodium chloride solution.

It is, I think, widely known that the simple hypertonic salt solution which had thus been arrived at was very extensively and effectively employed in the war in the treatment of those putrid lymph-bound conditions which result whenever surgical treatment of lacerated wounds is postponed.

Hand-in-hand with the therapeutic application of the hypertonic salt solution, its effect was studied both in the wards and in the laboratory. The ward experiments

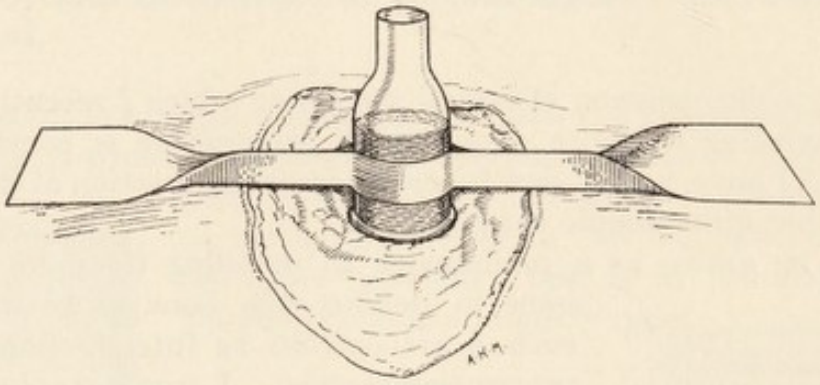


Fig. 6.

consisted in measuring the volume and the time relations of the induced lymph flow. In the case where scooped-out cavities in bone presented themselves, these were turned to use as collecting cisterns,[1] and where only flat superficial wounds were available artificial cisterns were made by strapping down upon the wound the upper ends of test-tubes which had been cut across in the middle. We called these lymph-cups, and one is shown in position in Fig. 6. In each case it was found that the filling-in of hypertonic salt solution into these cisterns produced an immediate in-draught of lymph, and that the in-draught diminished and finally staunched as the salt solution became more and more attenuated. These happenings in the wound correspond, as we shall presently see, with those witnessed when hypertonic salt solutions are brought in contact with serum *in vitro*.

Concurrently with the aforesaid *in vivo* experiments, laboratory experiments were made to find out whether the (let us call it now) *tractor action* of salt solutions

[1] Fleming, *Brit. Jour. Exper. Surgery*, vol. 7, p. 999 (1919).

was exerted upon water as such, or upon albuminous solutions as such. The experiments in question (they are illustrated *supra*, Figs. 1 and 2) brought out two things.

First, that when two receptacles which contain the one a strong salt solution, and the other water, are connected up in such a way that the water can pass, while the passage of salt is even by the lightest differential barrier impeded, then the level of the fluid gradually rises in the receptacle which contains the salt solution. This shows that the salt, provided it be ever so lightly confined, can draw up water against the opposition of gravity.

The second fact brought out was : that where, instead of water, an albuminous fluid and a confining barrier which is permeable to albumen are employed, there is a rapid and voluminous indraught of the albumen into the strong salt solution, and practically none into the superjacent and subjacent fluids. Proof of this is furnished by the coagulum obtained when we apply heat. (*Vide* Fig. 2 *B.*, p. 164.)

It will be noted that in the experiments which have just been summarised, cognisance was taken only of tractor effect exerted by the salt solution.

As a next step in the study of the *vis operans*, steps were taken to render visible the movements which occur upon the frontier when a lighter albuminous fluid is imposed upon a heavier salt solution. And here, inasmuch as traction exerted in a particular direction by an element A upon an element B must have as its counterpart traction exerted in the opposite direction by the element B upon the element A, the experiments were so planned as to render manifest not only a down-draught of the lighter albuminous fluid into the heavier salt solution, but also an up-draught of the heavier salt solution into the lighter albuminous fluid. To this end, first the one, and then the other, of the solutions was artificially coloured. The experiments here in question are those which were described by me in my first communication on intertraction (*vide supra*). These were put forward as demonstrating the operations of intertraction, and they furnish what is, in my judgment, conclusive proof of the existence of such a *vis operans*. For ordinary convection movements are here definitely ruled out, and diffusion can furnish no explanation of the configuration I have called '*pseudopodial invagination*' or of the rapidity of the movements of interpenetration.

But none the less, in bringing forward the experiments in question as ocular demonstration of the operations of intertraction, I did not fail to point out that there are in the experiment (let me call it for the sake of brevity the experiment of vertical intertraction) superposed upon the effects of intertraction also effects of other derivation.

In the first place, we have here effects due to changes in specific gravity which affect the invading serum and salt solution respectively, after they have interpenetrated deeply. What would seem to happen is that the invading serum, becoming condensed by loss of water, becomes heavier than the 'intracting' saline solution and so falls to the bottom of the vessel. And contrariwise, the invading saline solution having parted with some of its salt content, becomes lighter than the 'intracting' serum, and so ascends to the surface.

Superadded to the gravitational movements just indicated, there is also (visible when a colouring agent is employed) a visible diffusion effect. Diffusion (co-operating

with intertraction) finally brings about an equable dispersal of the salt and albumen and establishes uniformity between the subjacent and superjacent fluids.

These acknowledged (but I should have thought quite minor) blemishes in the vertical intertraction experiment have furnished Dr. Jessop [1] and Mr. N. K. Adam with the majority of the arguments by which they jointly, and the latter author also separately, have sought to make good that the phenomenon of ' pseudopodial invagination ' wherever obtained can be explained with any invoking of the concept of intertraction. With respect to that residue of arguments which those authors draw from their own experiments (I speak here only of those experiments which relate to salt and serum), these I must perforce (the reasons for this will appear later) ascribe to insufficiently thoughtful consideration.

To return to what is directly material to the subject matter in discussion, it was clearly of import for the general acceptation of intertraction as a *vis operativa* that an experiment should be devised which would display intertraction effects uncomplicated by effects due to alterations of specific gravity in the intertracting fluids. It was to this end that I planned the experiments (illustrated in Figs. 5 and 7) in which a paper disc impregnated with coloured serum and affixed to a cover-glass is floated face downwards upon the surface of a heavier salt solution.

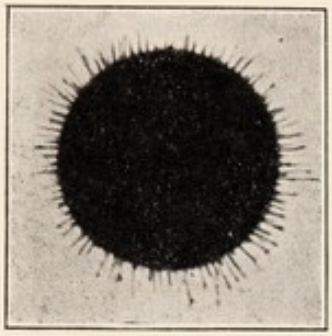


FIG. 7.

This experiment also has been censured by Mr. N. K. Adam as non-probative—the gravamen of his criticism being that, just as in the experiment on vertical intertraction, so here, those parcels of the saline solution which come in contact with the albumen would by the disbursal of salt to it, become specifically lighter, with the result that they would ascend through the serum and be deflected by the under surface of the cover-glass in such a way as to produce the horizontal streamers which come out radially from the margin of the filter paper.

With respect to the interpretation of the radial streamers I submit that it is inconceivable that rising currents, even if they started at separate foci, as Mr. Adam's theory would require, should, after passing through the texture of the filter paper, emerge from it in the form of discrete and sharply-outlined streamers. The very utmost that an upstreaming of salt solution (and it would be a general upstreaming) could be expected to effect would be an expulsion of coloured albumen in the configuration of a halo surrounding the disc.

Again *a priori* principles, and also direct inference from what is seen in the vertical intertraction experiment, combine to teach that ascending uncoloured streams of salt solution would be correlated with descending streams of coloured albumen. Now a distinctive feature of the experiment on horizontal intertraction in question is that there is here absolutely no visible downstreaming. Instead of that there can, under favourable circumstances, be discerned just within the periphery of the coloured paper disc a system of paler-coloured centripetal striae—striae which would, of course, be the natural counterpart of the coloured centrifugal streamers.

But in point of fact, the issue as to whether the horizontal centrifugal streaming

[1] *Roy. Soc. Proc.*, A, vol. 108, p. 324 (1925).

is produced by ascending currents impinging upon the filter paper disc is one which can very easily be set at rest by direct experiment. The following are elucidating experiments :

(1) To begin with we can, instead of floating our albumen-impregnated disc upon the surface of a heavier salt solution, take some three or four of such discs, lay them down one upon the other, dispose them between two glass slides, and then immerse the slides, after they have been firmly clamped together, into a vessel filled with saline solution. Here, in spite of the fact that ascending currents cannot come into operation, horizontal streamers exactly similar to those developed when the disc is afloat on the salt solution, come out from the periphery of the paper. (These are very delicate and difficult to photograph satisfactorily.)

(2) Again, we can, taking an albumen-impregnated paper disc, paint its upper and lower surfaces, except only the periphery, with paraffin wax, and then set the disc afloat upon the saline solution. Here again, despite of upward currents being shut off, the familiar pattern of horizontal streamers is developed.

(3) Further, abandoning for the moment the paper disc, we can make a mixture of equal parts of coloured serum and of a 1 per cent. melted water agar, and then transfer a drop of this jelly to the surface of a slide, upon either extremity of which we have placed thin slabs of glass as supports. We now bring down a covering slide upon our jelly in such a way as to flatten it out into a disc, and then we fill in all round it our saline solution. Here, again, despite the fact that no up-streaming currents can impinge upon the surface of the disc, horizontal streamers come out from its periphery.

(4) We take a square cover-glass and paint paraffin wax upon its upper surface, leaving bare only a narrow strip along one edge. We then take a *very little* coloured serum, dispose it along the length of this ledge, and then float the cover-glass, paraffined side uppermost, upon a 5, or, better, upon a 7·5 per cent. solution of salt, taking care in setting it afloat to bring down the margin that carries the serum last, and as gently as possible, upon the salt solution. From the launching raft thus provided the serum is automatically drawn off by the salt solution, and is now dispersed over the surface of the salt solution in the form of a palisade of horizontal streams. Here again it is clear—for the serum is reposing upon a ledge protected from below—that the horizontal streaming cannot be caused by any impact of ascending currents.

(5) Another also very simple experiment is the following—which was specially devised to dispose of Mr. Adam's general criticism that the water employed as a solvent for the salt will, as soon as it has been sufficiently lightened by the disbursal of its solute, ascend through the superincumbent serum. This potential source of fallacy will be removed if we substitute in our paper disc experiment for the solution of salt in water a solution of salt in serum. When having made that modification we set a serum-impregnated disc afloat upon a salted serum, we bring out, just as in previous experiments, horizontal centrifugal streamers. Those now obtained differ, however, in two respects from those obtained with the watery saline solution. In the first place, they develop much more slowly ; and again they are much less rapidly dispersed by diffusion. The slower development is no doubt correlated with

the greater viscidity of the serum, and the slower dispersal with the fact that here diffusion is limited to a diffusion of salt out of one albuminous fluid into another sample of the same albuminous fluid, whereas where albumen is superposed upon a watery salt solution, three several elements—to wit, albumen, water and salt—are transporting themselves by diffusion the one into the other.

Reflexion having now placed at disposal for use in intertractional experiments a saline fluid which does not lie open to the imputation of being convertible into a fluid lighter than the superincumbent serum, the next thing that required doing was to substitute in the vertical intertraction experiment, as had just been done in the disc experiment, salted serum for the plain saline solution. For clearly there was now prospect of converting by this device that combined, intertractional, gravitational and diffusional experiment into one that should be purely intertractional.

A comparison of photographs of down-traction exerted by watery saline solution upon serum, and up-traction by serum upon watery salt solution, with photographs of down-traction exercised by salt serum upon serum and up-traction by serum

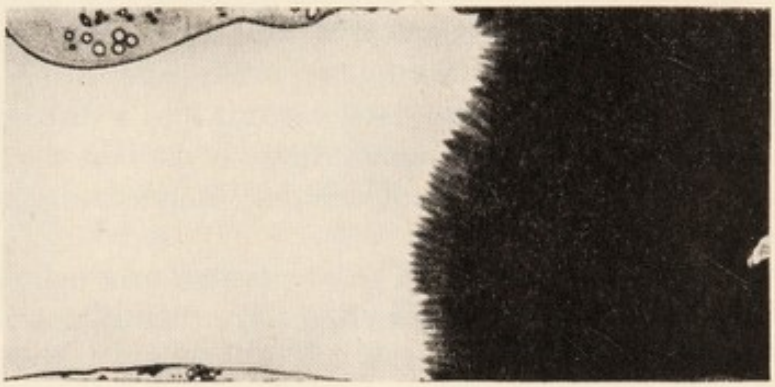


FIG. 8.

upon salted serum, show that the anticipation in question is in point of fact realised.

Finally there may be added a photograph of horizontal intertraction (Fig. 8) obtained by filling into one end of a slide cell serum containing Indian ink, and into the other end a 12 per cent. salt solution.

ADDENDUM

In the experiments on vertical intertraction described above it was assumed without coercive experimental evidence that the downward draught of the serum into the hypertonic salt solution, and the up-draught of the latter into the serum was due, not to the salt interacting with the water, but to its interacting with the proteins of the serum.

With a view to putting this to the proof the following experiments were undertaken.

Experiment 1

The lower halves of four compartments of a slide cell were filled with a 5 per cent. solution of sodium chloride—one pair of the compartments being distinguished as *A* and the other pair as *B*. Then was then superposed upon the salt solution in compartments *A*, serum to which a little eosin had been added ; and upon the salt solution in compartments *B*, water to which a similar addition of eosin had been made.

In compartments *A*, there immediately supervened upward and downward pseudopodial interpenetration. In compartments *B*, there was, even after the lapse of an hour, a perfectly sharp boundary line between the supernatant and subjacent fluids.

It seemed for a moment that there had been brought forward here convincing proof that intertraction between hypertonic salt solution and serum, is intertraction between salt and the proteins of the serum. But the experiment in question is, as consideration shows, fallacious in the respect that while there was not much difference in specific gravity between the overlying and underlying fluids in compartments *A*, there was a much greater difference in specific gravity in the fluids in compartments *B*.

That effect was remedied in the next experiment by substituting for the 5 per cent. salt solution a $2\frac{1}{2}$ per cent. solution.

Experiment 2

Here the lower halves of two compartments of a slide-cell were filled in with a $2\frac{1}{2}$ per cent. solution of sodium chloride, and into the upper part was filled the same eosin coloured water as had been employed in Experiment 1. No sooner had this been done than the subjacent and supernatant liquid began to intertract, and the result was very little different than that which is obtained when serum is superposed upon 5 per cent salt solution.

Experiment 1 was now repeated with the difference that there was now superposed upon the 5 per cent. salt solution instead of a diluted watery solution of eosin a solution of eosin which had the same specific gravity as the serum.

Experiment 3

In this experiment the lower halves of all four compartments of a slide-cell were again filled in with a 5 per cent. sodium chloride solution. And there was now superposed upon the hypertonic salt solution in compartments *A*, serum coloured with eosin, and upon the salt solution in compartments *B*, a watery solution of eosin of exactly the same specific gravity as the serum.

Immediately, as in experiment 1, the superimposition of the serum upon the hypertonic salt solution in compartments *A* was followed by upward and downward pseudopodial interpenetration. In compartments *B*, the result was quite different. There was after the lapse of 20 minutes no indication of intertraction. But after 45 minutes, intertraction had become very well marked and there was then not much to choose between compartments *A* and *B*.

This experiment would appear to settle the point that intertraction between serum and hypertonic salt solution is much more vigorous than that between hypertonic salt solution and water. It looks, in other words, as if intertraction between serum and hypertonic salt solution was intertraction between salt and the proteins in the serum, and not between the salt and the water in which those proteins are dissolved. But it was possible to put this conclusion to still further proof, and this was done in the next experiment.

Experiment 4

Here the lower halves of four compartments of a slide-cell were filled with 5 per cent. salt solution, and there was then superposed upon the salt solution in compartment 1, a watery solution of eosin of the same specific gravity as serum ; upon the salt solution in compartment 2, serum which had been diluted with an equal volume of the same eosin solution ; upon the salt solution in compartment 3, serum diluted with two parts of the same eosin solution ; and upon the salt solution in compartment 4, serum which had been diluted with three parts of the same eosin solution.

Here 20 minutes elapsed before any visual change occurred in compartment 1 ; in compartment 2 there was immediate intertraction ; in compartment 3 there was slightly delayed intertraction ; and in compartment 4 there was a somewhat slower intertraction.

Finally after the lapse of 30 to 45 minutes intertraction was nearly as distinct in compartment 1 as in any of the others.

Experiments on horizontal intertraction would seem to point to exactly the same conclusions, but they are, because of the difficulty of making exact comparisons, not recounted here.

APPENDIX

THE QUESTION AS TO HOW SEPTIC WAR WOUNDS SHOULD BE TREATED[1]

(BEING A REJOINDER TO SIR W. WATSON CHEYNE'S ADVOCACY OF ANTISEPTIC PROCEDURES AND HIS POLEMICAL CRITICISM OF PHYSIOLOGICAL METHODS OF TREATMENT)[2]

Prefatory Remarks.

It is a very open question whether polemical controversy is, or is not, an effective instrument for the advancement of the truth.

Of course, the man who has an open mind can always learn something from discussion. In dealing with complicated subject matters such as that of the proper treatment of wounds, trustworthy conclusions are reached only when we have been compelled to look at the facts from opposite points of view. And when in controversy one man sets up a thesis, and the next man disputes it, these conflicting suggestions may have intellectual value. They may tend to make our mental outlook less narrow, and make us balance alternatives.

But when all is said and done, only a small minority of mankind have their minds clarified by polemical controversy. The greater number come away confused and in perplexity as to where the truth lies.

And no wonder. It is difficult, even for the man who has under his hands full materials for controlling such inductions, to decide between competing generalisations ; and no one, knowing of the facts only what is put before him in controversy, would be in a position to reach such a decision. Again, it is in all ratiocination, and specially in that which deals with the concrete, difficult to avoid lapsing into fallacy. And in controversy this is specially difficult. For the ordinary controversialist is perpetually leading his reader into verbal snares and oratorical traps, and into all manner of logical pitfalls. But while for these reasons polemical controversy conducts into perplexity and error, this really holds only of the broader and more difficult, and not of the narrower and less difficult inductions. And when we come to definite statements concerning questions of fact, the truth or falsity of these is in the course of controversy definitely settled. Again, polemical discussion renders also other useful service. It corrects incidental misapprehensions caused by inadequacy and default in the original exposition ; and it rectifies more especially

[1] Republished from *The Lancet*, Sept. 16, 1916. *Vide* also p. 161, footnote [1].

[2] *British Journal of Surgery*, 1916.

those initial and fundamental misunderstandings which come from the expositor having failed to keep touch with his reader. What has generally happened in that setting out of a new generalisation is that the expositor—to keep things simple, and make a less circumscribed and less ephemeral appeal—has started off quite *de novo*, and has addressed himself to an entirely ideal type of reader. He has taken it that his readers will be of that sort that will be prepared to make a quite new start; and will have no fixed ideas to extirpate, and no cherished mental pictures to expunge. And he has further made the assumption that his readers will give to every argument its proper logical weight ; will, when qualifications are attached to a statement, take close note of these ; will not confuse things ; and will assign to every term its precise meaning and quantitative value. Now, more often than not, exposition conducted upon the aforementioned assumptions and on general lines will not come off successfully. It will make as good as no impression upon the man who is attached to another reading of the facts, and who treasures other mental pictures. And as for the ordinary reader, exposition on general lines will at best only start him upon the road. It will not prevent his being held up by all sorts of small difficulties. And when he is held up exposition of the same kind as before will not extricate him. What he will then require is that kind of intellectual assistance that is given in private coaching.

And it is just this sort of intellectual help that controversy is competent to supply. What polemical criticism really does do is to set out the difficulties encountered by the reader who approaches the new doctrine with the conventional conceptions. And the function of the controversialist who undertakes the reply is to stand beside the reader and to explain things to him, whenever in reading a polemical criticism he is saying to himself : ' Now what is the answer to that? ' And this discovery of and replying to objections is indispensable to intellectual progress. In the end it is always controversy—it may be public, it may be private ; it may be honest, it may be dishonest, controversy—that decides the fate of every generalisation.

But in polemical controversy we have not only a conflict between two ideas, we have also a personal contest. And intellectual progress, and in particular the advancement of logic and intellectual morality, would seem to depend upon this factor of personal contest being always present in controversy.

For the ordinary man will not, on the chance that these may possibly some day enable him to decide between competing theories, attend to facts of science that have no personal interest ; nor will he, on such a chance, listen to disquisitions on logical methods and the conduct of the intellect. But he can be got to attend to every kind of fact as soon as an important principle of practice, and the issue of a personal contest comes to turn upon it ; and, given these conditions, every man will quite gladly consider points of logic and intellectual morality.

That is as much as to say : Controversy gives to every matter that comes into its orbit a vivifying personal interest, and in particular it makes of logic and intellectual ethics really live issues.

It brings home to the mind that it really is desperately difficult in all ratiocination that deals with the concrete, to reason rightly. It shows up the confusion that

results from using ambiguous and non-quantified terms ; exposes loose and fallacious methods of proof which have got themselves accepted ; shows that we ought to give consideration not only to familiar and acceptable, but also to unfamiliar and unacceptable, explanations ; and makes apparent the moral danger of cherishing one's mental pictures till they turn into obsessions.

And were it not for the interest that attaches to personal combat, I cannot think that any of these things—and they are the rules and ethics of the intellectual game—could ever be instilled into the ordinary man.

Moreover, the fact that thereby not ideas only, but men also, are adjudicated upon makes of controversy something more than a mere educational instrument ; it also makes it an instrument of direct social service.

When one reflects that it is public reputation that designates a man for office where he influences important action, and that it is popular estimation which gives driving force to a man's words, one sees that there is wanted some court of appeal to which popular estimates could be brought for revision, and some sort of machinery for settling whether this or that man who is trusted by the lay or professional public possesses the only kind of ability worth having—the gift of getting at the truth.

Now, we have in point of fact in polemical controversy a machinery for settling this. While, as we have seen, controversy can never enable a man who is out of touch with the facts to decide between competing doctrines, it does give to every reader data by which he can adjudicate between the men who are disputing about those doctrines. It does show whether the disputants are competent, or incompetent ; logical, or illogical ; *honest*—eschewing fallacious arguments, and giving way if they can no longer conscientiously hold their ground, or *intellectually dishonest and immoral*—trying, when things go against them, to make the worse appear the better reason ; and resolutely holding out even when cumulative evidence piles up against them.

And what is really wrong with the world is that, through reluctance to involve ourselves in controversy, and fear of offending public sentiment (which is want of moral courage), we allow many a man who has neither a gift for getting at the truth, nor yet (in my meaning of the word) intellectual honesty, to continue in undisturbed enjoyment of reputation and authority.

Now this, of course, runs counter to what is generally accepted. You hear everywhere that the personal element is the unethical element in every controversy. And the cynic will confide to you that polemical controversy is always a personal vendetta.

And this is the point of view from which controversy is judged. Whenever the question is raised as to whether it was, or was not, justifiable to have said this or that in controversy, your man of the world goes and turns up the previous papers to see what amount of provocation was given, and what reprisals it was legitimate to take.

In other words, to the man of the world the whole thing is a question of retaliation ; and justification is to him a question of provocation given.

But, after all, polemical controversy is not on exactly the same ethical plane as the duel and vendetta ; and its psychology is a little different. In the duel or

vendetta there is always a personal and private issue, and only that. In controversy, though the private motive does often come in, there is always a matter of public concern—the question as to whether this or that generalisation should be accepted. And while in polemical controversy there is, as in the vendetta, always a joy of battle—a satisfaction when you get your shots in straight—you do not in reputable controversy, any more than in actual warfare, derive satisfaction from wounds inflicted. You even feel a little sorry for these.

But as soon as this possibility is hinted at, down there comes upon you the pacifist with his humanitarian proposals.

And the sort of thing he says to you is this: 'If you—the controversialist—are really not out for your pound of flesh, if what you want is to advance your cause, to smooth the way for the acceptance of your doctrine, and to prevent truth being obscured by false reasoning and intellectual immorality, then you could achieve all you want without hurting any individual. Whatever you have got to say, you can say impersonally.

'Or, if you really must have someone to attack, you could at any rate get rid of all that objectionable personal sting by attacking, instead of some unfortunate individual, the group or body corporate to which your particular antagonist belongs.'

The real answer to this sort of humanitarian appeal is that it takes singularly little account of what I have referred to under the heading of direct social service; and it proceeds upon fundamental misconceptions. It bases itself upon the—in exposition admissible, in controversy inadmissible—false assumption that your reader has no *parti pris*; that he is swayed only by his intellect; that he is with respect to competing theories and disputants completely neutral, and had as lief attach himself to the one doctrine and the one disputant as the other.

In other words, what you are asked to believe is that by pacific processes you can win all intellectual victories, and that you will in controversy get everyone over to your side if you point out, without censure, and quite quietly, mistakes in fact and reasoning committed on the other side.

But the brutal fact remains. All controversy is a warfare from which the one or the other of the parties has got to emerge discredited. And it is the task of every disputant to minish the prestige of the protagonist on the other side; and also, if possible, to bring home to the reader that he is, when reading an author whose views he shares, as liable to be led away into fallacy as is a man listening to an advocate setting out his cause.

But the pacifist still sees an opening left for his humanitarian intervention. It would still, so he thinks, be possible to attenuate the personal sting that controversy leaves by diverting the attack from the individual to the class to which he belongs.

Prima facie there would appear to be logical point and also justice in this proposal. For behind the man who is proceeded against, there are always others like-minded with himself. And in such a case equity would seem to require that the indictment should issue not against the individual, but against the group.

But the moment we begin to think, things always look differently. One discovers that it would be almost impossible to frame an indictment which could equitably be brought against an entire group, let alone against a body corporate.

For though men may hold a doctrine in common, you find, as soon as you come to investigate, that each holds it with a difference.

And again, as soon as one thinks it over, one realises that there are two distinct types of controversial writing.

In the one the materials upon which the inductions rest are revised, new data being brought forward, and data which ought never to have been accepted being discarded ; also fallacies are exposed ; issues which have been tangled up together are unravelled ; and throughout the prescriptions of logic and intellectual morality are observed. In critical comment of this kind everyone, of no matter what school of thought, will gladly be a partner.

But there is also polemical writing with which no one would willingly be associated. No one wants to be associated with controversial writing which takes its stand upon erroneous data ; which, no matter how intricate the facts, tells you that they can be construed in only one way ; which then introduces confusion by using undefined and ambiguous terms ; tangles up together issues which are logically distinct, and shows an intention to hold out everywhere against no matter what pressure of cumulative evidence.

Again, no one wants to have anything to do with endeavours to knock out a controversial antagonist by depreciatory comment directed to things quite foreign to the issue under discussion ; nor yet to associate himself with the unjust criticisms with which a man will relieve his feelings when he finds problems he piques himself on having settled reopened, and sees, where he before saw a limit to his work, fresh complications introduced, and more labour and more thinking piled upon him.

Now we have in most controversial writing critical commentary of each kind : on the one hand, comment which all the clear and honest minds on either side would accept ; on the other hand, comment which the writer's partisans would unanimously wish to disown ; and again comment which some of these partisans would approve, and others not approve.

And, carrying into actual practice the pacifist's injunctions would mean ignoring in controversy everything one's antagonist's partisans might wish ignored. But whosoever followed this counsel would place himself in an altogether false position. He would lay himself open to the charge of ignoring in criticism directed against himself all that was specially difficult to answer. And the controversialist who was thus edited would feel that his criticism was being bowdlerised of its best and most effective points.

At the same time the controversialist, who under a self-denying ordinance overlooked in his opponent's writings all that that opponent's partisans would themselves have eliminated, would be bound to feel that he had weakened his own case quite unfairly. For, of course, in his view the passages in question would be just those which showed the desperate straits into which the defence of an erroneous generalisation conducts.

And finally the reader also would be ill-satisfied. If a partisan, he would be sure to think that his cause and his protagonist had been prejudiced. And if simply an ordinary reader, he would be sure to feel that, with everything watered down and everything personal eliminated, he was getting absolutely no fun, and corre-

spondingly little use out of the discussion ; and, above all, that no light was being shed upon the capacities and moral characters of those who aspired to be his intellectual guides.

But to go into all this is perhaps to attach undue intellectual importance to the suggestion that controversialists should be sheltered from the consequences of their own action. And it is really beyond question that the only proper way of conducting controversy is to hold every man responsible for everything that appears over his signature, and nobody else responsible.

I have now set out the aims and ethics of polemical controversy as I see them, and though I full well know that no doctrine is on a safe foundation and no ethical principles have binding force until many thinking minds have accepted them, yet I feel with regard to what has been enunciated above, so sure of that acceptance, that I pass straightway to translate precept into practice.

In making my reply to Sir W. Watson Cheyne I propose to be mindful of all the issues pointed out in this preface ; and I shall venture also to ask of the censors of controversy that they shall not forget them.

Questions at Issue between Sir W. Watson Cheyne and Myself

Let me begin by formulating what is at issue between Sir W. Watson Cheyne and myself.

It is not, as a certain tone of exasperation in his writing might suggest, a question of his being at variance with me on every point ; of his wishing every wound to be treated with antiseptics right through from beginning to end ; and of my holding every application of antiseptics to be prejudicial.

Quite the contrary.

Sir W. Watson Cheyne's dicta with regard to antiseptic treatment are as follows :

(*a*) ' After *8 to 12 hours* [1] the chances of success are comparatively slight.' [2]

(*b*) ' Antiseptics used at a later period may seriously interfere with the protective granulation wall, produce a weak spot, and thus open a way to a general infection, or at least to a considerable local extension of the disease.'

And again :

(*c*) ' Hence I am very chary indeed as to the use of antiseptics in suppurating wounds . . . ; in fact, I never try to disinfect such wounds.'

It will be seen that Sir W. Watson Cheyne is very far from being an advocate of that indiscriminate antiseptic treatment which was in vogue in the earlier period of the war. What he advocates is that antiseptics should be applied at the outset, and that they should then be applied in a very thorough manner.

When the time for that prophylactic disinfection has gone by, or when the attempt to disinfect has been made and has failed, that is, so far as I can discern, the end of Sir W. Watson Cheyne's programme. His attitude is, I think, this :

[1] Here and elsewhere, unless the contrary is stated, the italics employed in citations from Sir W. Watson Cheyne are my italics.

[2] Sir W. Watson Cheyne, however, hopes that, with a proper selection of antiseptics, the period of grace for the application of these may be extended.

'I have opened up the wound; I have provided mechanical drainage; and the wound is being washed out with weak antiseptics; and it is being dressed; I do not see that I am required to think out the problem any further.'

On this point and on the question of the possibility of sterilising war wounds at the outset, I have ventured to take up a position diametrically opposite to that of Sir W. Watson Cheyne.

In respect to the sterilisation of war wounds at the outset I am, in common with everyone who has experience of wounds in France, and certainly with every bacteriologist who has investigated the matter, persuaded that severe war wounds have never yet been sterilised; and, moreover, I am, in common with, I think, everyone who has seriously studied such wounds, convinced that from the nature of the case they cannot be sterilised by any antiseptic.

On the issue as to how septic wounds should be treated I have contended that we can by what I have called *physiological methods*—i.e. by inducing in the wound the appropriate physiological reactions—help the body to combat the bacterial infection. By inducing a flow of lymph we can bring the blood-fluids into operation in the infected tissues and the wound cavity. By liberating trypsin from the leucocytes and turning this to account we can get rid of the sloughs. By the same agency we can resolve infiltration. And by bringing to bear always fresh serum, and inducing leucocytic emigration we can promote the destruction of the infecting microbes—beginning with those in the deeper tissues, and ending up with those on the surface and in the cavity of the wound.

And there is also this further issue between Sir W. Watson Cheyne and myself. It is one of the underlying assumptions of his paper that wounds come into treatment practically immediately, and are then continuously cared for in hospital. But the outstanding fact in this war is that it is often many hours, and sometimes instead of hours it may be days, before the wounded are got in from the field into an operating hospital; and that it is, when casualties are heavy, inevitable to postpone much of the extraction of projectiles and foreign bodies and the adequate opening up and draining of wounds until the men arrive at the Base.

And when all this initial work has been completed the conditions are not such as to permit of the further treatment being carried out uninterruptedly. If at the Front the men must be sent to the hospitals at the Base; and if at the Base they must be sent overseas, and often to long distances after landing; and, finally after a convoy has arrived, it takes quite a long time before all the examinations are complete and treatment is recommenced. So that in the case of the wounded in war, in contradistinction to what obtains in time of peace in accidents, adequate treatment is by necessity very often belated; and there are also comparatively long periods in which treatment is compulsorily suspended.

And this is the fact to focus attention upon. For it is what happens in the wounds in the periods when they go untreated that makes for disaster. The lymph-flow stanches; the exposed surfaces desiccate; the sloughs provide a nidus in which, and under which, all manner of microbes, and among these tetanus bacilli, may shelter themselves; and then not only the streptococci—to which the organism offers little resistance, but also the bacilli of gas phlegmon, microbes which encounter

in the normal organism very formidable resistance—make their way into the tissues, producing cellulitis or gas gangrene and afterwards blood infections.

All this is the direct result of the deterioration in the physiological conditions. And looked at from the point of view of treatment, this deterioration is the central element in the situation. It increases a hundredfold the difficulties which stand in the way of a successful application of antiseptics. And I cannot but believe that it calls aloud for rectification—and I would add prevention—by physiological treatment. To this whole problem Sir W. Watson Cheyne is, as it seems to me, blind. 'Of the City which we seek, he (I am quoting from Dante) has not sighted even the tower.'

Let me deal first with what Sir W. Watson Cheyne has to say on sterilisation of the wound at the outset.

I. Issue as to whether the Wound can at the Outset be sterilised by the Application of Antiseptics.

We may discuss here first the *a priori* considerations, in other words those which are based upon anatomical, physiological, and bacteriological study of the wound; and upon an examination of the behaviour of antiseptics.

A priori Considerations which bear on the Practicability of Disinfecting the Wound at the Outset.

Sir W. Watson Cheyne has a mental picture of the distribution of microbes in war wounds and of the sequence of events in war wounds which is quite congenial to the view that it is feasible to sterilise these.

He tells us, not distinguishing here between war wounds inflicted by projectiles and infected wounds met with in civil practice:

(*a*) 'Now we may meet with these infected wounds under two conditions: (1) At or soon after their infliction, and before granulation or suppuration has occurred; and (2) at a later date, after the establishment of granulation or suppuration.'

(*b*) 'During the first stage, which lasts from two to three days, the bacteria, *at first free in the wound*, penetrate into the tissues.'

(*c*) 'Now during the early stage the bacteria are fairly accessible to the action of destructive agents introduced into the wound; they *are not deeply embedded into the tissues* nor surrounded by dense masses of cells.'

(*d*) 'In the later stage, however, the organisms are lying in the granulation tissue, more or less protected from the destructive action of antiseptics.'

The reader will, as soon as his attention is drawn to the matter, see that all this assumes that the infected wound we have to deal with is a cavity, and a cavity with microbes implanted only superficially upon its walls. But often we have what may be called 'implunging wounds'—i.e. wounds in which the missiles, whether shrapnel bullets, or shell fragments, or detached portions of bone, or pieces of accoutrement or clothing are impacted into the tissues. And here the microbes are not lying in any wound cavity. Again, with a definite wound cavity, we have extensive

laceration and hernia of muscle, and where a bone is struck extensive splintering, with the result that many of the microbes are buried in pockets and crevices, while others have by the explosive force of the impact been carried far into the tissues.

Now quite obviously all these buried microbes are inaccessible to antiseptics.

A further point also deserves consideration. Those microbes which may be lying upon the face of the wound will, when lymph has exuded and has dried or coagulated, be buried under scab or fibrin. And these become incorporated in the tissues much in the same way as particles deposited upon the barked surface of a tree become buried in congealed sap or resin.

It does not appear that Sir W. Watson Cheyne has ever perceived any of these things. He sees in the wound nothing but the wound cavity. But the wound is not the wound cavity. It is in reality the infected walls that encompass that cavity.

Penetrating Power of Antiseptics.

This leads directly on to the question of the penetrating power of antiseptics. For if antiseptics are to sterilise the wound it will not suffice to insert them into the wound cavity. They will have to travel up from the embouchure of the wound into the head waters ; and to gain access to the tributaries and creeks ; and they will have to penetrate everywhere deeply into the banks.[1]

Now we have no antiseptics which can do this. And to find one which would be capable of doing it we should have to discover a substance which was very soluble in water, and with this, of course, was very diffusible ; and which would instead of combining indiscriminately with all albuminous substances, combine differentially with bacterial protoplasm.

And, moreover, this substance would have to be so indifferent to ordinary albumens as to remain chemically active not only when, as in the cavity of the wound, we can bring an indefinitely large quantum of antiseptic to bear upon a limited quantum of albumen ; but also when we bring into operation instead of a *full body* of antiseptic only that *emanation* which diffuses out from it ; and when we exact—as we do when we demand penetrative power—of this ' antiseptic emanation ' that it should penetrate into and do its work in quite overwhelming quantities of albumen.

To appreciate how utterly the capacities of our present antiseptics are outstripped by these requirements, it will be well to keep before the mind the plain fact that it is practically impossible to mix into pus enough antiseptic to sterilise it. Now, if antiseptics in full body cannot accomplish this, how much less can we ask of an antiseptic emanation that it should make its way up through the albuminous medium which fills in the channel of the wound and penetrate into tissues full of albuminous fluid or of albuminous fluid and leucocytes.

What really happens when an antiseptic and an albuminous medium are brought into contact without mixture is, as experiment shows, that the antiseptic is held back at the delimiting border instead of penetrating the contiguous albuminous fluid, as would happen if this were an indifferent menstruum. In correlation with this, when an albuminous fluid implanted with bacteria is superposed upon an anti-

[1] *Vide* here *supra*, p. 148.

septic, agar being added to each to prevent direct mechanical mixture, the microbic colonies in my experience always develop right down to the confines of the antiseptic.

I would suggest to Sir W. Watson Cheyne that he should have experiments of this sort carried out for him, and that he should take cognisance of the results. One asks oneself whether he would then still be positive that he and his collaborators have ' amply proved ' that antiseptics diffuse through the very densest albuminous media (blood clot and muscle) and kill microbes in a comparatively short time at a considerable distance from the original deposit ; and whether he would still valiantly assert : ' These facts are absolutely proved, and cannot truthfully be denied.'

Penetrating Power into Living Tissues.

But Sir W. Watson Cheyne does not stop short here. He goes on : ' Not only do antiseptics diffuse through dead or inert tissues ; they also penetrate into the living tissues.' And then bethinking himself that this ought to be established experimentally, he proceeds to cite two experiments, prefacing them and completing them with a scientific commentary of this kind :

(*a*) ' I admit that until recently this was only deduction on my part from several observations and from clinical results.'

(*b*) ' We are now investigating the facts of the matter.'

(*c*) ' It is by no means easy to devise experiments which will satisfactorily test the question.'

(*d*) ' But I may mention two preliminary trials which Mr. Edmunds made before he left Chatham.'

And after narrating these experiments [1] Sir W. Watson Cheyne clenches his argument by saying :

(*e*) ' As a matter of fact, such experiments are hardly necessary ; for we know from clinical experience how readily chemical substances are absorbed from wounds.'

None the less, it will be profitable to examine the experiments. They are on the same intellectual plane as the comment.

In each case a guinea-pig was anaesthetised. The gluteal muscles were then incised ; borsal was introduced ; and the wound was stitched up. Then after a certain interval the animal was killed ; the block of muscle was excised ; this was placed with the superficial aspect downwards on a freezing microtome ; and sections were made until the floor of the wound was reached—each section being separately tested with ferric chloride for the presence of salicylic acid.

In the sections from the first guinea-pig no salicylic acid was discoverable ; but the urine from the bladder gave the ferric chloride reaction.

In the case of the second guinea-pig the 28 sections obtained immediately before the floor of the wound was reached—corresponding, we are told, to 2·8 mm. of tissue—gave the reaction with ferric chloride ; and here again the urine was charged with salicylic acid.

When we are set down only to such a halfpenny-worth of bread it might seem labour lost to inquire into its nutritive value. But such inquiry may have indirect

[1] To these is added by way of a postscript, and in a footnote, another experiment.

advantage by showing us one of those grosser respects in which Sir W. Watson Cheyne, as a scientific worker, comes short. It ought to have occurred to him that his unembedded block of excised muscle may have failed to keep shape upon the plate of his freezing microtome, and that as the freezing propagated itself in the block the salicylic acid may have been carried forward—i.e. that it may have been forcibly driven from the floor of the wound into the tissues. Again, it ought to have occurred to him that salicylic acid may, as we see in connexion with salicylic ointments, eat into the tissues, and that he may have been registering results obtained with necrotic instead of living tissues. And Sir W. Watson Cheyne ought to have appreciated that his method of testing does not distinguish between salicylic acid in the tissues and salicylic acid in the blood-vessels.

But what is in these experiments a very real trial to the reader's patience is that their author should have so scamped the thinking part of his work as to have failed to perceive that *absorption into the blood* and *penetration* are two quite different things. For if absorption into the blood was to be taken as evidence of penetration it would have been more intelligent, in lieu of undertaking a set surgical operation, to have given a hypodermic injection ; and Sir W. Watson Cheyne might then, instead of cautiously writing, ' Such experiments are *hardly necessary*, for we know from clinical experience how readily chemical substances are absorbed from wounds,' have adventured boldly to say, ' Experiments such as I have done are simply waste of time, for everybody knows that chemical substances are absorbed when given by hypodermic injection.'

In brief, one perceives that if Sir W. Watson Cheyne had given a little more thought to his work he would, instead of seeing in absorption into the blood a proof of penetration, have recognised that this is just one of those factors which stand in the way of effective penetration and sterilisation of living tissues by antiseptics.

Summary of Experimental Evidence adduced by Sir W. Watson Cheyne

It is in point of fact—I take my courage in both hands in saying this—quite unprofitable to follow Sir W. Watson Cheyne any further in any matter where experimental work in the laboratory or deductions from experimental work are in question. But let me hasten to put myself right with my reader by assuring him that not more than any other man do I hold myself entitled to dismiss curtly experimental work and conclusions with which I am in disagreement without at the same time bringing proof to show that their author is in matters of the laboratory an amateur.

Let me therefore set to work to justify what I have said. Let me begin with Sir W. Watson Cheyne's announcement of his discovery of an important generalisation in connexion with antiseptics.

> ' Another point, which I confess had not occurred to me until I came across it in the course of my experiments, is also of importance—viz. that the antiseptic is used up in killing bacteria.'

It will be seen that we have here a generalisation which ranks in the order of obviousness with the adage that ' you cannot both eat your cake and have it ' ;

and with the scientific platitude that you cannot carry out a chemical operation without expending chemicals.

We may take next the announcement of a colleague's device for obtaining a cell of measured depth—the device being that of taking a metal ring, placing it upon a sheet of glass, and superimposing upon it another similar sheet.

'This difficulty (i.e. the difficulty of obtaining the proper depth of agar) has been overcome in a very ingenious manner, and though when two or more men work together it is not usual to refer to any one man's share in particular, still . . . I think I ought to say that it was devised by Mr. Edmunds, and I shall speak of it as Edmunds' cell.'

Some day we shall be told that the difficulty of carrying sugar into one's tea has been overcome in a very ingenious manner by the device of sugar-tongs, and that in connexion with it this or that reinventor's name ought to go down to posterity.

Next we may take this fiction :

'Lister observed the very curious phenomenon that if blood were drawn aseptically into a glass flask which had been sterilised by heat the clot which formed did not contract and squeeze out serum, as is the case when blood is received into an ordinary non-sterilised glass vessel.'

'I fancy bacteriologists are not familiar with this fact ; otherwise they would not,' &c., &c.

Everyone who has drawn blood into a sterile syringe, and, of course, every laboratory worker, knows that this is fiction. Let me tell Sir Watson Cheyne that the method of serum therapy, and indeed the whole serum industry, depends upon the fact that blood when drawn into a vessel which has been sterilised by heat *does* contract and squeeze out serum.

So far my task of criticism has been simple as child's play. For we have up to this remained entirely in the domain of the particular and the concrete, referring our author's utterances to the touchstone of fact. Let us now, rising to a more abstract and general point of view, deal with those three intellectual requisites of a scientific worker in which Sir W. Watson Cheyne comes, as it appears to me, hopelessly short.

I have already incidentally to the discussion of his experiments on the penetration of living tissues by antiseptics sufficiently illustrated his incapacity for seeing in connexion with the data of experiment the fact that they admit of many alternative interpretations. Let me therefore pass directly to the second heading and try to show that when Sir W. Watson Cheyne brings the data of laboratory experiments to bear upon clinical work he puts things to himself in a very loose way, and does not think in terms of definite quantities and measurements. Take the following sentence and let me italicise in it what is non-quantitative and amateurish.

'Almost all antiseptics have their bactericidal properties *much reduced* in presence of albuminous materials. Mercurial salts and iodine are good examples of *this*, these antiseptics combining *strongly* with albumin, and losing their antiseptic properties *to a very marked degree*. Carbolic acid is also acted on but not *to so great an extent*, salicylic acid *does not seem* to be *so much* affected, and the hypochlorites form a chloramine which is itself *antiseptic*.'

It will be seen that we have here only adverbial and adjectival quantitative expressions and nothing in the form of figures. And while it is, of course, in scientific as well as in general discourse legitimate to substitute for numerals, adverbs and adjectives, the point is that if we have not behind these a definite backing of figures, we are not talking the language of science. And that point one can very quickly determine. One simply takes these ostensibly quantitative statements and inquires whether they help or mislead the man who has to apply them to practical problems.

When we apply this test to utterances like those above it is immediately clear that the practical surgeon could never gather from them that it is all but impossible to mix into pus sufficient antiseptic to sterilise it. One might from the statements easily suppose that to sterilise pus would be a perfectly simple matter. Nor could the practical surgeon gather that in albuminous media antiseptics have as good as no penetrative power. Nor again could he gather that the antiseptic pastes and powders which Sir W. Watson Cheyne has recommended do not keep down infection in, let alone sterilise, wound cavities such as we meet with in war. And, lastly, the practical surgeon would be misled by that patter of 'hypochlorites forming a chloramine which is itself antiseptic.' In point of fact, Dakin has pointed out that the chloramine, which is formed when hypochlorites combine with albumen, loses its antiseptic power as soon as it encounters further albumen.

Everywhere both inside and outside the confines of this discussion we come up against the deplorable habit of leaving out of view the quantitative aspect. It is that unscientific method of thought that has begotten the dogma of the efficacy of antiseptics in wounds.

It still remains for me to make good that Sir W. Watson Cheyne, for all that he writes of these with assurance, has only a very nebulous idea of those biological processes which laboratory workers engaged in the study of the problems of immunisation have every day under their eyes.

The task I have here before me is, as I have already indicated, one of considerable difficulty.

It would be a different world if the non-expert could be made to feel as the expert does about discourse which brings up before the mind only foggy, inconsistent, and falsely outlined pictures. The expert knows that such language can proceed only from a man who is talking without knowledge of the facts. But in point of fact, this can be made plain only to those who are conversant with the subject matter and who have themselves striven after clear thinking. For example, it cannot be made plain to a layman in connexion with a quack that the man's way of expressing himself gives him away as one who has not studied his subject. And when it comes to much narrower confines we have still the same difficulty. It is only to those who are *bonâ-fide* workers in our own particular department of medicine that we can make fully apparent the vagueness and inefficacy of what is said by outsiders.

The reader will appreciate that I am in this difficulty when I set myself to make good to readers who are not laboratory workers that Sir W. Watson Cheyne's utterances on matters which lie in the domain of the laboratory are always nebulous, and floating in air, and, so far as one can affirm anything of nebulous matter, expressed in slipshod language, erroneous and inconsistent.

It may, however, be possible to convey some notion of Sir W. Watson Cheyne's want of grasp of his subject if I collect from different parts of his paper some of his pronouncements, point out where they fail in truth, and collate them to show what a hopeless tangle they make.

Let me select what he says on *the protective mechanism of the body* ; and again on *the effect produced in the wound by hypertonic salt solution*—first, however, notifying my reader that if he is not particularly interested in these subjects or the working of Sir Watson Cheyne's mind he can, by skipping to the end of the small print, escape from what may be tedious.

To the reader who determines to persevere I would suggest that he should, taking first each separate term and proposition, and then the whole series of propositions, ask himself critically whether it conveys anything to his mind, and whether he can conceive of its standing in Sir W. Watson Cheyne's for anything definite and precise.

I may begin with what he has to say on *the protective mechanism of the body* (the reader has, of course, been forewarned that he must not expect from Sir W. Watson Cheyne precise or logical phrasing, or clear and concinnous mental images).

(*a*) ' The bacteria (which, according to Sir W. Watson Cheyne's assumption, are at first free in the wound) penetrate into the tissues, and are having their first battle with *the tissues and the protective arrangements of the body*.'

The agents of defence in this passage are denoted quite vaguely by the term ' the tissues ', and again quite vaguely by the term ' the protective arrangements '. ' Protective arrangements ' will cover everything from phagocytes to whatever form you like of antibacterial substance.

(*b*) ' In my opinion the *protective substances of the serum* and their action on bacteria constitute only one part of the defence, and there are *local protective arrangements*.'

Here the agents of defence are, on the one hand, the ' protective substances of the serum ', and ' the local protective arrangements ' on the other. Under ' local protective arrangements ' we have presumably to understand ' tissues '. And one wonders in connexion with the phagocytes whether they are here simply forgotten or whether they are subsumed under ' local protective arrangements '.

(*c*) ' The tissues assemble their *forces* (*chiefly cells*) and if the bacteria have been damaged (by applications of antiseptics) they are very quickly disposed of by the *phagocytes*.'

It would defy anybody to picture to himself ' the tissues assembling forces (chiefly cells) '. Nor is it only the figurative texture of Sir W. Watson Cheyne's language which is entangled. The blood-fluids here fail to find a place in the bill ; and the phagocytes are accredited with giving the *coup de grâce* to the bacteria rendered helpless by antiseptics. Here Sir W. Watson Cheyne is composing imaginative fiction. In point of fact, leucocytes are (and we shall presently see the practical importance of this) invariably held at a distance by strong antiseptics, and they are paralysed by antiseptics long before the bacteria are damaged. Moreover

bacteria which have been digested with antiseptics are, so far as we know, not thereby made subject to phagocytosis.

(*d*) 'As the result of opening the abscess a quantity of serum is poured out, which in part sweeps away the cocci, and in part destroys them, as the result of the largely increased amount of antibacteric material which is thus brought into contact with them.'

In this account the rôle of the fairy godmother is assigned to the serum ; and Sir W. Watson Cheyne furnishes two commentaries on the serum—one of dispraise, the other of praise. A few pages back quite gratuitously ascribing to me the idea 'that the protective arrangements reside in the serum and lymph, and these are the most important materials', Sir W. Watson Cheyne writes : 'I may point out that I differ seriously from Sir A. Wright as to these protective arrangements.' To the passage cited above there is appended by way of relief this commentary : 'This explanation given in my book in 1894, and in my lecture in 1899, might have been copied from Sir A. Wright's papers at the present time. . . . I mention this, not from any vainglorious motives. . . .'

There is, in point of fact, very little reason for vainglory. For 'the cocci', if by these are meant staphylococci and streptococci, instead of being killed by the serum, flourish in it. And I now, leaving the reader to see whether he can make anything of this tangle, myself pass on.

We have still to see what Sir W. Watson Cheyne has to say on the *effect produced by hypertonic salt solution in the wound.*

In a communication to *The Lancet* dealing with a lecture given by me in March, 1915, Sir W. Watson Cheyne directs his criticism to my statement that hypertonic salt solution draws out lymph from the walls of the *wound*, and that it does this by bringing into play osmotic forces. His comment is as follows :

'Curiously enough, it is stated that this (the hypertonic salt solution) acts by osmosis, but this must surely be a slip of the pen. *Colloids such as lymph* dialyse very slowly, or not at all, and practically the only result of placing a strong solution of salt *outside a blood-vessel* would be the exit of water and salts *from the blood.* Any increased flow of lymph *into a wound* will be the result of *irritation*, and the question then arises whether salt is the best *irritant*, or whether, indeed, it is wise to use an *irritant* at all.'

It will be seen that Sir W. Watson Cheyne here glosses over the fact that hypertonic salt solutions exert a powerful lymphagogic effect in the wound. He sees no reason to concede anything more than what is conceded in the words '*any* increased flow of lymph'. Instead, he turns to the subordinate, and, from the standpoint of practice, irrelevant, issue of the causation of increased lymph outflow ; and he decides that *any* increase would be due, not to osmotic forces, but to the irritant action of the salt.

One hopes that here Sir W. Watson Cheyne was not unconsciously reasoning after this wise : 'If I allow the lymphagogic action to be ascribed to osmotic forces, it might be supposed that I allow that there is a scientific basis for the treatment ; but if I say that the salt acts by producing *irritation* that will prejudice the method.'

But whether Sir W. Watson Cheyne did or did not allow his scientific pro-

nouncement to be influenced by considerations of this order, he fell here into erroneous implication and into logical error. He fell into *erroneous implication.* For irritants appropriately graduated—and I think Sir W. Watson Cheyne must have been conscious of this—evoke hyperaemia and lymph effusion from the capillaries ; or, as the case may be, leucocytic emigration and cell-proliferation—all these being physiological reactions which find very useful application in wounds. And Sir W. Watson Cheyne fell into *logical error.* For if he had brought demonstration that hypertonic salt solution does not bring into play osmotic forces, this would not have made it an irritant. Any more than if he had brought proof that hypertonic salt solution acted as an irritant, this would have shown that salt does not bring osmotic forces into play. The one does not exclude the other.

But this is straying away a little, for what I have in view is to show that Sir W. Watson Cheyne has not, in matters such as we are here dealing with, any clear mental vision. Seeing in osmosis only the dialysing membrane, and remembering that colloids do not pass such a membrane, he recites that '*colloids such as lymph*' (let me tell him in passing that by this he means : *colloids such as the albuminous substances which are contained in the blood-fluids and lymph*) ' dialyse very slowly or not at all, and practically the only result of placing a strong solution of salt *outside a blood-vessel* would be the exit of water and salts from the *blood.*'

Now this, considered as criticism directed to the statement I had made, is quite irrelevant. My statement was : the outflow of lymph *from the tissues* is due to osmotic forces brought into play by the salt. Sir W. Watson Cheyne's rejoinder is : the outflow of lymph from the capillaries *into the tissues* cannot be due to these forces.

We have here the same error of inconsequence as before. My statement about outflow from the tissues into the wound cavity may be right without Sir W. Watson Cheyne's about outflow from the capillaries into the tissues being wrong. Again, we may both of us be wrong or both of us right. In reality Sir W. Watson Cheyne's mental vision is never sufficiently acute to discriminate between two issues which are distinct but interconnected.[1]

[1] The reader who is perusing this dialectic, not with a view to studying the quality of Sir W. Watson Cheyne's mind, but with intent to get if he can from one side or the other clearer vision of the problems which have to be solved in connexion with wounds, will perhaps look to me to set out here, so far as I can do so, my mental picture of the cause of the lymph flow obtained by hypertonic solutions of salt. I conceive that the outflow of lymph from the tissues into the wound is due in chief part to osmotic processes—i.e. to processes of ' diffusion ' and ' infusion ', processes in which salt ' diffuses ' from the hypertonic solution into the tissues ; and in which fluid with the albuminous substances contained in that fluid ' infuses ', or passes (in exchange) into the hypertonic solution. This is what happens when a mixture of agar with serum or egg albumen is covered in with hypertonic salt solution, and also I take it when a round of beef is put down into pickle. Moreover, neither in these cases nor yet in the comparatively recent wound, where the tissues are, except so far as they are crusted over by coagulated lymph and sloughs, lying bare, and where hypertonic solution finds its most useful application, can there be any question of a dialysing membrane interposed between tissues and wound cavity. I conceive that the active hyperaemia often produced by the hypertonic salt solution may play a subordinate part in the production of the lymph outflow. It may do so by increased exudation from the swollen capillaries. With regard to the outflow of lymph from the capillaries into the tissues, I can very easily imagine that the salt, in addition to causing hyperaemia, may by direct action upon the capillary wall modify that dialysing membrane in such a way as to facilitate the transudation of albumin. But obviously this is a question for direct experiment and not for *a priori* inference.

We now come to what Sir W. Watson Cheyne says in the communication to which I am here replying. He writes as follows :

' It is a well-known fact in physics that the interchange *between colloid and crystalline substances* is very slow and incomplete, and there is no doubt that any osmotic effect which would be produced by the introduction of brine into a wound would be chiefly the transudation of large quantities of water from the blood. At the same time, I have no doubt that the presence of brine in a wound does lead to a marked increase in the discharge which will contain a considerable amount of proteid material, derived not by osmosis from the blood, but from the irritant action of salt on the tissues.'

I will take it that when Sir W. Watson Cheyne makes, as he does in the first sentence, the statement that in dialysis ' crystalline substances are exchanged for colloids ', this is only slipshod writing. For he has told us above that salts draw only water and not colloids through a dialysing membrane.

That correction made, Sir W. Watson Cheyne's statements are a repetition of what he said before, except only for the admission that hypertonic salt solution does induce an outflow of albuminous fluid from the walls of the wound. And, except as relates to the point he has conceded, my criticisms also remain as before.

Up to this point we have been appraising the value of the *a priori* evidence which Sir W. Watson Cheyne has adduced in favour of the thesis that it is possible to sterilise the wound by antiseptics ; and have been trying to take the measure of Sir W. Watson Cheyne in his capacity as a laboratory worker and a scientific thinker. We now pass to consider the clinical evidence which he adduces to show that antiseptics may usefully be applied in wounds ; and in connexion with this it may be well—limiting ourselves, of course, to the question of antiseptic treatment—also to appraise Sir W. Watson Cheyne as a surgical thinker.

Clinical Evidence adduced by Sir W. Watson Cheyne to show the Efficacy of Antiseptic Treatment applied to Infected Wounds

The clinical evidence adduced by Sir W. Watson Cheyne in this paper may be catalogued as follows : One case of compound fracture of the leg reported by Lord Lister ; a case of acute osteomyelitis treated by himself ; and five cases of projectile wounds treated by his collaborator, Mr. Edmunds.

I propose briefly to summarise these and to consider what Sir W. Watson Cheyne wishes to make these cases teach, and what they really do teach.

We may begin with *Lord Lister's case of compound fracture* successfully treated by undiluted carbolic acid.

The description shows that this was a case where the integument was stripped off and the wound completely open ; where the bone was not comminuted ; and the muscles, though severely contused, were not much lacerated.

In other words, Lord Lister was dealing with a microbial infection limited, or all but limited, to the surface, and by consequence accessible to antiseptics. But in the wounds of similar gravity inflicted by projectiles, laceration and hernia of muscle and splintering of bone are the prominent features, and the microbic infection is disseminated in the tissues and has been carried down to inaccessible depths.

It will be clear from this that what Sir W. Watson Cheyne wants to make the case teach, and what the case does teach are quite different. He wants to make it teach that we can by antiseptics sterilise wounds which are inflicted by missiles. What it does teach is that where the mechanical conditions permit of the antiseptic being applied to the whole area and full depth of the infection success may be achieved.

Sir W. Watson Cheyne, considering the report of Lord Lister's case, sees opportunity also for yet another lesson. Certain details of the case furnish, as he thinks, materials by which he can confute by a *reductio ad absurdum* my suggestion that where the condition of a wound is improved by antiseptic applications this may be due not so much to a direct destruction of infective microbes by the antiseptic as to useful physiological reactions evoked in the wound.

'In the case which I have narrated a very interesting and instructive complication arose. On the fractured leg there was at one side a small wound which was not treated by carbolic acid. After some days it was observed that this sore, instead of healing, was increasing in size, and presently hospital gangrene developed in it and caused a good deal of trouble. Thus we have the remarkable fact that not only in the same patient, but in the same limb, we have a large and very grave wound following an absolutely aseptic course, while in the vicinity a trivial wound became the seat of hospital gangrene. If, as Sir Almroth Wright suggests, the main value of antiseptics is due to their production of a *flow of serum*,[1] why did that *serum* prevent hospital gangrene in the large wound, and not in the small one? The *difference between the two really lay in the presence or absence of the strong carbolic acid*.'

What this passage really does bring out is that confused cerebration and deficient logic may deduce a wrong lesson from the data of clinical observation. Sir W. Watson Cheyne conceives that *serum* is synonymous with *flow of serum*. In other words, he can see no difference between serum which has by stagnating in an infected lymph-bound wound lost its antitryptic power, and been transformed into an ideally favourable cultivation medium for all manner of microbes, and an antitryptic serum constantly renewed and constantly bringing fresh antibacterial elements into action. Moreover, he fails to discern that the untreated wound must —for this almost always happens—almost inevitably have become *lymph-bound*, while there must almost certainly from the carbolised wound have been a considerable outflow. For this is the rule with wounds treated with undiluted carbolic acid ; and, moreover, Lord Lister himself draws our attention to this point when he tells us that the wound which he carbolised was ' provided with a porous cloth to absorb the blood and serum which must escape '. It follows that *the difference* between the two wounds did not lie only in the presence or absence of the strong carbolic acid. And so even in this particular case we should be logically entitled to hold the view that the good result obtained by antiseptic treatment may have been referable, or may in part have been referable, to an outflow of lymph from the carbolised wound.

Following the order of Sir W. Watson Cheyne's paper, we now come to a case of *acute osteomyelitis of the fibula* treated by himself with antiseptics.

[1] The reader is reminded that the italics in citations from Sir W. Watson Cheyne are my italics.

Here a large abscess was found over the outer side of the fibula ; the bone was bare, and the medullary canal contained pus throughout its entire length. This was filled in with borsal, the whole surface of the wound was rubbed with the powder, drainage-tubes were introduced, and the whole healed by first intention, and the boy, ' when inquired for three weeks later,' was reported to be ' well and walking about '.

Upon this case Sir W. Watson Cheyne's commentary, arranged so as to set its points out to advantage, is as follows :

(*a*) ' Now I ask any surgeon who reads this account to consult his experience and see whether this is not something new.'

(*b*) ' Certainly in my experience it is.'

(*c*) ' I hope, however, that I will not be held to be recommending this as the treatment of osteomyelitis in preference to ordinary surgical measures.'

(*d*) ' But it is a very extraordinary and unique case.'

(*e*) ' And is, I consider, a very remarkable testimonial for borsal.'

All this shilly-shallying and uncertainty means that, not even for Sir W. Watson Cheyne has this case any probative value. Other surgeons who treat osteomyelitis without antiseptics will not have seen any case like it. Nor will surgeons who have treated osteomyelitis with antiseptics have seen anything like it. Nor has Sir W. Watson Cheyne himself with antiseptics seen anything like it. So that the case differs as much from cases which have been treated with antiseptics as from cases which have been treated without antiseptics. More than that, applying the criterion that ' what we believe, we can act on ', we see that Sir W. Watson Cheyne himself does not believe. ' I hope, however, I will not be held to recommend this.' And the sense of his words is : ' But, though borsal has never done as much before, and I do not think it at all likely that it ever will again,' ' I '—and here I quote his words —' consider it a very remarkable testimonial for my antiseptic.'

The judicious man, who recognises that in a case like this we are bound to remember that there is more than one possible explanation of extraordinary facts, will see that we need not here give any special credit to the borsal, and that it might quite reasonably be held that Sir W. Watson Cheyne's case was unique, not in the respect that the borsal was here specially effective, but in the respect that the microbes had all been exceptionally rapidly destroyed by the patient's mechanism of defence ; or else in the respect that those microbes which survived at the time of the operation happened, by special providence, to lie exposed to the action of any antiseptic.

We come now to five cases ' *bearing on the disinfection of wounds* ' which Sir W. Watson Cheyne ' hopes will be read and *studied* '. I propose therefore to study them ; in other words, to subject them to critical consideration as *crucial* cases adduced to demonstrate the disinfection of wounds by antiseptic treatment. And let us note in this connexion, *first*, that when the success of a treatment is under investigation we cannot admit as *crucial* any case in which any other well-accredited therapeutic procedure is superadded ; and, *secondly*, that it must be shown by

control experiments, or must be indubitable to those who are familiar with the evolution of untreated wounds, that the cases adduced as evidence of the success of the treatment are such as one could not find parallels to among untreated cases. Moreover, when it is suggested, as is done in the cautious words I have put into italics (*vide supra*), that the wounds are sterilised by the treatment, it is imperative to bring bacteriological evidence in support of this suggestion. The catalogue of cases cited from Mr. Edmunds is as follows :

The *first* was a perforating bullet wound of the skull with a small wound of entry and a small wound of exit into the mouth. The *second* was a contused wound of the scalp with a depression in the parietal bone. The *third* was a shrapnel wound in the region of the deltoid with longitudinal splintering of the humerus. The *fourth* was an extensive wound of the forearm with compound fracture. The *fifth* was an in-and-out wound in which the bullet passed superficially through the substance of the abdominal wall.

In the first two cases the wound was ' excised '. They ought therefore to go out of the list ; and Sir W. Watson Cheyne ought not to have adduced them as crucial. In the three remaining cases the treatment and clinical event were as follows :

Case 3.—Here cresol paste was injected among the fragments of bone ; the muscles were dusted with borsal and the wound was sutured except for a space left for a drainage-tube. The sutured portion of the wound healed ' quite naturally ' ; there was after the withdrawal of the tube ' a certain amount of discharge ' ; and when met about a month after his injury the patient was beginning ' to get use in his arm '.

Case 4.—Here paste was injected between the bone fragments ; and the surface was powdered with borsal.

' The patient was under observation '—let us remember that these are cases specially selected as crucial—' for *five to six days*, ample time for suppuration to become established, but this *never* happened.'

Case 5.—Here paste was injected in the trenches, and the wound without further treatment granulated up readily without any suppuration.

There being here no control cases, it of course rests with those who have experience of the evolution of wounds to decide whether the cases cited by Sir W. Watson Cheyne can be paralleled among those treated only by ordinary surgical methods without antiseptics. I think judgment will here not be doubtful. Cases essentially similar to Case 5 are seen every day ; Case 3 also could be paralleled ; and Case 4 is very unconvincing.

Sir W. Watson Cheyne would have known that Case 4 is unconvincing if he had either appreciated the principle that it is much easier to repress leucocytic emigration by antiseptics than to kill microbes ; or if he had ever at the base watched the evolution of cases which had been treated with his strong antiseptics at the front. After a delay he would have found all his antisepticised wounds suppurating and teeming with microbes.

The suggestion that in the cases cited by Sir W. Watson Cheyne from Mr. Edmunds, the wounds were sterilised is not supported by the evidence of any

bacteriological examinations. And *a priori* it is all but incredible that these wounds can have been sterilised.

With the exception of one further case casually introduced in the course of argument [1] and a very few trial experiments with hypochlorites which gave the impression that 'the treatment properly applied was promising', the reader has now seen every particle of clinical evidence which Sir W. Watson Cheyne brings forward in support of his contention that antiseptic applications will sterilise wounds such as we meet in war. But his tune is: 'What need have we of further witness?' 'I think I have'—this is how he sums up—'produced sufficient evidence to show that Sir Almroth Wright is not stating the fact when he says [2] that antiseptics have completely failed to produce aseptic wounds in war.'

Sir W. Watson Cheyne's 'Principles of Disinfection'

We shall presently have to consider how and by what steps a man arrives at quite unchangeable convictions; but first it will be well to see how far Sir W. Watson Cheyne goes. For this we cannot do better than turn to a section of his paper entitled 'Principles of Disinfection'. We are there informed that:

'There are four points of greatest importance in carrying out the disinfection of the wound.' They are as follows:

1. *The surgeon must believe in the possibility of disinfecting 'a wound'.* 'This is, *of course*,' writes Sir W. Watson Cheyne, '*self-evident*, and I "would" not mention it were it not that the possibility of disinfection has been "investigated"' (here the inverted commas are Sir W. Watson Cheyne's) 'by men who had previously expressed the opinion that such disinfection was impossible and would do more harm than good.'

This is the writing of a man who is blindfolded by prejudice or who sets out to lead his reader, if a fool, into pitfalls. Let us go and have a good look at the pitfalls. (*a*) In the use of the wording 'a wound' there is provision made for every kind of misunderstanding and evasion. 'A wound' may mean 'a simple uncomplicated wound' or 'a projectile wound', or 'a small or large percentage of projectile wounds' or 'all such wounds'; and it can according to the necessities of debate be made to take any one of these meanings. (*b*) The inverted commas used in connexion with the word 'investigated' are designed to insinuate that there has been in the investigation of antiseptics, or in some particular investigation which he has in view, incompetence or bad faith. I would suggest to Sir W. Watson Cheyne that that sort of thing is always best put quite bluntly. (*c*) It is asserted that those who have investigated antiseptics in France have been men with preconceived notions who have expressed opinions from which they could not draw back. In reality, however, the effect of antiseptics has been investigated by all sorts and descriptions of surgeons and bacteriologists, who had, before the war, never as much

[1] What Sir W. Watson Cheyne says about this case is referred to below.

[2] What I actually did say—I put it in a footnote because it is here of quite subordinate interest—is as follows: 'I have not myself come across—and I have the permission of all my fellow-workers to say that they also have not come across—any satisfactory clinical or bacteriological evidence of the utility of antiseptics as employed in infected wounds.'

as considered antiseptics in relation with projectile wounds. (*d*) While among all these investigators there must, of course, have been some who believed that '*disinfection*', if by that Sir W. Watson Cheyne means '*ineffective disinfection*', would be more likely to do harm than good ; it is difficult to suppose that there were any who held that '*disinfection*', if by that Sir W. Watson Cheyne means '*effective disinfection*', could be anything else than useful.

But we must beware lest we give here exclusive attention to what are minor immoralities. Here the great outstanding fact is that Sir W. Watson Cheyne, claiming rank as a man of science, says unabashed, 'You must believe a thing before you can find evidence of it!' ; and that Sir W. Watson Cheyne, posing as a scientific champion of antiseptics, announces that, 'If you do not set out with a belief in the efficacy of antiseptics, the facts will never bring that home to you.' Everybody will feel that a man who ventures to say things like this has got himself into a plight where he will say absolutely anything. And the pity of it is that everyone would have agreed with this author if he had contented himself with emphasising that before a man takes it upon himself to say that it is impracticable to sterilise the large bulk of projectile wounds, he ought to have made a conscientious laboratory study of antiseptics, and to have supplemented this by painstaking practical trial.

2. *The surgeon must choose a suitable antiseptic.*—There is (*a*) a trap in the appellation 'suitable'. It is a trap in the form of a *petitio principii*. For it is postulated in the word 'suitable' that we have at disposal antiseptics which are competent to sterilise our projectile wounds. And (*b*) on the top of the *petitio principii* we have an evasion. For Sir W. Watson Cheyne is studious not to particularise any antiseptic which would sterilise projectile wounds. 'I shall,' so runs his evasion, 'presently give a few examples of the results with several different antiseptics.' The reader has already studied everything that could possibly be called an example.

3. *The surgeon must see that the antiseptic has free access to every part of the wound.*—There are here two ambiguities. They are material to Sir W. Watson Cheyne. For when in controversy you employ ambiguous terms, and are then taken up in a way which is inconvenient, you can always assert—and if you are unable to think clearly, can with innocence assert—that the alternative meaning was your meaning. 'Free access' is ambiguous. It may signify either that the antiseptic must be so placed that diffusion if it were effective would carry your 'antiseptic emanation' to the place where it is required, or it may mean that the antiseptic must be directly placed where it is required. And again 'every part of the wound' is ambiguous. It may signify 'every part of the cavity of the wound' ; or again it may signify—and it must in connexion with sterilisation import this—every part of the wound cavity and of the infected tissues round about.

When these ambiguities are brought out we see that Sir W. Watson Cheyne is placed on the horns of a dilemma. If the expressions 'free access' and 'every part of the wound' are interpreted in each case in the former sense, Sir W. Watson Cheyne's demands are ridiculously less than what would be required for the sterilisation of the wound. If, on the other hand, they are interpreted in the latter sense,

everyone must realise that Sir W. Watson Cheyne is out of touch with the clinical facts, and that he is asking from the surgeon something quite impossible. And the practical surgeon will turn upon him and say something like this : ' Am I to understand that, as a preliminary to the application of antiseptics, you require me, in the case of a chest wound, to follow up the projectile into the lung ; in the case of a head wound, to open up the track through the brain ; and in a perforating wound of the arm or leg to hemisect the limb—to say nothing of supplementing in each case with a series of crimping incisions into the walls of the wound with a view to providing access to the microbes which are there ensconced? '

4. *The surgeon must arrange for some of the antiseptic to remain in the wound for a considerable time so that it may continue to act.*—The fact that Sir W. Watson Cheyne erects this into one of his fundamental postulates brings out that there is not before his mind any clear picture of what takes place when an antiseptic lies in a wound and lymph begins to pour in. What occurs is exactly the same as happens when I have an antiseptic at the bottom of a test-tube and let an albuminous fluid which is infected with microbes very gently run down upon it. The antiseptic does not penetrate into the albuminous fluid and the microbes grow in it unrestrained. And there is no question of the antiseptic ' continuing to act ' in the infected fluid. It does not as much as begin to act.

But it is not only on the possibility of disinfecting projectile wounds by antiseptics that Sir W. Watson Cheyne has unchangeable convictions. He has them also on all subject matters which are in any way associated with this belief. He is, for instance, incapable of conceiving that antiseptics in any strength or in any form employed in the early stages for the purpose of sterilising a wound can do harm. All I need say with regard to this is that the harm that can be done under any circumstances by his antiseptic pastes has repeatedly been brought to his notice. And he is in a position to know that this is one of the very few points in connexion with the treatment of wounds on which there is, one may say, universal agreement.

Sir W. Watson Cheyne is also impenetrable to the idea that antiseptic applications might bring advantage to the patient otherwise than by a direct destruction of microbes. The question has, as the reader will remember, already been discussed in connexion with Lord Lister's case of compound fracture. But I may further reinforce here the point there made. For recurring again to the subject in connexion with a case with many bomb wounds of which some were treated with borsal and remained aseptic, while others were treated with hypochlorites and suppurated, Sir W. Watson Cheyne reasons as follows : ' This again shows that, the lymph being the same in all the wounds, the difference in ascepticity was due to the antiseptic and not to the lymph.' There could not be a better example of what results from an incapacity to see anything other than what one allows oneself to see. For to every trained mind, coming fresh to the consideration of the data, it will be obvious that, on the top of the fallacies I have previously pointed out, we have here another very conspicuous fallacy. When you add to lymph in different wounds two different chemical agents which combine, perhaps the one in one way and the other in another, with albumen, you can no longer assert that ' the lymph is the same in all the

wounds '.[1] And it follows that you cannot, as Sir W. Watson Cheyne here does, infer by exclusion that the ' difference in asepticity ' must be due to the antiseptic having in the one case killed, and in the other case having failed to kill the microbes.

Finally, let me show that Sir W. Watson Cheyne, for all that continually he is bringing up Lord Lister's name, fails to see that master's work in any broad perspective.

The miracle in surgery which was wrought by Lord Lister was wrought by showing that septic infections of surgical wounds can be prevented by the use of antiseptics. There was here a *master-idea*—the conception that it was possible by prophylactic measures against microbes to avoid septic infection. And there was associated with this a *procedure for carrying the idea into practice*—that was the employment of antiseptics.

Let us see now the position Sir W. Watson Cheyne takes up. Fusing together by association in his mind the master-idea and the procedure originally suggested for carrying out that conception, Sir W. Watson Cheyne regards the two as inseparably welded together. He has never as much as heard that the master-idea endures, and the method of applying it changes and grows old ; and he deems himself to be doing battle for Lord Lister when he draws the sword upon all those who in loyalty to that master's ideal depart from the procedure which he taught.

Of them and of aseptic surgery Sir W. Watson Cheyne writes in the following exasperated and un-understanding manner :

> ' Unfortunately of late years a most unaccountable prejudice has arisen against antiseptics, with the result that students have not been educated in their use ; indeed, they have been taught to deny their value, and to look upon them as old-fashioned and very objectionable substances.'

Let us, coming to what is more directly in question in this paper, now follow the evolution of Lord Lister's thoughts from prophylaxis to treatment. Affiliated to his master-idea there came up in Lister's mind the therapeutic principle that it might be possible to arrest microbic growth in the wound and so overcome all sepsis. There followed Lord Lister's exploitation of antiseptics in the treatment of compound fractures and other infected wounds. And we have now Sir W. Watson Cheyne obsessed with the idea that antiseptics applied at the outset to projectile wounds will—despite all that we know about the anatomical characters of those wounds—prove efficacious.

And we now see to what this obsession conducts. It leads Sir W. Watson Cheyne to treat as enemies of the light, and therefore his enemies, all those who have urged that there is need of other therapeutic measures where antiseptics are ineffective.

[1] It may not be amiss here to indicate that wounds treated with hypochlorites which have recently come into use apparently suppurate less and heal better than did the wounds in the earlier period of the war with the antiseptics then in use, and to point to the probable explanation of this fact. That explanation is almost certainly to be found in the circumstance that the hypochlorites differ very markedly from antiseptics such as carbolic acid and iodine with respect to the effect they exert (*a*) upon trypsin, (*b*) upon the antitryptic power of the blood-fluids, and (*c*) upon such mixtures of trypsin and antitryptic lymph as are encountered in the wound ; and (*d*) upon blood and lymph coagulation and the outflow of lymph.

Sir W. Watson Cheyne's Verdict on Physiological Methods of Treatment

Let me in conclusion consider the judgment which Sir W. Watson Cheyne pronounces upon the measures I have proposed. It is, and every psychologist will recognise that it had to be, a verdict of unqualified disapproval. Let us see why this was bound to be so.

When an erroneous belief takes firm hold of a man, two bodies of thought will evolve side by side in his mind : one correlated with his obsession, and the other with the data of actual experience ; and these will before very long come into open conflict.

But things do not end there. For when truth and untruth lie very unquietly together in a mind, and untruth cannot be thrown out, Nature always steps in and deals with the patient. She compels him to take error as his postulate, she insists on his putting away from him all those data of experience which conflict with it, and she comes and blots this and that out of his mind, until he has there instead of insoluble contradictions, a corpus of coordinated erroneous thinking.

This process for dealing with the situation by extruding the incompatible—this process which the psychologist has very infelicitously termed ' rationalisation ' —can be seen in operation everywhere. We see it in the circle of medicine when a man, to conserve his obsession, passes condemnatory judgment upon a treatment alleging grounds conspicuously inadequate. We see it again when he in the interests of his fixed idea sets aside unscrupulously a consensus of favourable opinion upon that treatment. And we see it once more when such a one, to maintain what is to him a mental postulate, brings up in appraising a therapeutic method everything that tells against, and suppresses everything that tells in favour of that method.

Let us now see all this illustrated in Sir W. Watson Cheyne.

We may take first his critical analysis of the programme of treatment I have proposed for infected wounds. Let me here briefly point out that one may in making therapeutic suggestions follow one or other of two policies. One may set out only those points which tell in favour of the proposed method of treatment. Or one may deliberately set out in addition also, so far as one knows them, all the points which would tell against one's treatment.

It is this latter policy which I have—in connexion with prophylactic inoculation against typhoid fever and pneumonia, vaccine-therapy in general, here in connexion with physiological treatment of infected wounds, and I believe everywhere—pursued. And I have, I may say, done so in the face of much friendly *soi-disant* worldly-wise advice. Moreover, when there has been anything which appeared to me of moment to be brought up against my methods I have made it a matter of pride to try to be the first to say it.

Now I need not here consider what a critic might or might not appropriately do in appraising a therapeutic method which was represented to be faultless. And I am very far from thinking it a bad thing for a critic of a method to be more alive to its disadvantages than its author could ever be expected to be. But it will, I think, be disputed by nobody that every critic ought in the interests of science to make a genuine effort to hold the scales even, and that it is when, reporting on

accounts honestly furnished, inequitable to report everything which is set down on the debit side and nothing that is set down on the credit side.

Now this is the method of Sir W. Watson Cheyne. He has simply taken the account which I have rendered of treatment by salt in its successive stages, has suppressed everything which tells in favour of, and has, adding nothing new of his own, copied down from me all I could find to say against that treatment.

It would be futile to make reply to criticism of that kind. I have simply to refer back to my publications, for in these there will be found set out over against the debit side also the credit side of the account. But I must try here to do Sir W. Watson Cheyne scrupulous justice. I do find in his criticism one new point which I had not myself made. It is this. ' I have ', he writes, ' a strong suspicion that before long " brine " will disappear from Sir A. Wright's armamentarium.' I would remind Sir W. Watson Cheyne ' that it is many a true word is spoken in jest ' ; and let me in connexion with this spoken in sarcasm quite earnestly tell him this : That which is of permanent value in connexion with any new departure in therapeutics is, as we have seen, the master-idea, and not the particular procedure for carrying it out. To the fact that this must hold true also of the treatment of wounds by physiological methods I trust my eyes are open ; and I devoutly hope that as soon as there shall have been discovered a better agent for inducing in infected wounds the requisite physiological responses the prophecy of Sir W. Watson Cheyne's will be fulfilled, and ' " brine " will disappear from my armamentarium '.

We come now to what relates to the practical results obtained by physiological treatment of infected wounds. What Sir W. Watson Cheyne has to say about his personal experience of the results appears in full in the two following citations :

(*a*) ' As a matter of fact, some of the worst septic cases which I have seen since the war commenced have been in sailors who had been immersed in the *briny* ocean for *some time* after the infliction of the wounds. In such cases . . . even when the patients were received into hospital *only a few hours after* the injury, their wounds were already *exceptionally highly septic.*'

(*b*) ' *I myself have* seen *cases* which have been treated in this way, and the state in which *many* of these patients reach this country from France is *quite sufficient evidence* of the want of success of the treatment employed.'

In connexion with the *former* of these citations the reader who has studied Sir W. Watson Cheyne's paper will have perceived that there has been contrived for him an elaborate verbal trap. There has in the previous text been carefully substituted for the pretentious scientific appellation ' hypertonic salt solution ' the honest Anglo-Saxon term ' brine ', and we now see what Sir W. Watson Cheyne was after. Treatment by hypertonic salt solution is rebaptised ' treatment by brine ' to the end that the reader may judge of its harmfulness from what Sir W. Watson Cheyne reports of the effects of immersion in the ' briny ' ocean upon wounds. The wounds seen were, he tells us, ' only a few hours after the injury exceptionally highly septic '. Considering that ' exceptionally highly septic ' calls up in the mind a picture of wounds teeming with microbes ; considering that one really finds in wounds when only a few hours have passed—for the good reason that those implanted have not yet had time to grow out—only extremely few microbes ; and considering

that Sir W. Watson Cheyne does not appear to have in view a series of cases of fulminating gangrene or streptococcic invasion—one here inevitably suspects him of inaccuracy. And this at any rate is certain that he is trafficking in fallacy when he implies that immersion in the sea, with probably cold and exposure and extreme physical exertion thrown in, is the physiological equivalent of applications of warm hypertonic salt solution.

We pass now to the *second* citation. Its most striking feature is its quite hopeless indefiniteness. ' Cases ' and ' many ' are entirely non-committal as to number. No one can tell whether ' many ' stands for a large or small proportion of the cases seen. And I think it can be gathered from what Sir W. Watson Cheyne says that he has confined himself to the inspection of cases on first arrival from France ; and that he himself has not made any trial of physiological methods.

And as before here is also graver offence. Sir W. Watson Cheyne must perfectly well understand (*a*) that it is not permissible to judge of hypertonic salt solution scientifically applied by cases which have been treated by somebody or another, some time in the past, with some form or another of saline application ; (*b*) that it is fallacious in the case of an application which requires constant renewal to take as a criterion of its efficacy the condition found in a patient just arrived from overseas with wounds long undressed ; and (*c*) that when under such circumstances one finds the condition of a wound unsatisfactory—when, for instance, one finds pus—one is in connexion with hypertonic salt solution required to take cognisance of the fact that suppuration is inhibited by that solution only so long as this remains undiluted. And (*d*) Sir W. Watson Cheyne must perfectly well know that in judging of a therapeutic method you must always ascertain the condition of the patient before treatment ; and in forming your judgment you must always compare that condition with the condition found after treatment.

We now pass to Sir W. Watson Cheyne's procedure in dealing with a body of evidence which is favourable to physiological treatment.

' But it has been said to me,' writes Sir W. Watson Cheyne, ' it is all very well to criticise these elaborate and difficult researches unfavourably. Sir Almroth Wright's treatment must clearly be successful, otherwise the numerous medical men at the front would not have remained silent for seventeen months.' To this Sir W. Watson Cheyne replies : ' This is quite a natural retort ; but I have nothing to do with the actions of men at the front, and besides, there is such a thing as discipline.'

Sir W. Watson Cheyne is perhaps not fully alive to the implications which his words carry. If that is so, he will perhaps allow me to tell him that ' quite a natural retort ' is language which implies that those who reasoned with him were in that sort of tight place which invites to retort and evasion. But if the incompatible fact here adduced placed, not Sir W. Watson Cheyne's friends, but himself in a dilemma, could anyone wish for a more perfect illustration of the psychological law that a man who harbours a fixed idea will travesty everything which comes into conflict with it.

And one word about the surgeons in France who have, Sir W. Watson Cheyne is informed, employed hypertonic salt solution with satisfactory success. ' I have ', says Sir W. Watson Cheyne, ' nothing to do with the actions of the men at the

front, and besides, there is such a thing as discipline.' In other words, 'I am not my brother's keeper, and I refuse to be answerable when he palters with the truth. But one must not ask too much of human nature, and must make allowances when opinion is tongue-tied by authority.' Here, as I take it, we have Sir W. Watson Cheyne saying that he cannot seriously believe. He is too intelligent to suppose that private expression of opinion—and it is private expression of opinion which is in question—could ever be suppressed; and it is difficult to imagine that he does not know that in the medical service of the Army the public expression of opinion on questions of treatment is, and has always been, perfectly free.

We now come to Sir W. Watson Cheyne's summary of the practical results obtained; and to his attitude towards accepting from the laboratory therapeutic suggestions. Let me bring together from the four corners of Sir W. Watson Cheyne's paper his utterances on these matters. They are as follows—and I permit myself running comment and annotation:

(*a*) 'There are *evidently several*' (one wonders why 'evidently', and one wonders why 'several') 'fallacies at the bottom of Sir A. Wright's work, otherwise he would get clinical results which he could show us.'

(*b*) 'And what are the results?' (Sir W. Watson Cheyne means, 'Where are the detailed reports of clinical cases?') 'There is no mention of them.'

(*c*) 'Certainly it is a very annoying type of man' (Sir W. Watson Cheyne feels that he deserves well of the community for being that type of man) 'who wants some evidence before he accepts a statement as correct; but I do think we might at least have had one or two illustrative cases.'

(*d*) 'Instead of that we have to be content' (Sir W. Watson Cheyne means that he thinks he is invited to content himself) 'with *hypotheses* deduced' ('hypotheses' stands here for 'inductions') 'from a number of experiments with capillary tubes, and if the clinical facts' (Sir W. Watson Cheyne puts into my mouth this bluster) 'do not seem to agree with the *hypotheses*' (here again 'hypotheses' stands for 'inductions') 'so much the worse for the facts.'

(*e*) 'I would now ask the questions, Had Lister never lived, or introduced his system of *wound treatment*, would the method advised by Sir Almroth Wright have produced a similar revolution in *surgical treatment* to that effected by Lister? Would there have been the same remarkable pilgrimage of surgeons and scientific men from all quarters of the globe to be instructed in Sir A. Wright's *theories with their curious mixture of fact and fantasy*,[1] and to see no clinical *aseptic* results?'

(*f*) 'Let bacteriologists migrate from France to England. . . . Incidentally the surgeons at the front might take advantage of the absence of the bacteriologists to try what could be done by *more purely surgical methods*.'

We have in this series of citations, as the reader will see, something very different from clear scientific thinking and objective discussion.

Let me first clear up a fundamental confusion. Sir W. Watson Cheyne has

[1] One is at a loss to know whether Sir W. Watson Cheyne intends this to mean: 'Theories based upon a curious mixture of true and erroneous observations'; or, 'theories which are composed in part of fact and in part of phantasy.' If the words are intended to bear the former meaning the erroneous observations ought to be specified; if they are intended to bear the latter, it may be pointed out that a theory cannot be composed in any part of fact. It is all phantasy and imagination—in other words, it is a picture in the mind of something not directly brought to the cognisance of the senses.

misinterpreted ' that remarkable pilgrimage of surgeons and scientific men which came from all quarters of the globe ' to see Lord Lister's work. They came to see not an effective treatment for septic wounds, but an effective prophylactic procedure. Now—as everybody knows—prophylaxis is from the point of view of its achievements on an entirely different plane to treatment. In prophylaxis, we work up to an ideal of 100 per cent. of complete successes ; in treatment, we rejoice when we can in any considerable proportion of cases achieve something for the patient ; and there are cases where we know we cannot possibly succeed. It follows that in instituting a comparison between Lord Lister's great preventive work and any kind of therapeutic work, Sir W. Watson Cheyne is quite gratuitously weighing the latter with false scales and weights. But I may quite plainly tell Sir W. Watson Cheyne that, if instead of comparing prophylaxis with treatment he had wished to institute a comparison between treatment and treatment, he could very easily, in any hospital where physiological methods are applied to septic wounds, have found out that these give results much superior to those, as he himself recognises, deplorable results obtained by Listerian treatment.[1]

But let me here seize the opportunity for saying that just as there are in treatment by antiseptics fixed limits to its utility, so also is it with treatment by salt. Salt, though it can penetrate through albuminous fluids into all the recesses of the wound cavity, has yet, in the matter of penetration into the walls of the wound, a clearly delimited radius of action. It can draw lymph and effect leucocytic disintegration and emigration only down to a certain depth in the tissues. And a moment's thought will make it plain that it is not only where microbes have been carried in beyond the radius of action of the salt that we must expect physiological treatment to fail. We must expect it to fail also when the blood-fluids and leucocytes which are drawn to the seat of the injury are incompetent to deal with the infection.

Let me next take Sir W. Watson Cheyne's gravamen that I have not furnished any report of wounds treated with salt, and that I have, he thinks, asked him to accept statements unsupported by evidence, or supported only by such indirect evidence as is furnished by experiments conducted in capillary tubes.

There are here, in point of fact, two closely interrelated issues. The one is whether one is entitled to claim, *generally*, that no statement shall be made unless supported by evidence ; and, *in medicine*, that no therapeutic suggestion shall be made unless there are at the same time brought forward clinical cases establishing the utility of the treatment. The second issue is whether, in science *generally*, where only indirect experiments or observations are adduced in support of a proposition ; and, *in medicine*, when only laboratory experiments are adduced in support of a therapeutic suggestion—it is legitimate to set these aside as without force.

These are in reality questions not of logical obligation, but of expediency. For myself, the broad principles which I have taken as guide are as follows. When the evidence required for testing the value of a prophylactical or therapeutic method is not of easy access, or where for the formation of a trustworthy judgment evidence has to be brought together and presented as a whole, it seems to me incumbent upon the author of the method to bring together the evidence. When the method

[1] *Vide* in this connexion the citations from Sir W. Watson Cheyne at the outset of this paper.

was on its trial I did this for antityphoid inoculation ; and more recently [1] I have done the same in connexion with prophylactic inoculation against pneumonia and its treatment by vaccines.

There is, as I think, one other case where the author of a therapeutic suggestion must, if he wants to establish his case, publish clinical cases in detail. He will have to do this when his therapeutic suggestion has been taken up and tested by others, and has by them been put aside as useless. Sir W. Watson Cheyne, for instance, found himself in this plight in the matter of the sterilisation of wounds with antiseptics. If he did not want to let the thing go by default it was incumbent upon him to publish cases showing conclusive evidence of success.

But the evidence for judging of the utility of a therapeutic suggestion is not always difficult of access. In many instances there are abundant opportunities for testing its efficacy, and these come to practically every medical man. When this is the situation the scientific author has to remember that, even if the publication of a few successful cases may perhaps usefully serve as a decoy, despite of that, his own cases cannot, either with respect to numbers or probative force, for a moment compare with those impartially observed and adjudicated upon by the general body of the profession. Now we have in the treatment of wounds pre-eminently a case to which this applies. To-day thousands of medical men have opportunities for applying in connexion with wounds, and adjudicating upon, any therapeutic method that may be brought forward. And in the particular case of treatment by physiological methods, this had, when I wrote, already been extensively tried, and was every day being more extensively experimented with. There was therefore no occasion for me to publish any decoy cases—not even those ' one or two illustrative cases ' which Sir W. Watson Cheyne thinks ' he might have had '.

In reality the logical situation is quite other than he supposes. I was not claiming from anyone that he should accept statements unsupported by proof. Instead I was inviting every surgeon who might think physiological methods of treatment deserving of a trial to put these to the proof. And I was holding back my own evidence simply because this left the field clearer, and was superfluous.

We now come to the second issue—to the issue as to whether it is legitimate to put aside as unsubstantiated matter, a therapeutic suggestion which is substantiated by laboratory experiments. In suggesting that it is legitimate to do this Sir W. Watson Cheyne is kicking against the pricks.

It is now too late in the day to doubt that all prospect of advance in medicine, and all our hopes of good, lie in applying in practice what is learned in laboratory experiment. And Sir W. Watson Cheyne is fully conscious that he has in his advocacy of antiseptic methods throughout contended that they were methods substantiated by his laboratory experiments. He therefore deserves to be told to stand down when as soon as other laboratory experiments cast doubt on antiseptic treatment and support another method, he comes and tells us that all therapeutic suggestions which rest on laboratory experiments ought to be written off, and all bacteriologists should be withdrawn and surgeons should go back to ' more purely surgical methods '. He forgets that it is not the wounded man who would profit

[1] *Preventive and Therapeutic Inoculation in Pneumonia* (London, Constable, 1913).

from the withdrawal of the men whose special job it is to study the methods by which microbes can be destroyed in the body. In reality the only soul who could profit would be the man who is so obsessed with the old ideas as to extrude from the world, if he could, everything that is incompatible with them—suffering no new thing to come up which did not conform to tradition.

Let me, in conclusion, in return for that admirable admonition, 'By their fruits ye shall know them,' which Sir W. Watson Cheyne prints for me in the forefront of his polemical attack, address to him—and to any other who may be in danger of falling into his case—intellectual and ethical exhortation. I would invite them to the study of the psychology of obsession ; and would have as many as follow the intellectually laborious calling of medicine hearken to that saying of Emerson : 'God has given to every mind a choice between truth and repose.'

INDEX

Acidaemia. Produced by the restoration of the circulation after the production of local acidosis ; and (this being an unverified assumption) by the over-rapid warming-up of patients suffering from shock, 86–88. (*See under* Gas-gangrene.)

Acidosis (Local). Produced by the clamping of arteries, 86–87 ; by cold immersion, 87 ; by trench feet, 90 ; by violent faradisation of muscles, 88–89 ; by haemorrhage, 88 ; by shock, 90 ; by general anaesthesia, 90 ; by gas-gangrene, 91. (*See under* Gas-gangrene.)

Acidosed Sera. Comparative results of implanting pyogenic and anaerobic microbes into normal and ' acidosed ' sera, 53–57, 72, 94, 156. (*See also under* Carbonic Acid and Trypsinised Sera.)

Anaerobic Microbes. Culture of anaerobes in open tubes containing either a piece of animal tissue (Tarozzi), or a piece of potato (Ori and Wrzosek), 44 ; also cultures can be made by implanting microbes lodged in hair-fine capillary tubes (Fleming), 47. (*See also under* Acidosed Sera *and* Trypsinised Sera.)

Antiseptics. Futility of treating foul wounds with, 6 ; quenching of antiseptics in media containing albumen, 15 ; impracticability of sterilising pus by the addition of, 15 ; futility of treating pneumonia by the internal administration of, 15 ; application of, upon clean wound surfaces, 104.

Antitryptic power of the blood-fluids. Reduction of, by heating to 60° C., 7 ; diminution of, by the addition of carbolic acid, 18 ; '*The guardian of the blood*', 50 ; increased by auto-inoculations in all severe wound infections, 7, 37, 64 ; and in gas-gangrene, 65, 66–68 (Table 2) ; increased by the inoculation of bacterial vaccines, 7, 37. (*See also under* Corruption of Wound Discharges.)

Apo-phylaxis. (*See* Phylaxis.)

Auto-inoculations. (Conveyance of bacterial toxins into the blood-stream.) Produced by surgical procedures and by the pre-operative casting-loose of broken limbs, and the vigorous cleaning up of the site of operation, 39, 46.

Bacterial Power of the Whole Blood. (Haemo- as distinguished from Sero-bactericidal power.) (*See under* Leucocytes.)

Bio-pyo Cultures. Cultivation of living pus upon solid media under cover-glasses as distinguished from necro-pyo cultures, 101, 126.

Blood alkalinity. Marriot's method of measuring the pH of the blood compared with the Author's method of blood titration, 70–72 (Table A).

Carbonic Acid. Saturation with CO_2 converts the serum into a very favourable culture medium for Welch's bacillus, 156.

Carrel's Treatment of Wounds. Fleming's study of its *modus operandi*, 153–4.

Clean Granulating Wounds. Treatment of, 107 ; cycle of events which follow the washing of such surfaces with normal salt solution and antiseptics, 104, 108.

Corruption of Wound Discharges. Annulment of their antitryptic power by the setting free of trypsin from leucocytes, 5–7.

Dakin's Solution. (*See* Carrel's Treatment of Wounds.)

Dead Spaces. Importance of avoiding when suturing wounds, 105, 109.

Differentially Permeable Membranes. Examples of very porous — furnished by wicks and cotton-wool plugs, 163 and 164.

Ec-phylaxis. (*See* Phylaxis.)

Emigration Tubes. (*See under* Leucocytes.)

Enterococcus. (*See* Faecal Streptococcus.)

Faecal Streptococcus. (Enterococcus.) Morphology and cultural characteristics of, 34–35 ; presence in practically all War Wounds, 34–5.

Faeco-Sero-Cultural Methods, 35.

Flaps. Dispensing with amputation-, 19.

Fleming, Prof. A. Study of the effects exerted by Dakin's Solution on wounds, 148 ; demonstration of the fact that antiseptics cannot penetrate into the diverticula of the wound, 147-148 ; demonstration of the fact that Welch's Bacillus will grow in Open Tubes whenever any kind of holes and crannies are provided, 47 ; study of the effects of washing out a clean wound with salt solution and antiseptics, 104, 108 ; Bio- and Necro-pyo-Cultures of potent pus obtained from a wound, 126, Fig. 4 ; model of an infected wound which runs out into diverticula, 148.

Foul Wounds. (Wounds containing corrupted discharges and often slough-covered.) Treatment of, by removal of sloughs and restoration of antitryptic power of the discharges, 106, 146. (*See also under* Hypertonic Salt Solution.)

Gas-gangrene. Symptomology, air hunger, pallor, death-like coldness, collapse and 'acidaemic sudden death', 80 *and seq.*; development of — favoured by any interference with the arterial supply of a limb and all other conditions which deprive the muscles of oxygen, 157; unlikelihood of a microbic toxin playing any important role in —, 159; clinical histories of gas-gangrene patients and data of blood examination made upon, 66–68, Table III, p. 74–76 (Table A); derivation of the acid which produces the gas-gangrene acidaemia, 91; treatment of gas-gangrene acidaemia by intravenous injections of 5 per cent. bicarbonate of soda followed by oral administration of lactate of soda, 68, 174–6 (Table I), 82 *and seq.*, 158 *and seq.*; treatment of the stumps after amputation for gas-gangrene, 21, 83.

Haemo-bactericidal Power. The bactericidal power exerted upon serophytes is dependent on the way in which the microbes are implanted, 42–4. (*See also under* Bactericidal Power of Leucocytes.)

Hypertonic (5 per cent.) Salt Solution. Drawing of wounds by, 21; the soap and sugar local applications of folk-medicine suggested the treatment of wounds by hypertonic salt solution, 166–8; the sovereign treatment for the 'physiological misery' which is associated with corrupted wounds, 161–2; application as a *pansement d'attente* (retardative dressing), 161; clearing off of sloughs by —. (*See* Sloughs.) (*See also* Lymph-cup.)

Intertraction. (The drawing of one fluid into another by pseudopodial invagination.) 149–51; ascending and descending —, 163–7; horizontal —, 167–72; more vigorous between 5 per cent. salt solution and diluted serum than between salt solution and plain water, 149–50, 172–4. (*See also under* Differentially Permeable Membranes.)

Kata-phylaxis. (*See under* Phylaxis.)

Leucocytes. Emigration tubes for observing the movements through a blood plasma clot, 8–10; emigration response to streptococcus increased by the inoculation of streptococcus vaccine, 11; spontaneous (*eleutherotropic*) and *chemotropic* emigration, 9; *stereotropism* of —, i.e. the fullest application of leucocytes to the surface of any foreign body, 137; massive collection of — on a glass lath centrifuged in freshly drawn blood and then incubated in the clot, 97, 99, 140–1; liberation of trypsin from — is responsible for the corruption of the wound discharges, 6–8; bactericidal effect is exerted both intra-cellularly and extra-cellularly, 100, 141; bactericidal effect of pus derived from a clean wound (bio-pyo cultures), 101–3, 126, Fig. 4.

Lymph Cup. Employment of, for demonstrating the drawing power of hypertonic salt, and incidentally also showing that the surface of a granulating wound functions as a differentially permeable membrane—in other words a membrane through which *dialysing contact* can be established between two fluids.

Lymph Leech, 4–5, Fig. 1. Explanation of its uses and properties of the lymph collected in it, 4, 123.

Mass Effect. Growth of microbes favoured by massing them together either by setting the capillary tubes containing cultures upright instead of laying them flat, 46–9; or by centrifuging or allowing the microbes to sediment in tubes drawn out into a conical end, 118 (Fig. 1).

Medical Services of the Army, 26 *and seq.*; suggestions regarding the treatment of the War-time Sick and Wounded, 27–9.

Necro-pyo Cultures. Cultivation of pus after its leucocytes have been killed; or under conditions which are incompatible with their survival, 101. (*See under* Bio-pyo Cultures.)

Pansement d'Attente. (*See under* Retardative Dressing.)

Phylaxis. From *Prophylaxis* there may be coined the term *phylaxis* (natural protective power); *apo-phylaxis* (diminished protective power); *epi-phylaxis* (increased protective power); *ec-phylaxis* (region of diminished bacteriotropic pressure); *kata-phylaxis* (conveyance of protective substances from the blood into infected regions of lower bacteriotropic pressure), 115–9.

Primary suture. Conditions under which it can be employed, 105. (*See also under* Secondary Suture.)

Pyo-Sero Culture. Method of, 37–9.

Resuscitational Acidaemia. (*See under* Acidaemia.

Retardative Dressing (*Pansement d'attente*), 111, 161. (*See also* Hypertonic Salt Solution.)

Secondary Haemorrhage. Due to the digestive action exerted upon the wall of an artery by corrupted pus lodged at the bottom of the

wound, 143; prophylactic precautions against, 162.

Secondary Suture of Wounds. (Suture after the wound infection has been brought under control.) An essential requirement is to give effective support to the walls, so as to restrict lymph exudation, and to provide at the same time more favourable conditions for leucocytic access to the microbe, 109, 110.

Self-sterilisation Power of Wholesome Pus. Over-plus bactericidal power of, 92, 126.

Semi-permeable Membranes. (*See* Differentially Permeable Membranes.)

Serophytic Microbes. (Microbes which grow in the unaltered blood-fluids.) Capacity of growing in serum dependent upon the capacity of digesting the albuminous substance of the blood and so overcoming by the antitryptic power of the serum, 3, 135.

Sero-Saprophytes. (Microbes which grow in the corrupted blood-fluids), 3, 34.

Serum. Comparative results of making cultures into normal, acidified and trypsinised serum, 51, 72. (*See also* Serophytic and Serosaprophytic Microbes.)

Shock. Physiology of the condition, 129; resuscitation acidaemia probably produced by the over-rapid warming up of the patient, 92.

Slide Cells, 135 (Fig, 2), 165 and 166 (Fig. 4).

Sloughs. Dissolution of — by hypertonic salt solution, 106, 151–2.

Streptococcus Faecalis. (*See* Faecal Streptococcus.)

Trypsin. Addition of — converts the serum into a more favourable culture medium for serophytes and also into an eminently suitable culture medium for non-serophytes, 6–7; suggested explanation of this, 6, 136; employment of trypsinised media for making blood cultures, 135; method of testing for — in wound discharges, 162. (*See also under* Corruption of Wound Discharges *and* Trypsinised serum.)

Trypsinised Serum. A very favourable cultivation medium for anaerobic, pyogenic and practically all other microbes, 51–3, 94 (Table I).

Tryptic Effect of Serophytic Microbes growing in Plasma, 135, Fig. 2.

Vaccines. Non-specific effect of, goes hand in hand with an increase of the antitryptic power of the patients' blood-fluids, 37.

War Wounds. Classification of, 31–3, 130.

Wash and After-wash Sero-Cultural Method. This serves for obtaining pure cultures of streptococcus and other serophytic microbes from pus and faeces, 35; serves also for demonstrating the fact that the serum from auto-inoculating patients possesses increased bactericidal power, 37–9.

Welch's Bacillus. Its cultivation in serum is favoured by the diminution of the natural antitryptic power of the blood-fluids, 50 *and seq.*; its growth favoured also by reduction of the alkalinity of the blood, 53 *and seq.*; the pullulation of the microbes in the post-mortem blood is due to a reduction in its alkalinity, 55 *and seq.*; the antitryptic power of the blood-fluids is increased in every non-moribund gas-gangrene patient, 66–8 (Table III), 74–76 (Table A); reduction of the antitryptic power of fluids in gangrene-infected tissues, 66 *and seq.*; — does not grow better in serum to which glucose has been added, 78–80; changes which occur in the blood of living rabbits inoculated with Welch's Bacillus, 59–60; changes which occur at the seat of inoculation in guinea pigs and rats, 60 *and seq.*; results of implanting into acidified and trypsinised sera, 73, 77; increased growth of — in blood of patients suffering from gas-gangrene; and in blood of animals after they have been immersed in ice-cold water, and after violent faradic stimulation, 31, 33.

PRINTED IN GREAT BRITAIN BY ROBERT MACLEHOSE AND CO. LTD.
THE UNIVERSITY PRESS, GLASGOW