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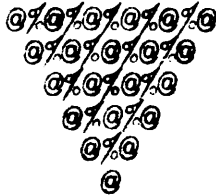
on

(i) Rheumatoid Arthritis and its treatment, with special reference to the use of the Non-specific Protein Reaction.

(ii) Ionic Medication

by

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A STUDY ON RHEUMATOID ARTHRITIS AND ITS TREATMENT

WITH SPECIAL REFERENCE TO THE USE OF THE NON-

SPECIFIC PROTEIN REACTION.

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Introductory.

In spite of the accumulated skill and experience of centuries, the problem of the successful treatment of rheumatism and rheumatic diseases is one which, broadly speaking, may be said to be unsolved. It is true that considerable progress has been made in certain directions. The salicylic treatment of acute rheumatism has established its efficacy, and to-day this drug is rightly regarded as belonging to the small group of specifics employed in the treatment of disease. Again, the more general recognition of the essential morbid anatomical changes underlying the disease known as chronic rheumatism, chronic muscular rheumatism, or fibrositis, has led to more rational and more effective treatment, even though no specific remedy is known which will cause the absorption of pathological fibrous tissue. But here unfortunately the story of progress ends, and when we turn to that particular group of diseases known as chronic non-suppurative or rheumatoid arthritis we find that, though many forms of treatment have been adopted in the past, the results obtained have not been in any way brilliant or even satisfactory. The most striking/

striking commentary on the efficacy of all the therapeutical measures hitherto employed is the frequency with which, in the wards, in the Out-patient departments of large infirmaries, and in ordinary life, there are to be seen cripples suffering from the permanent sequelae of rheumatoid arthritis.

It will readily be granted therefore, that the disease demands further investigation, and that any avenue which gives the slightest indication of leading to more satisfactory treatment, should be explored to the utmost.

I propose in this thesis to detail the results of observations on the treatment of 70 cases of rheumatoid arthritis, which I have made in the course of an investigation extending over the past three years. The scope of the investigation was mainly therapeutical, but, in addition, efforts were made by cultural experiments and by the inoculation of animals, to determine the aetiological basis of the disease. The results obtained will be recorded and discussed, and opportunity will be taken to make some remarks on the theory of focal infection which, at the present time, is being pressed as the chief causative factor in this condition.

The/

The Disease.

As a preliminary to the discussion, I have thought it desirable to state exactly what is meant by the term chronic non-suppurative or rheumatoid arthritis, for there exists an amazing diversity of opinion as to the nomenclature to be adopted for joint affections of this nature. We find the terms atrophic arthritis, hypertrophic arthritis, chronic articular rheumatism, rheumatoid arthritis, chronic infectious arthritis, and chronic rheumatic arthritis, used by different writers to denote what seems to be the same form of disease. For the most part, these terms serve merely to emphasize some obvious but often comparatively unimportant point in the clinical manifestations of certain cases, and their indiscriminate use tends to lead to confusion. The terms osteo-arthritis and rheumatoid arthritis are even regarded by some writers as synonymous. It will help to clear the ground, therefore, if I offer some preliminary remarks regarding my conception of the disease. At the same time, in doing so, I hope to establish the methods and the limits of efficacy of any rational therapeutical procedure which may be adopted.

It seems to me, and this view is held by the majority/

majority of those who have studied the arthritides, that the disease is undoubtedly due to the action of some organism or organisms. It bears so many resemblances to diseases which have been proved due to organismal activity, that this must be accepted. The infective agent manifests its presence by attacking the white fibrous tissue, not only of the joints, though that is the most important feature, but also of the fascia, aponeuroses, periosteum, and subcutaneous tissue. This point, which is emphasized by Stockman, ⁽¹⁾ is of fundamental importance for two reasons. In the first place, it provides a clear and definite pathological basis on which rheumatoid arthritis can be differentiated from osteo-arthritis. In the second place, as will be seen later, it indicates the lines along which rational treatment should be directed. It explains, too, the variety of the clinical manifestations of rheumatoid arthritis, depending on the virulence of the infective agent and the number of possible points of attack. The disease may manifest itself by a slowly progressive thickening/

congestion of the synovial membrane, synovial villi, and fibrous capsule of the joint, while the whole connective tissue is proliferating. At the same time, similar changes may be, and generally are, taking place in the fibrous tissue of other parts of the body, in the fascia lata of the thighs, in the aponeuroses, at the attachment of muscle to bone, in the fibrous tissue of the muscles clothing the pectoral and pelvic girdles, in the panniculus adiposus of the abdomen, legs, and arms, and occasionally in the periosteum of various bones.

The progress of the disease resolves itself into a contest between the infective agent and the defensive powers of the patient. In some cases the individual overcomes the infection and returns to normal, but in the great majority of cases the disease progresses over a long period of years, though not necessarily continuously. Sometimes the process ^{temporarily} ceases, the symptoms diminish, and for a time the patient is comparatively well. Then the infection breaks out afresh, new joints are affected, while those which were originally the seat of the disease become worse. In the end, it may be that the disease-process is arrested, but generally not before irremediable damage is done. The proliferating and congested connective tissue becomes organised, more fibrous, and less vascular, while, in the affected joints, fibrous ankylosis, partial or complete, is a common sequel.

Symptomatology.

Symptomatology.

In the early stages, the symptoms and signs which accompany these pathological changes are pain, stiffness, swelling, and limitation of movement of the affected joints. In some cases, it will be found that the limitation of movement of a joint, particularly the shoulder joint, is not due to any articular lesion, but is solely the result of the pain produced by an accompanying fibrositis of the fasciae of the muscles which control its movement. In fact, even when the joint is affected, the chief factor in limiting the movement of the joint at this stage, is the pain which the patient suffers. In the later stages, the joint deformity is increased as a result of muscular contractures, and, at this time, movement is limited chiefly because of the ankylosis produced by the fibrous tissue changes in and around the joints. The pain caused by the associated fibrositis and panniculitis in other parts of the body increases the disability of the patient, who, in the end, becomes either a complete cripple or, at any rate, an invalid for the rest of life.

Such is the depressing story of the development and progress of the disease known as rheumatoid arthritis. It will be observed that, in the description given, no reference has been made to bony changes. These, when they do occur, come on late in the disease and result from the spread of the infective process to the cartilage and bone, giving rise to erosions of/
of/

of these structures and to the formation of little irregularities of bone by irritation. In this way the changes in the bone differ entirely from those seen in the disease known as osteo-arthritis, where, as is pointed out by Stockman,⁽²⁾ there is primarily a combined process of bone absorption and bone production. In the latter type, the fibrous tissue structures of the joint are practically unaffected until a late stage in the disease, and then chiefly by a deposition of new bone in the ligaments and synovial membranes, though occasionally the synovial membrane is increased by mechanical irritation. Clinically also, this type is entirely different in its development and progress. In this investigation, only cases of rheumatoid arthritis as defined above were dealt with.

Aetiology.

The aetiology of the disease is quite unknown. There is a fairly widespread opinion that many, if not all, of these joint affections are the direct sequelae of infections in some other part of the body. Pyorrhoea alveolaris, septic conditions at the roots of the teeth, tonsillitis and septic diseases generally of the naso-pharynx, middle-ear disease, chronic disease of the genito-urinary organs, chronic lung conditions, have all at different times been claimed as the original foci of infection./

infection. When these have failed the speculating physician, he has turned as a last resort to the alimentary tract, talked vaguely of intestinal toxæmia, and saddled the gut with the whole responsibility. This view of focal infection is based largely on the analogy of gonorrhoeal arthritis arising from a focus of infection in the genito-urinary passages. It is difficult either to prove or disprove such a theory, though it is not easy to conceive such a multiplicity of causes of rheumatoid arthritis, and it is even more difficult to explain how so many people suffer from the infections enumerated and yet how few of them actually suffer from arthritis. It will be readily conceded, however, that the infective agent must enter the body at some point, and that this point could be called the focus of infection. In the cases under review, the most careful search was made for the presence of foci of infection in other parts of the body and, with the possible exception of three cases (Cases X, XVI and XVII), none was found which could be regarded in any way as causative of the disease. Furthermore, the chief therapeutical measure adopted, namely "protein shock" therapy, is one which, as will be shown later, would have caused any hidden focus of infection to flare up. This happened in only three cases and in at least one (Case/

(Case 70), the focus lit up had obviously nothing to do with the joint condition. It can only be concluded from these observations that, if originally there did exist foci of infection, they had cleared up long before the patient came under observation, and that the main seat of infection was then in the tissues of the affected joints.

In every case where synovial fluid could be got from a diseased joint, and in one case where, after operation, diseased synovial membrane was obtained, examination of films for the presence of organisms was made but, except in two cases, always with negative results. Attempts were made to cultivate organisms from the fluids and the synovial membrane, but only in one case was this successful. In case 46 a diphtheroid organism was obtained on culture.

The fluids obtained from joints, and suspensions of the organisms cultivated, were injected into rabbits intraperitoneally, subcutaneously, and directly into the joints, but in no instance did they produce lesions in the animals under experiment. This experience coincides with that of most other workers in the same field, and suggests that the ordinary methods of bacteriological investigation are useless for the purpose of determining the causative organism of these joint affections.

Treatment/

Treatment.

Enough has been said of the development and progress of rheumatoid arthritis to show that rational treatment should be directed along two main lines. Efforts should be made, not only to destroy the infective agent, but also to prevent or minimise the disabilities which arise from the local changes in the joints. It has already been pointed out that, in the early stages of the disease, the chief factor in producing limitation of movement is pain in the tissues of and around the joints, or, almost as frequently, in the fibrous tissue of the muscles controlling the movements of the joint. On the ground that pain is a demand on the part of the body for physiological rest to the affected part, the patient is frequently advised not to move the diseased joint, if indeed efforts are not made by splints or other mechanical means to secure this end. It is my firm conviction that no more pernicious advice could be given. Counter-irritants and local anodyne applications should be used to diminish pain as far as possible, but, from the beginning, the patient should be encouraged to use the affected joints, and this can be aided by massage and passive movements. If that is not done, it can result only in disaster, for adhesions form in the joints, and contracture/

contracture of muscles takes place, leading to deformity and disablement which will tax and often defeat the efforts of even the most skilled expert in orthopaedic methods. If there is any septic focus of infection present, it should be removed even though it bears no causative relationship to the joint infection, for the toxins absorbed from such a focus will act detrimentally on the general health of the patient, and at the same time will irritate the already inflamed fibrous tissue, thus causing an increase in the disabling symptoms. In view, however, of the relative infrequency with which such a focus can be found, this method of attack is not of much help, and I am of opinion that, in the majority of cases, the removal of a septic focus is to be regarded as a general measure to improve the health of the patient, rather than a specific act to remove the source of the infection.

It is a mere platitude to say that the chief aim of treatment is to destroy the infective agent. That is exactly where the difficulty lies, for there is no drug known which acts specifically in these cases, like quinine in malaria or salicylates in rheumatic fever. Furthermore, general antiseptics, when administered by the mouth or parenterally, cannot be obtained in the blood or tissues in/

in concentrations sufficient to produce any effect on the causative organism. Nor can drugs be introduced directly through the skin into the affected joints by inunction, or, as will be seen in another part of this thesis, by an electric current, in quantities sufficient to affect in the slightest the disease process.

Since there is no known method by which a direct attack may be made on the infective agent, attention must be directed towards attacking it through the natural defensive mechanism of the body. This cannot be attained by the use of a specific vaccine, for the causative organism of the disease is unknown; and it is hopeless to expect that the injection of a vaccine made from one of the multitude of organisms which constitute the flora of the alimentary canal, respiratory passages, or genito-urinary tract, could lead to the production of anti-bodies which would affect specifically the unknown microbe. Accordingly, it would appear that the most which can be done is to take measures to avoid the sequelae of the disease by movement and massage, and to improve the general health and hygienic conditions of the patient in the hope that in this way the infection may be overcome.

One of the most striking features in the development and/

and progress of a case of rheumatoid arthritis, is the very slight reaction of the host to the invading organism. The stimulus is apparently small, and in general the reaction is slight. If a greater reaction could be produced by an applied stimulus, it might reasonably be expected that the beneficial results would be increased proportionately. The therapeutical measure which suggests itself as being suitable for an experiment of this nature is that known as intravenous protein therapy, non-specific protein therapy, or protein shock therapy.

History of Protein Therapy.

Intravenous protein therapy implies the treatment of disease by injecting a protein into a patient by the intra-venous route. In general, the protein is one which is not normally present in the tissues of man. This method of treatment, which, as the name implies, is essentially non-specific had, curiously enough, its origin in a therapeutical measure which was based on the idea of the strictest specificity - namely vaccine therapy. As a result of the strenuous advocacy of Wright and other immunologists, the treatment of disease by vaccines expanded until it included practically every form of infection. The greatest emphasis was laid on the importance of preparing these vaccines from the organisms which/

which were actually invading the tissues of the patient; they must be autogenous, or, if that was impracticable, they must be made from organisms similar to those which were the causative agents of the disease. These views were strictly in accordance with modern conceptions regarding immunity. The dead bodies of the organisms introduced into the tissues of the patient were expected to lead to a production of specific anti-bodies which would reinforce the defences of the body in their struggle with the invading forces of disease. Further, the work of Wright on "opsonins" seemed to show that there was a negative as well as a positive phase of resistance following the injection of vaccine, and the greatest care had to be exercised that no general systemic reaction on the part of the patient should take place, lest a negative phase of resistance should develop which might do irreparable damage.

The eminently successful results following the use of typhoid vaccine in the prophylaxis of typhoid fever gave a fillip to its use in the treatment of that disease, but the clinical successes, when the vaccine was given subcutaneously and with all precautions against a general reaction on the part of the patient, were not great. In 1912 and again in 1914 Ichikawa, ⁽³⁾ still with/

with the idea of specificity, administered typhoid vaccine by the intravenous route and reported on the greater benefit which accrued from this method of administration. He found that more than half of his cases treated in this way were cured after the first or second injection, and he further made the startling observation that, when he treated patients suffering from para-typhoid fever with the same typhoid vaccine, he obtained equally good results. He noticed also that there was invariably a general reaction on the part of the patient in the form of chill, temporary elevation of temperature, and increased pulse-rate, but that this did not influence detrimentally the results obtained. About the same time, and independently, some workers in the Argentine ⁽⁴⁾ reported similar successful results, following the intravenous use of typhoid vaccine, and Kraus and Mazza, ⁽⁵⁾ struck with these findings, investigated the use of B. Coli-vaccine intravenously and found that it produced results which were quite as good. Here, then, were two very interesting and, from the immunological point of view, rather startling observations - Typhoid fever successfully treated with B. Coli vaccine, and paratyphoid fever with typhoid vaccine. It is true that the supporters of absolute specificity in the vaccine treatment of disease could still point to the fact that all the organisms used were closely allied, and that the results obtained/

obtained might be due to something of the nature of a group reaction. Very soon, however, it became clear that this argument could not be accepted, for the intravenous injection of vaccines of other organisms which were entirely different from the causative organisms of the disease, was found to be followed by considerable benefit.

From these clinical results it became obvious that, to the various defensive agents which the body had been found to possess,—agglutinins, precipitins, opsonins, bacteriolysins and others,—there had to be added something else which had some therapeutical power. That "something" was induced by the injection of agents which were entirely different from the organisms causing the disease, and must therefore be not only entirely non-specific, but must also depend in some way on a general reaction of the body. The exact nature of that "something" was, and still is, unknown, but as the intravenous injection of dead bacteria always resulted in a train of symptoms which resembled in some ways those of shock, an easy way out of the difficulty was to call it the "shock" reaction. Further, it was soon found that this "shock" reaction could be induced by the injection, not only of a bacterial protein, but also of any other protein, such as normal serum or proteoses, and it was realised that, in some way or other, this "protein shock reaction" (to combine in a term its various attributes) on the part of the patient might be of advantage in ridding the body/

body of disease. It was very natural that a therapeutical measure which seemed to be so general in its action should be employed in other infections, and already there exists an extensive literature reporting on its use in many diseases which are beyond the scope of this thesis.

In 1916, Miller and Lusk⁽⁶⁾ reported on a series of cases of arthritis of various types treated in this way. Since then, other workers in America,⁽⁷⁾ and Gow⁽⁸⁾ in this country, have published their experiences with non-specific therapy, and in general they conclude that in a certain proportion of cases great benefit has been derived. An examination of the cases reported shows that attention has been focussed chiefly on the treatment of acute rheumatism, though Cowie and Calhoun⁽⁹⁾ have studied a small series of 7 cases of chronic arthritis which proved intractable to other forms of therapy, and Gow has reported three cases of rheumatoid arthritis which showed very marked improvement under this method of treatment. None of the investigators, however, has confined his observations to one type of disease, and in no instance have the cases been followed for a longer period than a few months.

For these reasons, it seemed to me to be a matter of considerable practical importance to investigate the efficacy of this procedure in rheumatoid arthritis. If the conclusions were to be of any value, the series must be made large enough to include nearly every form of the disease, early or advanced. Furthermore/

Furthermore, the cases must be followed for a prolonged period to observe the ultimate effects of treatment. Again it will be obvious, from what has been said regarding the nature of the disease, that, while it would be perfectly justifiable to enquire whether the non-specific protein reaction brought the infective process to an end, it could hardly be expected that it would remove the adhesions from a joint, stretch a contracted muscle, or soften organised fibrous tissue.

Accordingly, in treating the cases to be described, every measure was taken to prevent deformity, if it had not already taken place, or to correct existing deformities and increase the range of movement of joints by massage, passive movements, splints, and other orthopaedic resources available. Though the treatment is complicated, it does not appear that this complexity invalidates any conclusions which may be drawn regarding the effect of protein shock therapy, for the ultimate test applied was cessation of infection. As far as possible, the cases were followed over periods up to three years from the time they came under treatment, and the last report on each case will be noted. An attempt will therefore be made to answer the following enquiries:-

- (i) Is non-specific protein therapy to be regarded as a valuable addition to our therapeutical armamentarium, in dealing with joint diseases of this nature?
- (ii) If it is to be so regarded, in what particular type of types of cases are the best results to be expected? In other words, what are the limits of efficacy of this treatment?

(iii)/

- (iii) If beneficial results follow this therapeutical procedure, can these be regarded as permanent, or is the improvement only temporary?

In addition to these enquiries, which are chiefly of practical interest, there will require to be considered the broader question of the mechanism of the non-specific protein reaction, which is of some importance because it may throw light on the problems of immunity.

The first point to be decided was the choice of a foreign protein. Consideration of the results of previous workers showed that the choice could be with advantage limited to three, - solutions of proteoses, normal horse serum, and bacterial proteins, - all of which produce similar effects. The first was rejected because of the very great care which has to be exercised in its administration for, even if a solution of proteoses be injected very slowly into a vein, the injection is sometimes followed by collapse of the patient. The second presented even greater possibilities of danger, for the intravenous injection of serum, if given at too long an interval after a previous injection, might precipitate a true anaphylactic shock and thereby jeopardise the life of the patient. The final choice, therefore, lay between several bacterial proteins and, as the use of typhoid vaccine had been reported to be free from serious consequences, there was no good reason for using any other. Further, typhoid vaccine had the advantage that it could be made up according/

according to well-known rules, the dosage could be fixed with a fair degree of accuracy, and its sterility could be guaranteed. At the commencement of the investigation, ordinary typhoid vaccine alone was used, and in general each patient received as a first dose 100 million organisms in 5 cubic centimetres of normal saline solution.

The Reaction.

When this dose was injected intravenously into a patient, no symptoms made their appearance during the next 30 minutes. At varying intervals after that, but generally within one hour from the time of injection, a very definite train of symptoms ensued, and often quite suddenly. In some cases, there was only slight twitching of the muscles of the arms and legs, accompanied at times by a feeling of coldness. In others, this twitching extended to the muscles of the trunk, became general, gave rise to an actual rigor, and the patient complained of feeling very cold and shivery. This was by far the commonest result and accordingly, in order to increase the comfort of the patient, it became a routine measure to put extra blankets and hot water bottles in the bed as soon as the injection was given. The duration of the rigor was variable, sometimes lasting as long as one hour, but in the majority of cases it began to pass off in 30-45 minutes. During the shivering, the patient practically always complained of headache, in some cases/

cases slight, in others pronounced and lasting sometimes for as long as 24 hours. Frequently there was associated with the rigor, abdominal discomfort, nausea and vomiting, and in one case the patient suffered from slight diarrhoea. The nausea and vomiting was not generally severe, but in order to reduce it to a minimum it was found advisable to give the injections in the morning several hours after breakfast, and then give nothing but fluids until the discomfort following the administration had passed off. In a few cases, where the rigor did not appear at all, the patient suffered from headache and a general feeling of malaise, and sometimes, when the appearance of the rigor was delayed for several hours, there was headache for an hour or two before the shivering started. Cases have been recorded in which the reaction was unusually severe, and where the patient became very restless, dyspnoeic, and cyanotic. In such cases, it is said that the symptoms are relieved by a hypodermic injection of 1 cubic centimetre of 1 in 1000 solution of adrenalin hydrochloride or 1/100th grain of atropine sulphate. In the series of cases investigated, the necessity for administering such an injection did not arise. No reaction took place which was suggestive in any way of endangering the life of the patient.

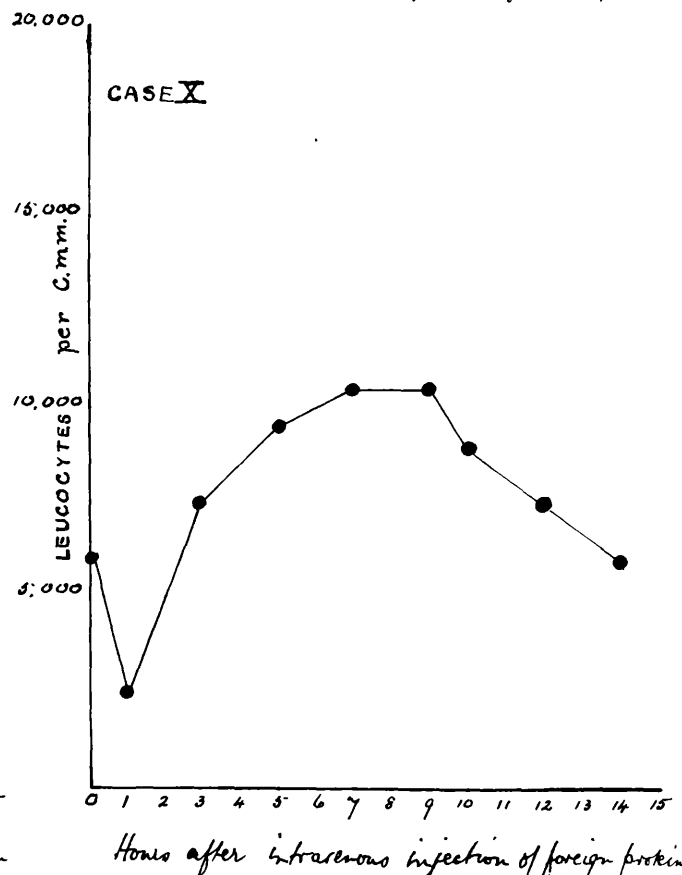
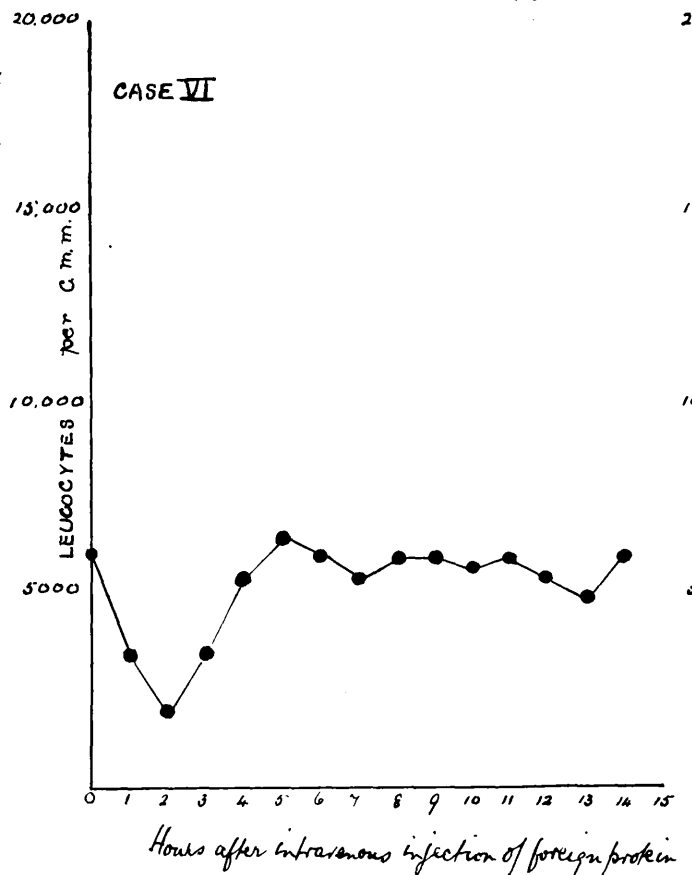
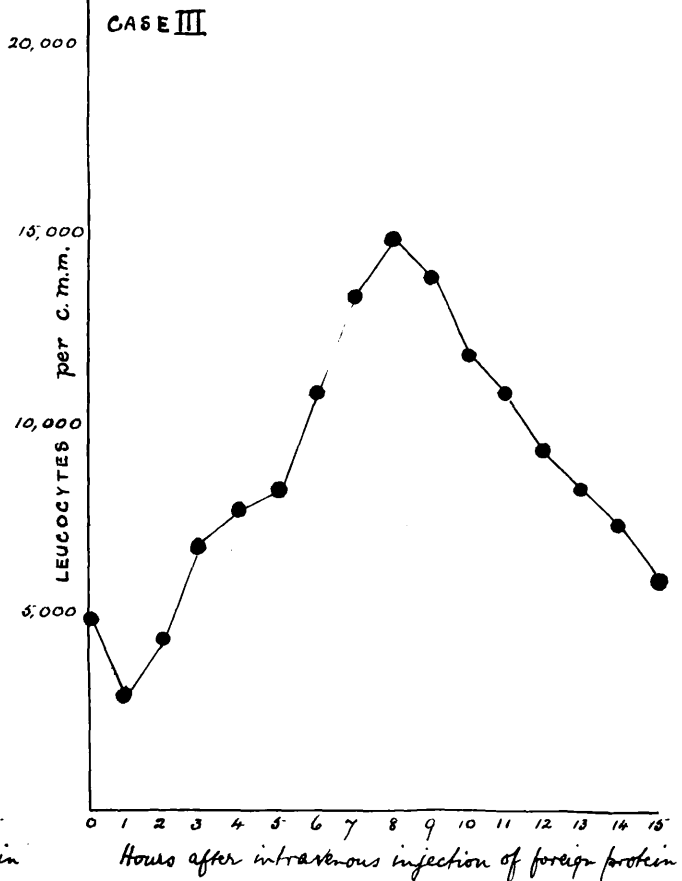
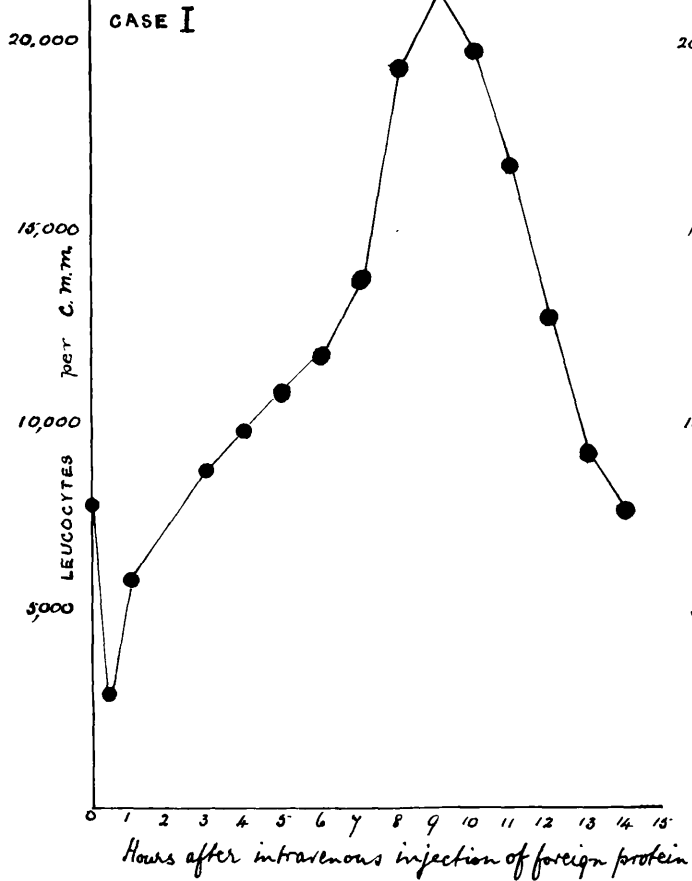
Soon after the onset of the chill, or prior to it
if/

if the chill was delayed, the patient's temperature began to rise and continued to do so until it reached a maximum, sometimes in two, but more generally in six to eight hours, and occasionally even in ten hours. The average range of maximum rise in temperature was between 102°F . and 104°F . the highest rise recorded being 106.8°F . in case XI. Even with this very high temperature, the patient did not appear very ill and there was no cause for alarm. Coincident with the increase in temperature, the pulse rate was increased generally from 20 to 30 beats per minute. Though the above may be taken as a general statement of the rise in temperature which follows the injection, it must be noted that in some cases it is impossible to get such a rise. In case VI, for example, though repeated injections were given, only in one instance did the temperature rise to 100°F . The significance of this observation will be discussed later. From the time the rigor ceased until the temperature reached its maximum, the patient as a rule felt hot and uncomfortable, but then a profuse perspiration developed, and with this the temperature began to fall. The patient continued to sweat freely for several hours and during that time often fell asleep, while the temperature fell to normal. Generally speaking, even though there was pyrexia previous to the injection, the temperature came down/

down to normal in 24 hours and in some cases did not rise again. Occasionally at the end of 24 hours the temperature was still elevated but, if this happened, the normal was reached during the next day. From this description of the events which follow the intravenous injection of typhoid vaccine, it will be obvious that the picture resembles in its essential qualities that seen in a malarial paroxysm. There is the "cold stage" associated with chill, an abrupt rise in temperature, nausea and vomiting. That is followed by a "hot stage" during which the patient feels uneasy and uncomfortable, and then ensues the "sweating stage" when the patient, bathed in perspiration, sinks into a refreshing sleep and the temperature falls to normal. It can hardly, however, be inferred from this, that the mechanism of the production of a malarial paroxysm is by the sudden introduction into the blood-stream of a foreign substance, either the parasites or the altered haemoglobin, but the remarkable similarity in the two pictures is at least suggestive.

During the general reaction, certain changes take place in the blood pressure and in the number of white cells in the blood. For practical reasons, it was quite impossible to study these changes in all the cases described in this thesis. It would have meant living with the patients during the investigation for changes/

changes in the blood occur from hour to hour. A few selected cases were studied in detail, and the observations made coincide with those of other workers. Immediately after the injection, there is a slight fall in the systolic blood pressure and a diminution in the number of leucocytes, particularly of the polymorphonuclear type. This decrease in number reaches its lowest level about 1½ hours after the injection. ⁽¹⁰⁾ Gow and Cowie and ⁽¹¹⁾ Calhoun, who have made similar observations, suggest that the reason for this leucopenia is the emigration of the leucocytes from the superficial blood to the internal organs. It seems to me that a more rational explanation is that it is due to the slowing of the circulation resulting from the fall in blood pressure, and to the consequent dropping out of the leucocytes from the main stream. The number of leucocytes now begins to increase, and from the 7th to the 9th hour reaches its highest level. At this time, a leucocytosis of 15,000 to 25,000 per c.m.m. can be observed, and the increase is chiefly of the polymorphonuclear type. In Case XI, where the temperature rose to 106° 3F., the number of leucocytes rose to 40,000 per c.m.m. In some cases only a small rise takes place, and in others (e.g. Case VI) there is no alteration in the number of the white cells. The leucocytes then diminish in number and in 15 to 24 hours have/



have returned to normal. The leucocyte curve in general follows the temperature curve.

Examination of films made a few hours after the injection, showed the presence of myelocytes, and frequently nucleated red cells were seen. The appearance of these young cells in the blood-stream suggests that the effect of the intravenous injection of a foreign protein is to stimulate the tissues which produce the white cells of the blood, and lead to a leucocytosis.

The attached chart shows the leucocyte curves of typical cases.

In addition to the general reaction already described, there was frequently observed an aggravation of the symptoms of the disease from which the patients suffered. They complained that the affected joints were more painful, that their feeling of stiffness was increased, and objectively there was no doubt that the joints were more tender to touch. Many of the patients who suffered from fibrositis in different parts of the body and from panniculitis, complained that they felt "sore all over" - a complaint which indicated that the inflamed fibrous tissue which was the basis of these lesions had in some way been irritated.

Accentuation of the symptoms of the disease lasted until the temperature returned to normal, and generally for some hours after. This "focal" reaction, as it may be/

be called in contradistinction to the general reaction, is of some importance from the therapeutical point of view, and its significance will be discussed later. When the symptoms of the general reaction had subsided, the temperature had returned to normal, and the increased pain and tenderness in the affected joints had passed off, the patients, in the majority of cases, experienced a sense of well-being. They stated that they felt very much better, that their joints were less painful, and that they could move them more freely. In some cases this improvement was maintained, in others, after a day or two, the pain returned, the mobility diminished, and, in cases which had originally been febrile, the temperature began to rise again. It will be seen, therefore, that the reaction which follows the intravenous injection of typhoid vaccine is diphasic in type. The first phase is marked by general malaise and by an exaggeration of the symptoms of the disease. The second is associated with a general feeling of well-being and with considerable clinical improvement, though this improvement may be only temporary in character.

It could hardly be expected that a disease so resistant to ordinary methods of treatment as chronic arthritis, would be cured by one injection of typhoid vaccine, and therefore consideration had to be given to the questions of the frequency and dosage of subsequent injections.

Cowie/

(12)
Cowie states that, in the treatment of acute arthritis, we may be justified in giving daily injections but that, in view of the severity of the reaction and the condition of the patient, it is good practice to let a day intervene between the injections. After observing the effects of the first injection on a number of patients, I came to the conclusion that, in the circumstances, it was not justifiable to repeat the injections after so short an interval. In the treatment of acute rheumatism, where speed is an all-important factor in order to minimise the risk of cardiac involvement, such a procedure may be perfectly justifiable. But in the more chronic forms of arthritis, where the disease has already lasted from several months to several years, there is not the same necessity for haste. In such cases, it seemed to me that it would be better practice to allow several days to elapse between the injections, for, if the method of cure was non-specific and therefore depending on some reaction on the part of the patient, it seemed that more benefit was likely to accrue if the patient was allowed to recover completely from the general upset induced by the previous injection. In some cases the reaction was a severe ordeal, so much so that, on one occasion, where an attempt was made to repeat the injection in two days, the patient refused to submit to it. Therefore it was decided to allow an interval of at least four days between the injections, the second and subsequent injections/

injections being given from five to seven days after the preceding. This decision was justified in its results, for in those cases where no improvement followed treatment at these intervals, more frequent injections were given, with no gain in therapeutic efficacy. Naturally, the number of injections varied inversely as the beneficial results obtained. As a rule, ~~from~~ four or five were given, and in some cases, where the condition proved very resistant, as many as nine were administered. In general, the conclusion was reached that, if there was little or no improvement consequent on five intravenous injections of typhoid vaccine, there was no use proceeding further with this form of treatment.

The question of the dosage of subsequent injections presented a little difficulty at first, as it was found in some cases that the repeated injection of the original dose resulted in the patient reacting less and less as each dose was given. It was noted further at an early stage that unless there was some definite reaction, little or no benefit resulted. Accordingly, it was decided to give as the second dose 125 million or 150 million typhoid organisms, depending on the extent of the original reaction. The third and subsequent doses were increased to 200 million and 250 million, but the latter was the maximum employed. It cannot be too strongly emphasised that the dosage is,

as/

as may be expected, not a fixed one. A small dose may be sufficient to induce a severe reaction in a sensitive patient, but, judging from the experience gained in giving a large number of such injections, it is quite safe to start with 100 million typhoid organisms. If the patient has a good temperature reaction, the same dose can be repeated or increased to 125 million. If, however, the reaction is not great, 150 million should be given. The physician, when he becomes familiar with this form of therapy, can gauge from the previous reaction whether the dose should be diminished or increased, but no additional benefit is likely to accrue if the dose of 250 million typhoid organisms is exceeded.

(13)

Cecil states that, by accident, three of his patients were given 400 to 500 million typhoid bacilli intravenously, yet the reaction was little, if any, more severe than that caused by smaller doses, and the therapeutic effect no better. I have not attempted to administer such doses, for I am convinced that the best procedure is to administer a dose sufficient to produce a sharp temperature reaction and as few side-effects, in the shape of headache, nausea, and vomiting, as possible. This can be attained, as has been indicated, by commencing with 100 million organisms, slightly increasing the next dose, and then basing the dosage of subsequent injections on the reaction manifested by the patient. If this is done, it will be found that the reaction/

DISEASE

Rheumatoid Arthritis

Notes of Case

N.G.

Name } Case LVI

Age 46 YEARS

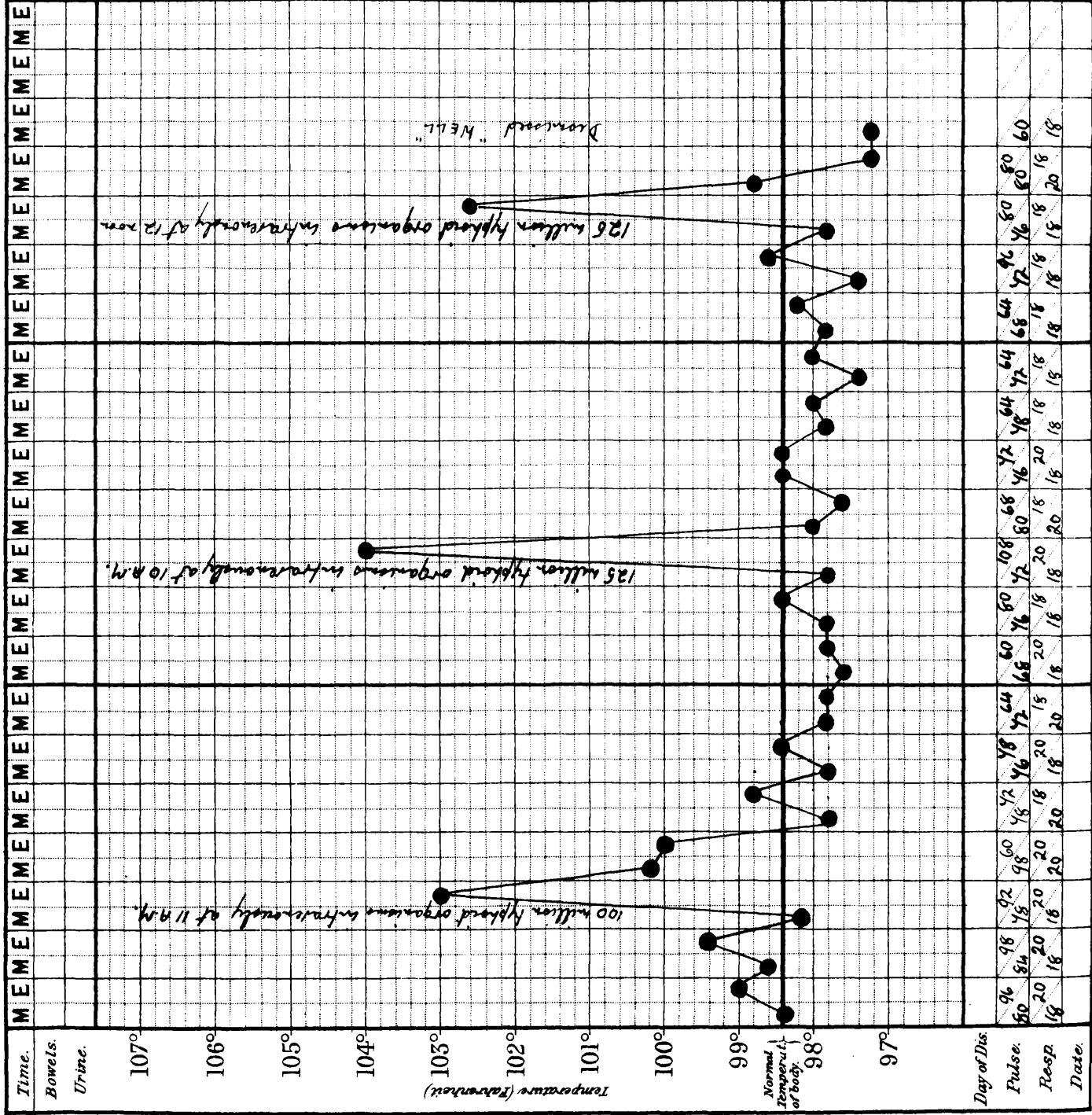
This is the temperature chart of a case which was cured by three intravenous injections of ordinary typhoid vaccine.

Date of admission

10th July 1923

Result

WELL



DISEASE

Rheumatoid Arthritis

Notes of Case

W.C.

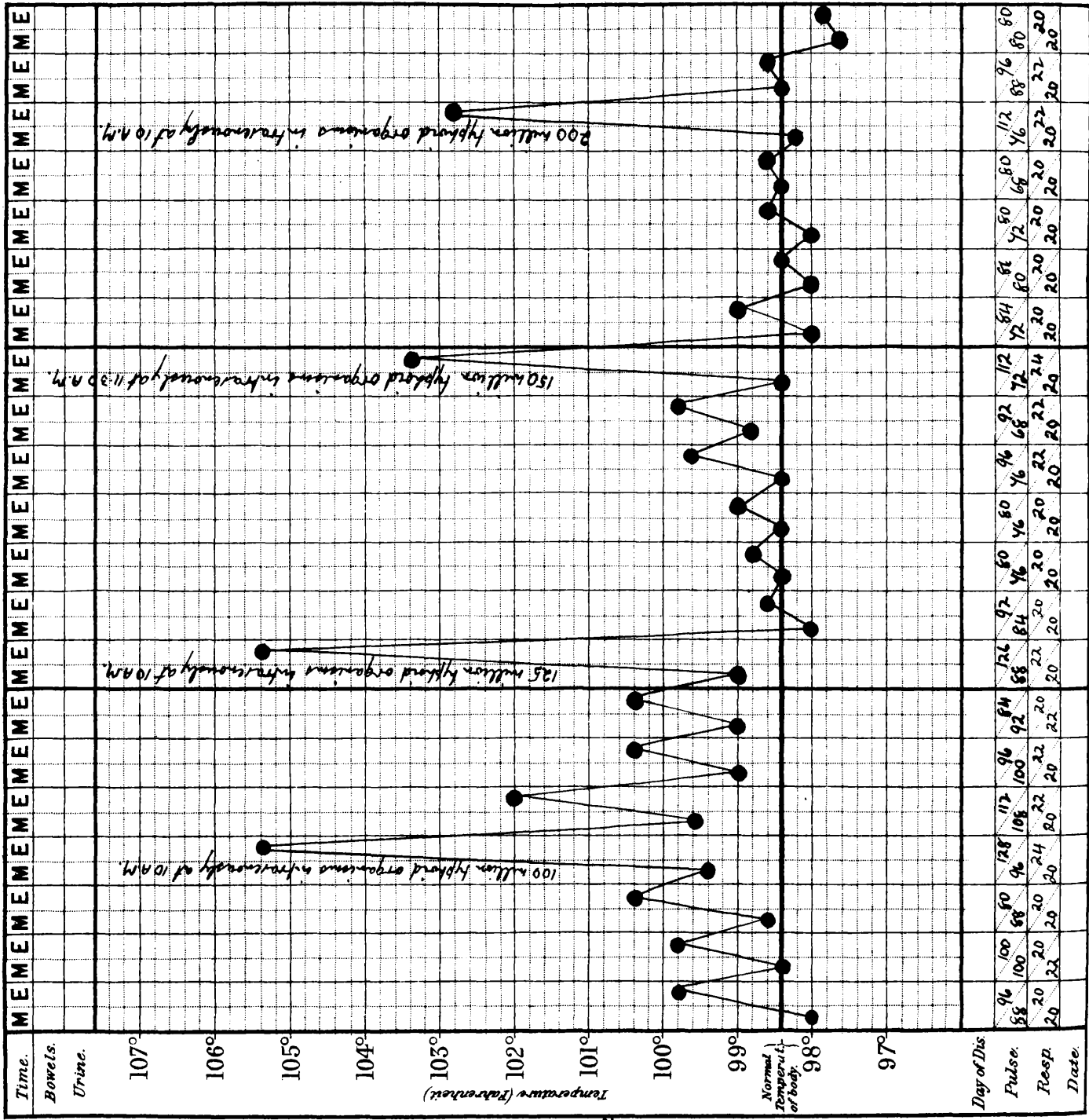
Name

Age 34 YEARS

In this case the symptoms diminished, and the pyrexia disappeared, only after the second intravenous injection of hybrid vaccine. A few days afterwards, the temperature rose again and the symptoms became more acute. The pyrexia disappeared after the third injection.

Date of admission
4th December 1923

Result WELL.



DISEASE

Rheumatoid Arthritis

Notes of Case

T. L.

Name } CASE III.

Age 23 YEARS.

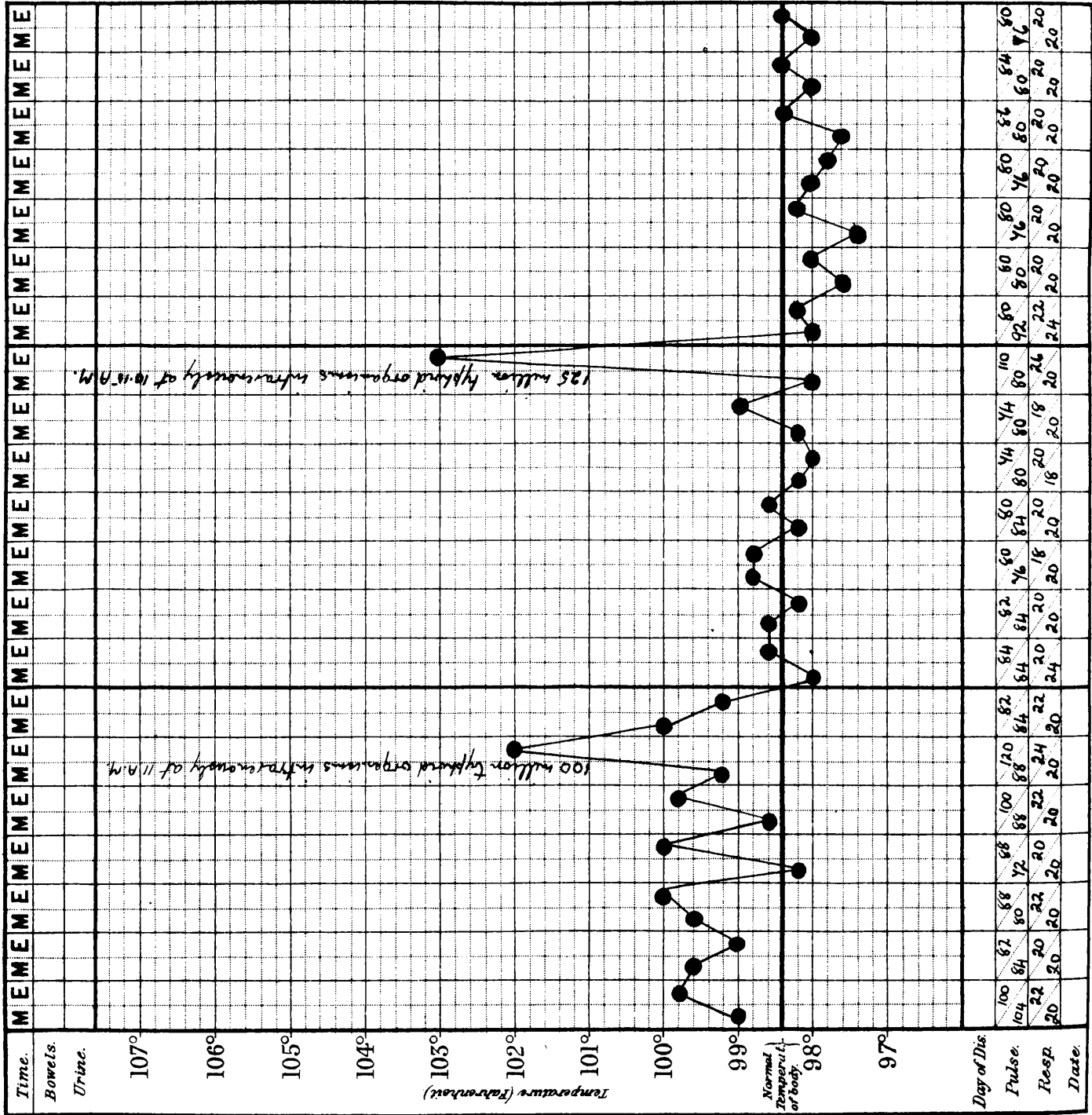
This chart shows the disappearance of pyrexia after one intravenous injection of typhoid vaccine

Date of admission

25th February 1921

Result

WELL



4 HOUR CHART

DISEASE

Rheumatoid Arthritis

Notes of Case

R. L.

Name { CASE I.

Age 32 YEARS.

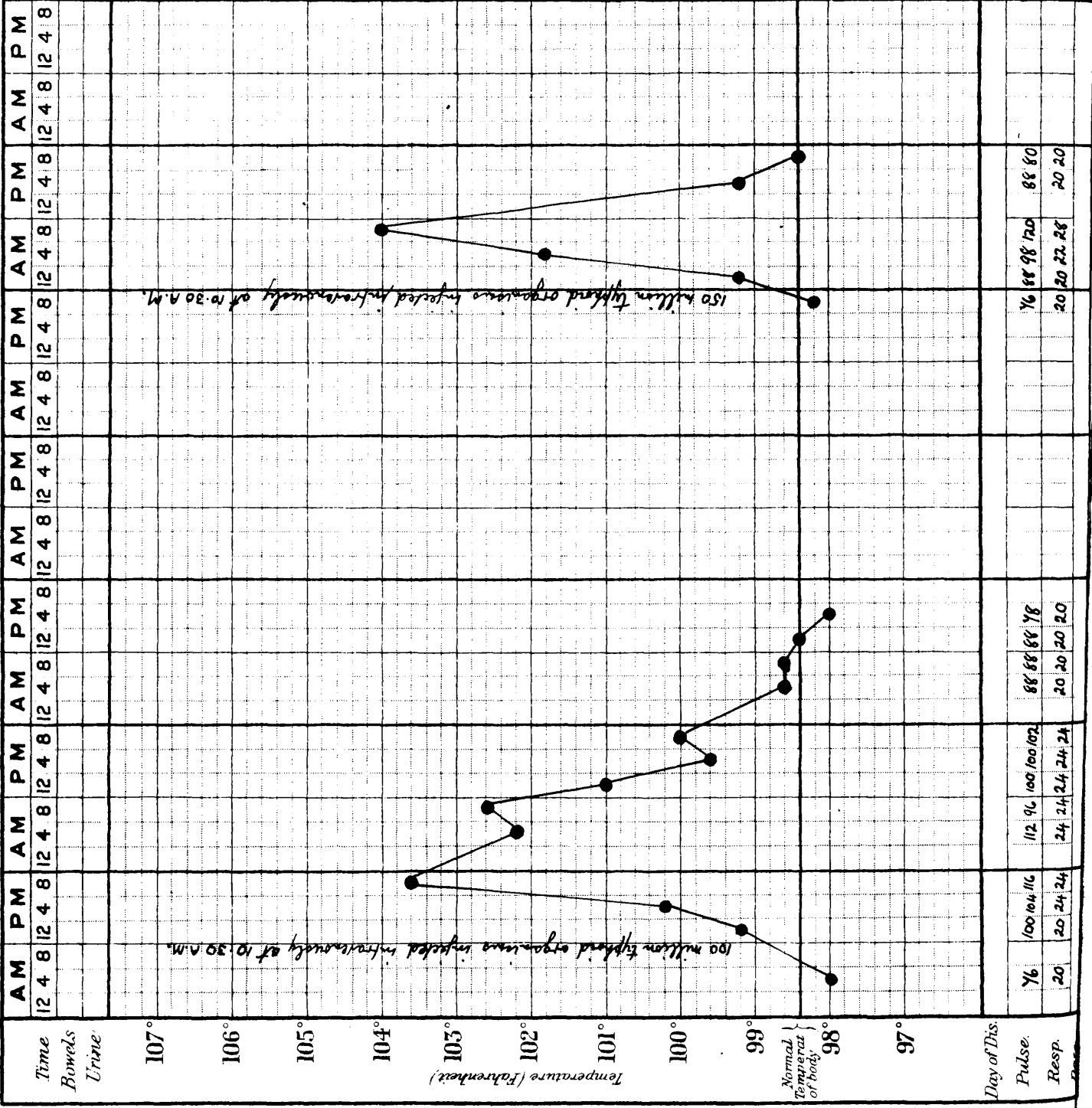
This chart shows details of variation of temperature after he had his intravenous injections of typhoid vaccine in Case I (R.L.).

Date of admission

14th March 1921

Result WELL

42 41 40 39 38 37 36 35 34 33 32 31 30



100 million typhoid organisms injected intravenously at 10:30 A.M.

150 million typhoid organisms injected intravenously at 10:30 A.M.

Normal Temperature of body

Day of Dis. Pulse. Resp.

DISEASE

Rheumatoid Arthritis

Notes of Case

Name } R. L.

CASE I.

Age 32 YEARS.

This chart shows

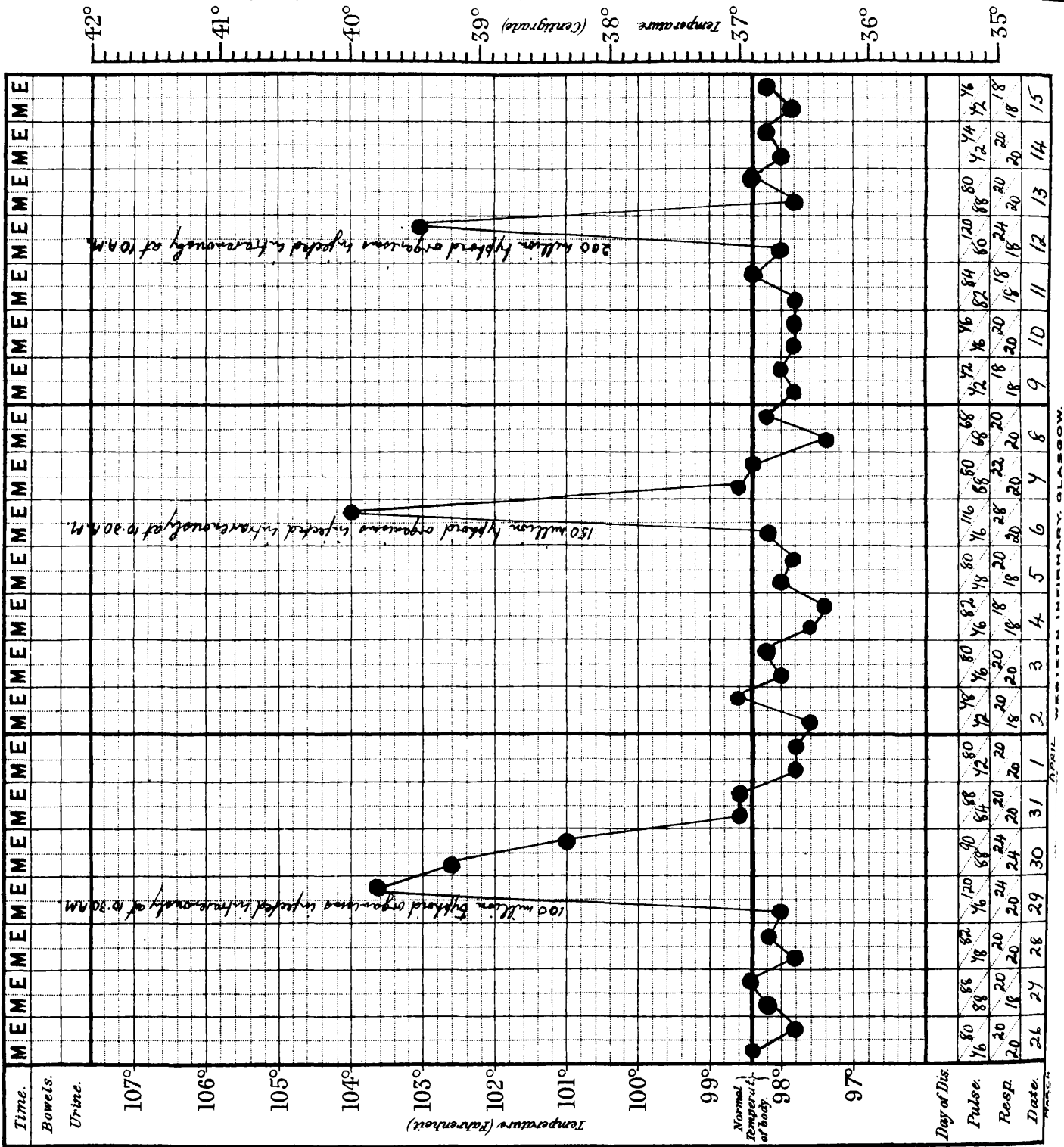
①. Return of temperature to normal in 48 hours after the first intravenous injection of typhoid vaccine

②. Return of temperature to normal in 24 hours after the second intravenous injection of typhoid vaccine.

Date of admission

14th March 1921

Result WELL



reaction following the second and further doses is similar to that described in detail as following the first dose, the only difference being that the initial malaise is generally of shorter duration, and the uncomfortable effects on the patient less severe. The attached temperature charts give a clear idea of the train of events which constitute the protein shock reaction in typical cases.

In the first fourteen cases, ordinary typhoid vaccine in doses as described above was used, and the following are the clinical records of six of those cases. The other eight cases are recorded in Series I of the Appendix.

Case 1. R.L. Male. Age 32. Admitted 14th March, 1921.

History:- Illness began in December, 1920, when the left shoulder-joint became very painful, tender, and slightly swollen. A week later, the right shoulder joint became affected in a similar fashion, and during the next few weeks the disease spread to the elbow, wrist, and finger joints of both arms, and to both knees and ankle joints. He received treatment from his own medical attendant, but no improvement resulted. At times he suffered from considerable pain in the affected joints, at times the pain was slight, but stiffness and consequent limitation of movement persisted.

Previous History:- He had always enjoyed good health except for an attack of Rheumatic fever when 15 years of age.

Condition on Admission:-

The /

The right elbow is very painful and tender and, as a consequence, the fore-arm can be flexed only through an angle of 30°. There is slight thickening of the peri-articular tissues of the joint. There is no swelling or pain in the left elbow, but movement of that joint is stiffly performed. Both wrists are swollen, as a result of thickening of the peri-articular tissues; they are tender, and movement is associated with a considerable degree of pain. The proximal inter-phalangeal joints of both hands are swollen and painful, and he can only half-close his hands. These joints of the ring and middle fingers of the right hand are fusiform, due to swelling and hypertrophy of the synovial membrane and capsular ligaments, and the patient can hardly move them. There is swelling of the right knee as a result of thickening of the synovial membrane, and there is tenderness on pressure over this swelling. There is no evidence of fluid within the joints. The left knee, both ankles, and both shoulders, are painful and slightly tender, but there is no swelling in any of these joints, though all movements thereof are stiffly performed. This pain and stiffness is most marked in the morning and becomes less as the day advances and the patient moves his joints.

The temperature is normal. The heart and lungs are unaffected. No Septic Focus can be found.

Treatment:- 29/3/21. At 10.30 a.m. 100 million typhoid organisms /

organisms in 5 c.c. of normal saline were given intravenously. The leucocyte count before injection was 6,000 per c.mm. At 12 noon, headache developed which was severe for 45 minutes and then became dull. Temperature at that time was 99.2°F. , and leucocyte count was 3,800 per c.mm. At 4 p.m. the temperature was $100^{\circ}.2\text{ F.}$ and leucocyte count was 8,600 per c.mm. At 6 p.m. he developed a slight rigor which lasted for 30 minutes, and at 8 p.m. the temperature had risen to $103^{\circ}.6\text{ F.}$ The leucocyte count at this time was 15,600 per c.mm. At 10.30 p.m. he began to perspire and by 11 p.m. was bathed in perspiration.

30/3/21. At 8 a.m. Temperature was $100^{\circ}.6\text{ F.}$ and leucocyte count 7,500. He complained of increased pain and stiffness in his affected joints which were more tender on pressure.

31/3/21. Temperature $98^{\circ}.6\text{ F.}$ Leucocyte count 6,500 per c.mm. There was diminution of pain, swelling, and stiffness, in the affected joints, and he was much more supple.

6/4/21. At 10.30 a.m. 150 million typhoid organisms in 5 c.c. of normal saline were given intravenously. At 11 a.m. a rigor developed which lasted for 30 minutes. The temperature gradually rose, at 2 p.m. was $101^{\circ}.8\text{ F.}$, and at 4 p.m. reached its highest level, viz. 104°F. He then began to perspire freely, fell asleep, and at midnight his temperature was $98^{\circ}.6\text{ F.}$ Next morning, the temperature was /

was normal. The leucocyte counts were as shown on the diagram indicating the typical changes which take place in the number of white cells of the blood consequent on the injection of a foreign protein. During the reaction, he suffered from headache which was not so severe or prolonged as during the first reaction. His joints were at first more painful, but during the next day the pain and stiffness receded and the range of movement was increased.

For the third injection, a dose of 200 million organisms was administered. The general reaction was not so severe, the temperature rising to 103°F., and the leucocyte count to 16,800. Again all the joints began to ache after the rigor, but this aching gradually passed off, and two days afterwards the following clinical note was made "To-day the swelling of the right knee-joint and of the inter-phalangeal joints has almost disappeared. He still complains of stiffness, but the range of movement of all joints is much greater, and the pain associated with movement is considerably diminished."

Two more injections were given in doses of 250 million organisms, and consequent on these injections the following note was made. 30/4/21 "All movements are now of full range. There is no swelling of any joint and no pain on movement. He still complains of some stiffness and tiredness in the joints of his legs after walking about for some time."

Other two injections of 250 million organisms were given but /

but the reaction following the injection in each case was slight.

On 13/5/21 he was discharged well.

After History:- In March, 1923, I learned that this patient had returned to his work as a miner. Since that time, I have not been able to get into touch with him.

Case III. T.L. Age 23. Male. Admitted 25th Feb., 1921.

History:- Illness commenced in October, 1920, with pain, swelling, and stiffness, in the right wrist-joint. This continued for one month, and then the left knee became stiff, swollen, and slightly painful. The disease spread to both ankles, the right knee, left elbow, right wrist, and several of the joints of the fingers.

Previous Health:- Good.

Condition on Admission:- The patient looks ill, worn, and cachectic. He sweats freely, and the temperature is elevated. Both wrists show a swollen hypertrophied synovial membrane, are very tender to touch, and painful on movement. The metacarpo-phalangeal joint of the right index finger is affected in the same way, and there is some atrophy of the intrinsic muscles of the hands.

Both knees are markedly swollen and tender. They contain fluid, and the synovial membrane is hypertrophied. The fluid withdrawn from the joint and examined for organisms showed none in film or on culture. There is marked atrophy of the muscles/

muscles above the knees and of the calf muscles. The ankle-joints show thickening of synovial membrane and periar-ticular tissues, and are very painful and tender. No focus of infection is discovered.

Treatment:- During the first five weeks of this patient's stay in hospital, carbolic oil dressings were applied to his ankles, knees, and wrists, and he was treated with intramuscular injections of Intramine, (Colloidal Sulphur) and Colloidal Iodine by mouth. There was no improvement; indeed, the infection had spread to the right elbow-joint which was painful and swollen, and the biceps muscle was beginning to show some degree of contracture. During all this time the temperature remained elevated, being seldom normal and never rising above 100°F. He was quite unable to walk, and movement, even in bed, caused considerable pain.

29/4/21. 100 million typhoid organisms were injected intravenously. There was a considerable reaction, and in 48 hours the temperature had fallen to normal. During the remainder of his stay in hospital, it did not rise again. Following on a second injection of 125 million organisms, there was a better temperature response than on the first occasion, and improvement began to take place. The knees, elbows, and wrists, became less swollen and tender.

He was given a series of injections, nine in all, in doses rising to 250 million organisms. This was done at /

at an early period in the investigation, when it was not quite clear how many injections should be given. There is little doubt that the last four were unnecessary. After each injection, there was a fairly good temperature reaction, though the headache and general malaise diminished as the number of injections increased.

Condition on Discharge:- "Left elbow and all finger-joints are now normal, though there is still some atrophy of the intrinsic muscles of the hands. Both wrists and both ankles show some thickening of the periarticular tissues and synovial membranes, but there is no pain or tenderness on pressure, and movement of these joints is only very slightly restricted. There is still some thickening of the tissues round both knees, but movement is complete in range, and there is no pain or tenderness. The patient's general health has shown marked improvement. He walks well but stiffly."

After History:- 20/4/23. The patient was seen to-day. Since his discharge from hospital, he has completed his apprenticeship as a boiler-maker. He walks perfectly, and it would be impossible to say that he had ever suffered from disease of his joints.

Feb. 1924. The patient, having failed to get work at his trade, has been employed for the past five months as a postman. He is well.

Case V. J. McC. Female. Aet. 35. Admitted 29/3/21.

History/

History:- Illness began $2\frac{1}{2}$ years ago with swelling in the right ankle and lameness, followed soon by pain in both knees, without swelling. She continued at work for 6 months, though the pain in her knees caused much loss of sleep. The disease has been progressive, and gradually all the joints, with the exception of the hip joints, have become affected. The ankles, wrists, feet, and hands, are now deformed.

Previous History:- She states she has always had good health.

Condition on admission:- The patient is thin but looks healthy. There is marked thickening of the synovial membrane of both wrist-joints and of the metacarpo-phalangeal joints of both hands. The interossei muscles are atrophied, and there is marked ulnar deviation of the fingers. The wrists cannot be extended, but they can be flexed to a right angle. Swelling of the interphalangeal joints prevents the closing of the hands completely. Skigrams show thinning of cartilage and atrophy of bone at ends of phalanges.

The elbows show thickening of synovial membrane, and contracture of both biceps muscles limits extension to about 30° from the straight position, though flexion is complete.

There is partial ankylosis (fibrous) of both shoulder joints. They can be abducted to almost a right angle with the body, but further flexion causes the scapula to move with/

with the humerus.

The knees are only very slightly thickened, but are very painful, particularly during the night. The ankles are slightly tender on pressure. There is marked external deviation of the toes of both feet, the meta-tarso-phalangeal joints being swollen, painful, and tender on pressure, and partially dislocated by the contracture of the extensor tendons of the toes. There is pain in other parts of the body, particularly at the back of the neck, on the shoulders, and on the soles of both feet, due to fibrositis.

No focus of infection can be found. Heart and lungs are normal.

Treatment:- This patient was obviously suffering from what may be regarded as the permanent sequelae of rheumatoid arthritis, and the deformities of the hands and feet had reached such a stage, that nothing in the way of treatment would be likely to correct them. It was decided to try the effect of intravenous protein therapy, in the hope that it might at least diminish the severe pain, and quell the infective process.

8 injections in all were given intravenously. After each injection, pain was increased in the affected joints for 24-48 hours, followed by a considerable diminution. Following on the third injection, the pain which the patient /

patient suffered at night disappeared, and she could move her joints more freely. Five more injections were given, and though the deformities persisted and she could handle things only with difficulty, and walk slowly and awkwardly, she left hospital improved in the sense that she suffered much less pain than she did before treatment, and there was greater mobility of the affected joints.

After history:- March 1924. This improvement has been maintained. There has been no recrudescence of the disease. No other joint has become affected.

Case VI. J.G. Male. Aet.41. Admitted 6th April, 1921.

History:- In 1909, he began to suffer from stiffness and pain in his feet and ankles. Gradually the condition spread, his knees, ankles, and shoulders, becoming very swollen and painful. From time to time remissions took place, but the swelling and pain always returned, sometimes affecting other joints, each recurrence leaving him more and more crippled. His spine became stiff, the temporo-mandibular joints on both sides became affected, and when he was admitted to the Western Infirmary in October, 1919, he was a complete cripple. It was found, at that time, that he had marked pyuria and that the bladder was very small and contracted, its capacity, when attempts were made to fill it, being not greater than 6 fluid ounces. No tubercle bacilli or gonococci were found in the urine, which contained, on culture, a gram positive diplococcus resembling/

resembling the pneumococcus, and a few colonies of a coarse diphtheroid bacillus. Fluid withdrawn from the knee-joint showed no organisms on film, but a scanty growth of a gram negative bacillus on culture.

He received vigorous treatment for the Cystitis, but little or no improvement resulted, and he was discharged in statu quo.

He was admitted again in September, 1920, but no improvement resulted from the treatment he received in hospital.

Condition:- On re-admission in April, 1921, it is found that his head is quite immovable on his shoulders, and that his neck is rigid - the result of ankylosis of the cervical vertebrae. The temporo-mandibular joints on both sides are ankylosed, and the gap between the upper and lower teeth is not more than $\frac{1}{2}$ inch. The knees are permanently fixed, due to contracture of the flexor muscles, and any attempt to straighten them causes considerable pain. There is marked loosening of the ligaments of the fingers and toes, and atrophy of all the muscles of the limbs. He still passes a large quantity of pus in the urine, and the bladder is small and contracted, so that he has incontinence of urine day and night.

Treatment- This patient was in a very low state of health. He was bed-ridden, and the alterations which had taken place in his joints and muscles were obviously permanent. It was possible that his disabilities were increased by the constant toxic absorption from his septic bladder, and as this condition had /

had been absolutely resistant to treatment by lavage and all the ordinary urinary antiseptics given by the mouth, it was decided to try the effect of protein shock therapy.

The first injection consisted of 100 million typhoid organisms. After the injection he felt shivery, had some nausea, and his temperature rose to 100°F. There was no alteration in the amount of pus in his urine, and no change in his joint condition.

Eight other injections were given in doses rising to 300 million organisms, but although, after each injection, the patient had nausea and occasionally shivering, the temperature did not rise above 100°F. In addition, it was noted that there was no increase in the leucocyte count after each injection, the highest count being 6,500 per c.mm.

There was no improvement in his joints, and there was no diminution in the amount of pus in his urine. He was dismissed from hospital in statu quo ante.

Remarks:- This case is of interest in that, though the dosage was increased to 300 million organisms, it was impossible to produce a reaction on the part of the patient, either in the form of increased temperature, or of increase in the number of white cells of the blood.

Case/

Case X. C.M. Female. Aet.30. Admitted 27th May, 1921.

History:- Illness commenced in October, 1919, with pain and swelling in the feet. In December, 1919, the joints of the fingers became swollen and painful, and she was incapacitated for work. She had suffered for some years from chronic bronchitis.

She was admitted to the Western Infirmary in January, 1920. There was synovial thickening in the joints of the fingers, and ulnar deviation of the fingers on both sides. The metatarsophalangeal joints of the 1st and 2nd toes of the right foot were swollen. She exhibited all the signs of chronic bronchitis.

She was treated with injections of normal horse serum, and showed some improvement, as the swelling of the finger joints partially subsided, and movement of the joints of the feet increased. She was discharged from hospital in March, 1920.

This improvement was maintained for a short time, but the condition recurred and she was readmitted in May, 1921.

Condition on admission:- The right wrist is markedly swollen and tender, and feels pulpy to touch. Movement is considerably restricted. All the proximal inter-phalangeal joints are painful, and that of the left middle finger shows distinct fusiform swelling. The skin over the swelling is /

is bluish in colour. There is ulnar deviation of the fingers of both hands, and some atrophy of the intrinsic muscles of the hands. The knees are slightly swollen but not tender, and movement is unimpaired. There is thickening of the synovial membrane of the left metatarsophalangeal joints and in that of the right great toe, which are painful and tender on pressure.

The chest is ~~emphysematous~~; the respiratory murmur is harsh and accompanied by sibilant and sonorous rhonchi and coarse râles. She perspires freely. The heart is normal.

Treatment:- Six injections were given in doses rising to 250 million typhoid organisms. After each injection there was considerable reaction, the temperature rising to between 102°F. and 103°F. with the usual increase of pain, followed by a diminution in the symptoms.

There was no marked improvement as a result of the treatment in this case. It is true that there was less pain and swelling in the right wrist and fingers, and movements were freer. But there was still tenderness on pressure over all the metatarsophalangeal joints of the left foot and the right great toe, which interfered with walking. The infective process was still active.

Remarks:- It is possible that there was a focus of infection in this case, namely, the severe chronic bronchitis from/

from which she suffered.

Case XI. J.M. Male. Age 30. Admitted 14th June, 1921.

History:- One evening in the beginning of May, 1921, he felt a tingling sensation in his feet, and, the following day, he had pain and swelling of the metatarsophalangeal joints. He continued at work till the end of May, when the pain and swelling increased, and he was forced to remain in bed. During the 14 days prior to his admission to hospital, the right knee and then the left became very painful and swollen, and several of the finger joints became similarly affected. Both elbows and the left shoulder were painful for a time, but this passed off.

Previous Health:- From 1917-1919 he served with the army in Egypt, and, while there, suffered from malaria and bronchitis. Otherwise his health was good. He stated he had never suffered from gonorrhoea.

Condition on admission:- The left knee is swollen and the joint contains a considerable amount of fluid. A film made from this fluid shows the presence of a considerable number of leucocytes, some gram-negative bacilli, and a few gram-positive diplococci. Repeated attempts to grow these organisms proved unsuccessful.

The right knee is very little affected, but the patient states that before admission it was worse than the left.

There /

There is marked swelling of the periarticular tissues of the metatarsophalangeal joints of both feet. These are very tender to pressure, and the slightest movement causes pain.

The proximal inter-phalangeal joints of the little finger of the right hand and of the fourth finger of the left hand are swollen and painful, and normal movement is impossible.

His general condition is poor. Temperature and pulse are elevated. No septic foci can be found. Heart and lungs are normal.

Treatment:- Six injections were given at intervals of 5 days, before the patient's temperature settled to normal and remained there. During that time, there was gradual and continuous improvement of the joint condition, and a note made a week after the 6th injection states "Temperature has remained normal since last injection. The left knee-joint now contains no fluid, but has some thickening, and is still stiff and slightly tender on pressure. The joints of the right hand are now normal. There is some pain and stiffness in the proximal inter-phalangeal joint of the left ring finger, and still some swelling and tenderness of the metatarsophalangeal joints of both feet."

No more injections were given for 14 days, during which time the temperature remained normal, and all the affected joints/

joints became well except those of the toes and the left ring finger. He then received a dose of 250 million typhoid organisms and his temperature rose to $106^{\circ}.8$ F. (This was the highest recorded temperature in the whole series of cases and, as I have already indicated, was not associated with any alarming symptoms.) The leucocyte count at the height of the reaction was 40,000 per c.mm. The temperature reached normal in 24 hours and did not rise again. No further injections were given, and the painful condition of the metatarsophalangeal joints was treated by massage, brine baths, and active and passive movements. For a time, there was considerable hyperaesthesia of the skin of the feet, resembling somewhat the condition seen in trench feet, but this slowly passed off, and he was discharged from hospital practically well.

After History:- March, 1924. The patient has returned to his work as a baker. He states that after a long walk his feet are sore and stiff. This is caused by several callosities which have developed over the interphalangeal joints of the toes of both feet. All the joints of the body appear normal. The infective process has been completely checked.

From this comparatively small series of cases, certain definite conclusions could be drawn. By the use of the non-specific protein reaction, better results could be obtained in the treatment of rheumatoid arthritis than by any other therapeutical measure. Seven of the fourteen cases had shown very marked improvement; in one case, the infective agent appeared to be quelled in all joints except one; two had, to some extent, been improved; and in four cases only, no benefit had been derived. Whether complete cure had been attained in any case, remained for time to show. Certain features of this therapeutical measure were however objectionable, in that it was an uncomfortable ordeal for the patient who, on occasion, complained of the sickness or, more frequently, the severe headache which followed the injection. I decided, because of this, to investigate as to whether such a powerful reaction was essential, and whether similar results could be obtained by the use of an agent which was less toxic to the patient. For this purpose, I used a residual or detoxicated typhoid vaccine made according to the method described by Jenkins.⁽¹⁴⁾ The essential characteristic of this vaccine is that the endo-toxins of the organisms are removed by various chemical means, and that it consists solely of the protoplasm of the bodies of the organisms. If similar therapeutical results, without most of the associated malaise, could be obtained by the use of a vaccine of this type, it would be of great advantage. In the next series of cases to be recorded, this vaccine was used in doses similar to those given in the first series.

During the investigation of the cases in which ordinary typhoid/

typhoid vaccine was used, some observations were made on the production of agglutinins. As was to be expected, the intravenous injection of ordinary typhoid vaccine invariably resulted in an increase in the agglutinin titre of the serum of the patient. In the new series, when detoxicated vaccine was injected intravenously, it was found that in every case except one, Case XVI, there was no increase whatever in the agglutinin titre. The exception was so striking, that further comment is reserved until the case is dealt with in full, for the observations made in this case appear to throw some light on the mechanism of the non-specific reaction.

In this series, 16 cases were treated, and the clinical records of six of these are described here. The records of the other ten cases will be found in series 2 of the Appendix.

Case XV. M.A. Female. Age 30. Admitted 20th Sept., 1921.

History:- Illness commenced 10 years ago, with pain in soles of feet along the balls of the toes. This persisted for one year, but was never very severe, and she was able to walk about. About that time she suffered from a profuse leucorrhoeal discharge. The left ankle then became swollen and painful, and the condition spread to both wrists and both shoulders.

During the next seven years, the joint condition underwent a series of remissions and exacerbations. Sometimes she had little or no pain, at other times she was very stiff and her joints/

joints were tender, but she was able to carry on her housework.

In 1919, 6 weeks after the birth of her child, the left ankle became very much swollen and painful, the left wrist became affected in the same way, and she began to have difficulty in raising both arms above the level of the shoulders. This, she states, was due partly to pain in the shoulders and partly to weakness. These joints remained affected for the next nine months, and then considerable improvement took place and she was able to get about fairly comfortably.

In June, 1921, the disease returned to the joints which had originally been affected, and has persisted until date of admission.

Previous History:- She has always had good health until the commencement of this illness.

Condition on Admission:- There is still occasional white discharge from the vagina, but this is not more than ordinary leucorrhoea. There is no evidence of gonococcal infection, and no septic foci can be found.

There is considerable wasting of the muscles of the shoulder girdles. Movements of the shoulder-joints are not limited, but are stiffly performed and associated with pain over the anterior aspect of the joints. Pressure over these parts shows that there is slight thickening and tenderness of the synovial membranes. There is a painful fibrous /

fibrous nodule on the right suprascapular region.

The elbow-joints are not affected, but the wrists show thickening of periarticular tissues and are tender on pressure. There is marked limitation of movement. In the right wrist, no extension is possible, and flexion only through 15° . The left wrist can be extended through 15° and flexed through 10° from the straight line.

The only finger joint affected is the proximal interphalangeal joint of the right little finger, the synovial membrane of which is swollen and tender. The hip, knee, and right ankle joints, are not affected, but the left ankle is swollen and tender to pressure just below the internal and external malleoli. There is marked deformity of all the toes of both feet. There is tenderness on pressure over the metatarsophalangeal joints, and there is fibrous tissue creaking on movement.

Treatment:- A first injection of 100 million detoxicated typhoid organisms was given at 10.30 a.m. Two hours afterwards, she had a rigor which lasted for 30 minutes, and then there followed the usual train of symptoms associated with the injection of ordinary vaccine. There was the hot stage, after which she perspired freely. She had slight nausea and severe headache, the temperature rose to $102^{\circ}.4$ F. and returned to normal in 24 hours. The leucocyte count rose from/

from 4,800 to 18,000 the next day, and returned to 6,000 per c.mm. in 48 hours.

During the sweating stage, the patient had sharp pain in all affected joints. It is interesting to note that the pain was increased in the fibrous nodule on the right supra-scapular region.

This exacerbation of symptoms passed off, and in three days there was considerable improvement. All the affected joints were freer in movement, and the swelling in the left ankle had diminished.

A second injection of 200 million organisms was given, the same train of symptoms followed, but the rigor was of shorter duration. There was no nausea, and the highest temperature recorded was 100°.8 F. There was again exacerbation of symptoms, and the affected phalangeal joints became very painful and red.

Four days afterwards, a third injection of 250 million organisms was given. Following this, there was no rigor but merely a feeling of cold. The temperature rose to 100°.8 F., severe headache ensued, and all the affected joints became sore and stiff.

Three further injections of 250 million organisms were given and even though, in one instance, the temperature only reached 99°F., the patient had the same feeling of coldness and then of heat and sweating, with severe headache and pain in/

in all affected joints.

Continuous improvement in the joint condition was observed. She was given exercises and massage to render her more supple, and, on her discharge from hospital on 7th November, 1922, the following was her condition. "All movements of the shoulder joints are performed freely and without pain. The finger joints are now normal. There is still thickening of the periarticular tissues of both wrists, but the range of movement is markedly increased and is not associated with pain or tenderness.

The swelling of the left ankle is much less, and all movements can be performed completely and without pain. There is now no pain on pressure over metatarsophalangeal joints."

After History:- 2nd February, 1924. This patient was seen to-day. The improvement has been maintained. She is able to perform all her household duties, and can walk five miles without fatigue. On occasion, she has pain in her shoulders which is relieved by massage. This pain is due to fibrositis. There is still some thickening of the periarticular tissues of both wrists.

Case XVI. J. McK. Female. Age 17. Admitted 20th Sept., 1921.

History:- The illness began acutely in December, 1919, with headache, vomiting, and general malaise, and a transient rash/

rash appeared on the arms and legs. The right knee-joint became very painful and swollen, and, in a few days, the disease spread to the left knee and to both ankles. Associated with these symptoms there was marked elevation of temperature, which persisted in spite of treatment with salicylates.

After two weeks, the affection of the knees and ankles became much less, but the high temperature persisted. Her doctor could not account for this, and sent the blood to be examined by Widal's test. He received a report saying that the test was positive, but, in a letter which accompanied the patient to hospital, he remarked that he doubted if she really suffered from enteric fever. This positive Widal reaction is of great interest in view of the subsequent history of the case.

The temperature settled gradually, and the joint condition improved, but she still had some pain and stiffness in the affected joints, and was unable to move about freely.

In March, 1920, there was another acute attack, the temperature rising and remaining high, while both wrists became affected. This attack persisted with varying degrees of intensity of symptoms until June, 1920, when the temperature settled to normal, and the patient was able to get up and go about for the first time since December, 1919, though the wrist-joints remained swollen and painful.

In/

In October, 1920, she had another bout of fever with sickness and vomiting. In this, as in the former attack, all the affected joints became sore and swollen. This attack gradually subsided about Christmas, 1920.

In February, 1921, there was a fourth similar attack, and this time the proximal inter-phalangeal joint of the left index finger became affected. This gradually subsided, but in April, 1921, she had another attack, and all the joints of the fingers became affected. This attack lasted till June, 1921, when she definitely improved. Since that date, there have been no further attacks.

The salient facts in the history are therefore
 (1) Five quite definite attacks of high fever with pain and swelling in joints recurring at irregular intervals, and on each occasion involving some new joint and (2)
 A Positive Widal Reaction.

Condition on admission:- The shoulder-joints are unaffected. The elbow joints show a little thickening of the periarticular tissues, but there is no pain or tenderness on pressure. There is slight contracture of the right biceps muscle and greater contracture of the left biceps, which limits movement of the forearms in extension.

The right wrist shows marked thickening of
 the /

the periarticular tissues. and synovial membrane, is very tender on pressure, and only very slight movement is possible without causing the patient a great amount of pain. There is wasting of the intrinsic muscles of the hand.

The thickening of the tissues of the left wrist is not so marked as on the right side. There is only slight pain and tenderness, and the joint can be extended through an angle of 10° and flexed through an angle of 30° from the straight line.

All the proximal interphalangeal joints are swollen and fusiform, due to the thickening of their synovial membranes, and they are very tender on pressure. There is some contracture of the flexor muscles of the fingers, and the ring and little fingers of both hands show very considerable deformity.

The knee and ankle joints are now normal, yet these were the first to be affected. The metatarsophalangeal joints of both feet are swollen because of thickening of the synovial membrane, and are tender on pressure. There are also some areas on the soles which are tender, and she states that, when she walks or stands about for any length of time, her feet become hot and painful on the soles and along the roots of the toes.

The temperature on admission is normal.

Treatment:- The temperature remained normal for the first /

first few days after admission, and then began slowly to rise. On 29th Sept., the first injection of 100 million detoxicated typhoid organisms was given. In 90 minutes, there was a rigor which lasted for 45 minutes, followed by the usual hot and sweating stages, and with increase of stiffness in affected joints, but no increase of pain. The temperature rose to 102°F. and in 18 hours returned to normal. Thereafter, however, it became of the remittent type, and on 1st October the spleen was palpable. On 6/10/21 a second injection of 200 million organisms was given, and this was followed by the usual train of symptoms. Consequent on this, four doses of 250 million organisms were given on 11/10/21, 19/10/21, 25/10/21, and 3/11/21.

After the second injection, the temperature became irregularly intermittent, and, following the fourth injection, it became normal and remained so during the remainder of the patient's stay in hospital. The spleen was palpable until the 19/10/21. The temperature curves following the last two doses of vaccine were of normal type. At no time was there any diarrhoea, and the patient, although fevered, did not feel ill. No typhoid organisms were found in repeated examination of the stools.

The following is the record of the Widal Reactions.

<u>Date.</u>	<u>Standard Agglutinin Units.</u>
29/9/21 (before treatment)	8.6
11/10/21	355
19/10/21	714
25/10/21	205
23/11/21	35

The joint condition showed some improvement. The swelling of the proximal inter-phalangeal joints diminished, there was less tenderness, and the range of movement was increased. The only change in the wrist joints was that the left wrist was less painful. There was diminution in tenderness of the metatarsophalangeal joints of both feet, and she could walk more easily.

Remarks:- The most striking features in this case were the extraordinary changes which took place in the agglutinin titre, the appearance of intermittent fever, and the enlargement of the spleen, occurring after the injection of detoxicated typhoid vaccine. Vaccine from the same ampoule had been given to Case XV., but here the temperature returned to normal in 24 hours, and there was no change in the agglutinin titre of her serum. Furthermore, none of the other cases treated with detoxicated vaccine exhibited a similar train of symptoms, and no alteration was observed in the agglutinin content of their sera.

To explain these curious results, attention must be drawn to the fact noted by her usual medical attendant that some weeks /

weeks after the onset of the disease the blood showed a positive Widal reaction. It is possible that the infective agent responsible for her first condition was the B.typhosus, that she was really a typhoid carrier, and that the effect of the non-specific reaction was to stir up an attack of typhoid fever. Against this must be put the fact that repeated examination of her stools for B.typhosus gave negative results, and that, though she had intermittent fever, she felt well, took her food well, and appeared to be very little upset. Another possible explanation is that the intravenous injection of a foreign protein resulted in the flushing out into the blood-stream of agglutinins already formed and lying in the tissues. In this connection, Conradi and Bieling⁽¹⁵⁾ have reported that they treated rabbits with typhoid vaccine and found that, at a later period, the injection of colon, dysentery, and diphtheria bacilli, led to a marked increase in typhoid agglutinins. Furthermore, Mektöen⁽¹⁶⁾ sensitised rabbits to horse serum and found that later on, when the specific antibodies to this serum had disappeared from the blood, they could be made to reappear when quite different types of sera were injected. I am therefore inclined to the belief that in this case the detoxicated vaccine acted as a non-specific stimulant to the tissues, and caused the agglutinins lying there to be flushed out into the blood stream.

This/

This may be part of the general mechanism by which the non-specific protein reaction is of benefit in disease.

After History:- March, 1924. This patient remained comparatively well for 9 months after leaving hospital, but the condition then returned, and she is now as bad as ever.

Case XIX. R.McC. Female. Admitted 1st April, 1922.

History:- Illness began 3½ months ago with pain, stiffness, and swelling, of the wrists and finger-joints. The patient was able to carry on her work until 7 weeks before admission, when the pain became severe and she was forced to go to bed.

Condition on Admission:- There is thickening of the periarticular tissues of both wrists and of several of the finger-joints. These joints are very painful and tender. She has a marked degree of panniculitis in the shoulders, back, arms, and thighs. No focus of infection can be discovered.

Treatment:- Two injections of detoxicated typhoid vaccine in doses of 100, and 200 million organisms were given intravenously. There was no reaction, and no improvement was observed. Some fresh detoxicated vaccine was prepared, and three doses of 100, 150, and 200 million organisms were injected. These injections were followed by shivering, headache, and temperature response, with increased aching in the affected joints and all over the body.

She /

She showed marked improvement, and on discharge from hospital had no pain in the affected joints.

After History:- 28th February, 1924. There is still slight thickening of both wrist-joints, but very much less than on admission. These joints are not painful, movement is of full range, and she can do all her household duties. Her fingers are normal.

Result:- In this case the infective process has been completely stopped.

Remarks:- This case illustrates the necessity for some reaction on the part of the patient, if benefit is to be derived from the intravenous injection of a foreign protein.

Case XX. M.S. Female. Age 46. Admitted 14th April, 1922.

History:- Illness commenced in July, 1921, with swelling and a little stiffness in the right wrist, and soon afterwards the left wrist became affected in a similar fashion. There was no pain in the joints. The swelling persisted, and in January, 1922, both ankles became painful and swollen. At that time, she developed a dry scaly eruption on her face and arms. In 10 days time, the eruption left her face, but has continued on the fore-arms. Since January, the condition of the wrists and ankles has not altered greatly, but has crippled the patient in the performance of her duties.

Previous /

Previous Health:- She has always had good health.

Condition on Admission:- There is very marked swelling and thickening of the periarticular tissues and synovial membranes of both wrists, and pressure over these swellings causes considerable pain. There is marked limitation of movement of both wrists.

There is no pain, swelling, or tenderness, of any of the joints of the fingers, but there is marked laxity of the ligaments of these joints, and there is slight ulnar deviation of the fingers of both hands.

There is some thickening of the periarticular tissues of both ankles, and the patient has pain and discomfort in them when she walks.

There is tenderness on pressure over the metatarso-phalangeal joints of both feet, though this is most marked on the left foot.

Treatment:- The first injection of 100 million detoxicated typhoid organisms resulted in very slight reaction, and, following it, there was no alteration in the joint condition. This was the same batch of vaccine which had failed in its action in case XIX. Accordingly, a new vaccine was used, and she was given three injections of this in doses of 200, 250, and 300 million respectively. Following each injection there was no rigor, but a feeling of coldness, headache, and rise in temperature, the highest recorded being 100°F. After /

After the first injection, the patient felt pain in the right shoulder which became tender. This was due to ~~the~~ lighting up of a fibrous nodule which had not been troubling her, and the joint was not affected.

At the time she was receiving injections, she was treated with massage, active and passive movements, and she was discharged on 8th June, 1922, in the following condition:- "General health much improved. The ankle and toe joints are now normal except for slight thickening of the synovial membrane on the anterior aspect of the right ankle. Both wrists are now freely moveable, but there is still definite thickening of the synovial membrane, and there is still some tenderness on pressure over these thickenings, but very much less than on admission. The general result is, however, not satisfactory."

After History:- She remained fairly well for two months, but in August, 1922, her ankles and wrists again became painful and swollen. The infective agent had only been inhibited in this case.

Case XXI. M.F. Female. Age 19. Admitted 14th April, 1922.

History:- She states that in 1919 she was in Paisley Infirmary for a period of 7 weeks, suffering from rheumatic fever. She was quite well when she left that institution, but, a week afterwards, the right knee became swollen and painful. This continued for some months, but apparently was /

was not severe enough to prevent her from carrying on at her employment as a starch-worker. In time it passed off completely, and she states that she was quite well until March, 1921, when both knees became painful and the right knee again swelled up. She continued at work and, for a time, there was considerable variation in the pain and swelling of the knee. Finally it ceased to trouble her, and she states that she was quite well until March, 1922, when the right knee again became swollen and painful. Two days after this, the left knee became painful. Next day the right shoulder and right wrist were affected, and she was compelled to go to bed. She received treatment without improvement.

Condition on Admission:- There is no apparent affection of the interior of the right shoulder-joint, but the tissues around and external to the joint are painful and very tender. As a result, the arm can only be raised with difficulty to the level of the shoulder.

There is some swelling of the synovial membranes of both wrists, which are tender on pressure.

The left knee is slightly swollen, owing to the presence of a small effusion. There is very slight thickening of the synovial membrane.

The right knee is very much swollen and tender. The skin over the joint is slightly red. There is considerable swelling/

swelling of the synovial membrane, and there is effusion present in the joint.

There is marked generalised panniculitis, the worst parts being the shoulders, inside of thighs, and legs.

There is a blowing murmur, systolic in rhythm, in the mitral area, conducted into the axilla, and the second sound of the heart is reduplicated. Temperature 99°.2 F.

Treatment:- Two injections in doses of 100 and 200 million organisms were given, but there was no reaction and no improvement in the patient's condition. This was the same vaccine which had failed to act in cases XIX and XX. 200 million organisms of the new vaccine were given, causing headache and increase of pain in the joints, with a rigor but no nausea. The temperature rose to 102°.5 F. The next day the temperature was normal, and two days afterwards the swelling had gone from both knees, and there was no pain in any of the joints. No further injections were given. The panniculitis was treated with massage, and she left hospital on May 13, well.

After History:- March, 1924. Since discharge from hospital, this patient has been fit and well, and has had no recurrence of the disease.

Remarks:- The last three cases show clearly that it is necessary to produce a reaction on the part of the patient, if beneficial results are to be obtained. This particular case /

case is unique in the series, in that one injection was apparently quite sufficient to effect a cure.

Case XLVI. P.R. Male. Age 22. Admitted 26th July, 1922.

History:- Illness commenced in April, 1922, with stiffness and swelling of the wrists and finger-joints. This condition spread slowly to other joints, the ankles, toe joints, both knees, and elbows, becoming affected in turn, and the swelling was associated with a good deal of pain.

Previous History:- The patient states that in 1919 he suffered from "rheumatic fever" and was in bed for 3 months. After this, he remained well for a year, but then began to suffer from occasional attacks of pain in the joints now affected. This did not prevent him from working until April, 1922, when the present illness began.

Condition on Admission:- The interphalangeal and metacarpophalangeal joints of both hands are swollen and stiff, and movement is limited. There is wasting of the intrinsic muscles of the hands and the grip is much weakened. There is some thickening of the capsule of the right wrist-joint which is tender on pressure, and there is slight limitation of movement. The elbows and shoulders are not affected.

Both knees show some thickening of the synovial membrane. There is limitation of flexion of the right knee, and, when attempts are made to increase the range of /

of movement, there is a good deal of pain.

There is thickening of the synovial membrane of the ankle joints, but there is no pain or tenderness in them, and movement is free.

There is pain on pressure over the ball of each great toe, and the capsule of the metatarsophalangeal joints is thickened.

There is a presystolic murmur present in the mitral area.

Treatment:- Two injections of detoxicated vaccine in doses of 200 million organisms were given. After each injection there was the usual train of symptoms. The joint condition showed rapid improvement, and he was discharged from hospital on August 18, very much better than on admission.

After History:- He remained fairly well, and was able to resume his employment, until November, 1922, when his ankles and knees again became swollen.

Remarks:- This case illustrates the necessity of giving several more injections in those cases where very marked improvement follows the first or second injection, and where the physician is therefore tempted to discontinue treatment.

While treating the above cases with detoxicated typhoid vaccine, it became quite clear that, unless there was a definite reaction on the part of the patient, there was no beneficial result. Some of the patients showed marked improvement, but, in these cases, the injection of detoxicated vaccine had been followed by a train of symptoms similar to those seen when the ordinary vaccine was used. There was certainly less headache and nausea, but the difference was not great. Furthermore, the use of this form of vaccine was unsatisfactory in that, in some cases, it was uncertain in its effect. In cases 27, 28, 29, and 30, I was forced to use ordinary vaccine because no reaction followed the injection of detoxicated vaccine. I therefore decided to abandon its use, and to treat the remainder of the series of cases with ordinary vaccine. Clinical records of these 40 cases will be found in the Appendix. (Series 3).

Discussion.

It is in general comparatively easy to make accurate observations, but, even in the most accurate of sciences, to assess the value of observations made, and still more to draw accurate conclusions from them, are tasks of considerable difficulty. The history of therapeutics shows quite clearly that this difficulty is enormously increased in dealing with the results following any remedial measure, for the factors requiring consideration are so numerous, so varied /

varied, and so difficult to control, that it is impossible to draw conclusions with precision. The result has been that methods of treatment which, in the past, have had strong adherents among even the most able physicians of the times, are to-day regarded merely as curiosities, and it is more than probable that, in the future, the same view will be taken concerning many forms of therapy in common use at the present time. In spite of this difficulty, I am of the view that sufficient evidence has been produced in the 70 cases reported to warrant the statement that non-specific protein therapy is to be regarded as a valuable addition to our therapeutical armamentarium in dealing with rheumatoid arthritis. In some cases, the infective process was checked with extraordinary rapidity. In others, though several reactions were required before the infection became quiescent, the diminution of pain and tenderness of the affected joints, which followed each reaction, permitted more vigorous and therefore more effective massage, active, and passive movements. This, even in cases where there was marked periarticular thickening, had the effect of increasing the range of movements of the joints, and thus diminishing more rapidly the disability of the patient. Of the 70 cases, only twelve were not improved in any way by the treatment received in hospital. Among these ^{were} 12/cases in which no reaction took/

took place, either because of inability on the part of the patient to react, or because of the nature of the vaccine used. The others were cases in which very marked changes had taken place in the joints, the infection had died out, and the patients were really suffering from the permanent sequelae of the disease. Previous experience showed clearly that the means at the disposal of the physician in dealing with the infective agent of this disease were very limited, and that no other method of treatment has been productive of such good results. It seems clear, therefore, that, in the non-specific protein reaction, there has been placed in the hands of the therapist a weapon which he may justifiably use with greater probability of success.

The next point to be discussed is the type or types of cases in which most benefit is to be expected from this therapeutical measure. An analysis of the cases shows clearly that the maximum benefit was obtained in those in which the patient came under treatment at a stage in the disease before marked changes had taken place in the joint structures. This stage might be early or late in the history of the case, depending on the rate of progress of the infective process. In the cases where the disease started in more acute fashion with some constitutional disturbance and a fairly rapid involvement of many joints, complete cure with no relapses was obtained. In the cases/

cases in which the disease commenced insidiously, affecting only a few joints of the fingers and toes and gradually spreading over a prolonged period to other joints, the patient generally retained some disability in the thickening of the tissues round the joint, and consequent stiffness, even though the infection was completely subdued. In some of these cases too, relapse took place. It is possible that these two types represent diseases which are aetiologically distinct, and that the infective agent is more easily destroyed in the first type. In my view, the true explanation is that those cases, in which the disease commences more acutely, come under treatment in hospital at an early stage. On the other hand, in the cases where the joints gradually swell, with little or no constitutional disturbance, the patient, particularly of the female sex, is able, in the beginning, to perform her ordinary duties in a more or less efficient fashion. But the inevitable tendency is for the joints to become slowly and progressively stiffer and less useful, and it is only at a late stage that hospital treatment is sought. At this time, the new-formed connective tissue round the joints has become less vascular and more fibrous, and it is then that the infective agent appears to be more resistant. Even though the infective process be checked, the thickening of the joints remains, and /

and vigorous massage and movements must be kept up for many months, in order to dissipate the pathological fibrous tissue. It has to be remembered further that, once these fibrous thickenings have become established, the symptoms of aching, pain, and stiffness, are liable to arise from a multiplicity of causes in no way connected with the original cause of the disease. To sum up, it can be said that the efficacy of the non-specific reaction in the treatment of rheumatoid arthritis is in inverse ratio to the extent of the pathological changes which have taken place in the joints when the patient comes under treatment.

The next question of importance is whether the improvement shown is permanent or merely temporary. Three years is perhaps too short a period in which to formulate general conclusions on this point. Of the 58 cases in which improvement was obtained under treatment, at least 40 had, for varying periods up to three years, been able to perform all their ordinary duties, and there had been no exacerbation of the joint condition nor spread of the disease to other joints. In 16 of the cases, relapse was known to have taken place. All the cases in which relapse took place had reached a fairly advanced stage before they came under treatment. Furthermore, of the 16, 5 had been treated with detoxicated vaccine where /

where the reaction had not been great, and a few had shown so much improvement after one, two, or three injections, that no further treatment had been given. This is a point of considerable practical importance, for it raises the question as to what should be the duration of treatment. The protein shock reaction is, as has been indicated, not a pleasant one for the patient, and there is a tendency on the part of the physician to minimise the discomfort by giving as few injections as possible. Yet there is some evidence to show that the infective agent may only be inhibited, and that it would be good practice to give one or two more injections, even after the activity of the process has apparently ceased. Even though that is done, there is, in some cases at anyrate, the possibility of exacerbation of the disease months after all infection has apparently disappeared.

There now remains to be discussed the mechanism by which the non-specific reaction affects the disease process. The student, reared in the atmosphere of strict specificity as applied to the problems of immunity, is apt to consider the defensive agents of the body solely in terms of specific antibodies,—the precipitins, lysins, agglutinins, and others. He will admit that these antibodies are intangible, but he can produce ample evidence of the existence of certain properties of serum which are represented /

represented by these terms, and he can show that these properties aid the body in its struggle with disease. But this conception of strict specificity fails when it is applied to the problem of natural immunity or insusceptibility to infection, for it can be shown that many animals are immune to certain diseases, and yet their blood contains no demonstrable specific antibodies. Nor is it any more satisfying in the explanation which it offers of the phenomenon of recovery from infection. It is no doubt an alluring theory that, as soon as an individual is infected with the causative agent of a disease, his body cells begin to react and produce antibodies which gradually increase in amount until finally they overwhelm the infecting organisms, and thus lead to recovery. But it is known that the agglutinin titre of the serum of a patient suffering from enteric fever is no guide to the possibility of recovery, and indeed Howell⁽¹⁷⁾ has shown that patients who suffer from leukaemia do not produce antibodies to typhoid infection, and yet they recover from the latter disease. Furthermore, it offers no satisfactory reason why certain patients should recover so rapidly from diseases, long before specific antibodies have developed in the blood in sufficient quantity to be a dominating factor in the recovery. It will be clear that the conception of specific methods of defense against infection is not the /

the whole truth.

The elaboration of specific antibodies is, in general, a slow process. Time is required for their production, as is readily seen in typhoid fever, where the Widal test does not become positive until the end of the first week of the disease. Has the body therefore no means at its command for dealing with infection in its early stage? Locally, we know that it has, in that series of reactions which are grouped under the general term "inflammation". Whether the inflammation be acute or chronic, it is easy to see in the process the attempts on the part of the body to neutralise the effect of the harmful agent by increasing local metabolism, by diluting the toxin, by digesting the causative organisms either within the phagocytes or outside the cells, or, if these efforts fail, by surrounding the irritant with a wall of fibrous tissue so that it is shut off from the rest of the body. If, however, the infecting agent or its toxin escapes into the general circulation, the body reacts in other and more general ways. There may or may not be a rigor, but the temperature in general rises above normal. There is often a decided increase in the number of white cells in the blood stream, the metabolism of the whole body is increased, the tissue enzymes become mobilised. Are these/

these manifestations to be regarded as purely incidental to the infection, and therefore of no special significance, or do they constitute an integral part of the body's mechanism of defence?

The answer to this question is beset with great difficulty. The work of Metchnikoff has demonstrated conclusively that the process of phagocytosis is of advantage to the body in its fight with disease, and it may therefore be inferred that the increase in the number of the white cells of the blood, which occurs in disease, is, in some way, one of the natural methods of defence against organismal invasion. So it is with the increase in the enzymes of the body, which has been observed by Jobling and Peterson.⁽¹⁸⁾ But whether elevation of temperature alone is harmful to fever-producing organisms or their toxins is a subject open to debate. The physiologist is inclined to look on fever as the result of an accidental derangement of the mechanism by which the temperature of warm-blooded animals is regulated. He regards it as a profitless and harmful process, a part of the price we have to pay for a complicated mechanism. This view does not recommend itself to the physician who has observed that, in many acute infections, a slight, instead of a marked rise /

rise of temperature, is of grave prognostic significance. He is disposed to see something more than accident in a reaction which so frequently accompanies the invasion of the body by pathogenic organisms. Clinical observation can hardly settle the point at issue, but certain facts are worth considering. It has been observed that an intercurrent acute infection, associated with high temperature, sometimes has the effect of clearing up a more chronic associated disease. Furthermore, cases of pyogenic infection of the genito-urinary tract sometimes disappear very quickly when the patient develops a rigor and a marked elevation of temperature. Again, the opinion is generally held that the use of antipyretics, - antipyrin, acetanilide and phenacetin - ~~does~~ not improve the condition of the fevered patient. On the contrary, it does more harm than good to treat pyrexia in this way. It is beside the point to argue that a high temperature may of itself endanger the life of the patient. Any defensive mechanism, such as cough, may, if over-stimulated, be a source of danger to the person it is intended to defend.

On the experimental side, there is a certain amount of evidence which favours the view that fever is a protective agent. Pasteur⁽¹⁹⁾ observed that fowls, which are /

are not susceptible to anthrax bacilli, succumb if their temperature be lowered artificially. Loewy and Richter⁽²⁰⁾ produced elevation of temperature by puncturing the corpora striata of rabbits, and then infected them with the bacilli of diphtheria, fowl cholera, swine erysipelas, and pneumonia. They found that, if animals, whose temperature was raised in this way, received a dose two or three times as large as that necessary to kill an ordinary animal, they recovered. They found further that, when a local injection of swine erysipelas was made into a rabbit's ear, the local reaction was most marked in those animals in whom the corpus striatum had been punctured, but they invariably got well. Similar observations have been made by Ludke⁽²¹⁾ and others. It is admitted that these do not furnish a complete proof that fever is essentially a protective mechanism, but they suggest that it is.

In this way, we begin to see something of the mechanism of the non-specific reaction. What is this reaction other than a method of producing artificially the phenomena already described as occurring naturally in disease, and producing them in a controlled fashion? Furthermore, the observations made in Case 16 suggest that the reaction mobilises even specific antibodies which/

which are apparently fixed in the tissues and not free in the blood-stream. In rheumatoid arthritis, as has been already mentioned, the body does not, as a rule, react to any great extent against the causative organism, and so a warfare of low activity is carried on. When, however, a foreign protein is injected intravenously, the body reacts vigorously, and it is reasonable to suppose that in certain cases this will result in the inhibition, or even destruction, of the microbes of the disease.

At the same time the local reaction may be of some value. It has been shown that, during the general reaction, the affected joints in **many** cases became more painful and tender and appeared more swollen. There was **apparently** a stimulation of the low-grade inflammatory process, or, in other words, an increased reaction on the part of the body locally against the disease. That this was of benefit was indicated by the fact that, in many cases, after the aggravation of symptoms passed off, the joints became less swollen, tender, and painful, and more supple.

If this conception of the mechanism of non-specific protein therapy in bringing about amelioration of symptoms and cure of rheumatoid arthritis is correct /

correct, it will be clear that it has certain limitations. If it is to be of advantage in the treatment of disease, there must be power of reaction on the part of the body. There is ample evidence of the existence of this limitation in the cases reported. Case VI. appeared to have reached the stage at which his defensive powers were completely exhausted. Even very large doses of typhoid vaccine failed to produce the slightest reaction, and there was absolutely no change in his condition. Furthermore, the use of detoxicated vaccine showed conclusively that, if the nature of the injection was such as to produce little or no reaction on the part of the patient, no improvement followed. Yet the same patients showed marked improvement, if a protein was used which caused definite reaction. It seems reasonable to infer from these observations that this therapeutical measure should be used early in the disease, when the body is not exhausted and is capable of reacting to the fullest extent, if it is hoped to get the maximum benefit.

It would be foolish to expect that a general biological reaction of this nature could cure every case of rheumatoid arthritis. Even though the whole defensive mechanism of the body is stimulated to the full, there is always the possibility that the infective agent//

agent of the disease may resist the attack, or may be inhibited only for a short period. That, at any rate, has been my experience in the practical use of this form of therapy. In a number of cases, the results have been brilliant. In many, there has been improvement so marked that the individuals have been able to carry on their ordinary duties of life in an efficient manner, although they are crippled to some extent by the fibrous changes which have taken place in their joints. In other cases, the improvement has only been of a temporary nature, and the disease, after periods of quiescence up to ~~nine~~ months, has broken out afresh. A few have not been benefitted in the slightest.

I am aware that it is the duty of an investigator, in laying down any new plan of treatment, especially if that be applicable to diseases which have hitherto been considered either very obstinate or incurable in their nature, not to say more in its favour than the facts brought to light during its investigation warrant; for experience teaches us that many remedies, the prudent use of which might have rendered essential service to medical science, have suffered, often irremediably, in consequence of rash and inconsiderate praises heaped upon them. Nevertheless I am convinced that, until we can treat rheumatoid arthritis /

arthritis in the ideal fashion by means of a specific drug, the best known method of treatment is that set forth in this thesis.

Summary of Conclusions.

(1) Any attempt to elucidate the aetiology of rheumatoid arthritis by the ordinary methods of bacteriological examination and experiment is not likely to meet with success.

(2) In the majority of cases of rheumatoid arthritis, no septic focus of infection can be discovered.

(3) In all cases, strenuous orthopaedic measures, especially massage and re-education, should be adopted from the beginning, to increase the mobility of the affected joints. These measures should be continued after the infective process has ceased.

(4) To rid the body of infection, the best known method of treatment is by means of the non-specific protein reaction.

(5) This mode of therapy acts best in early cases, but is effective even in advanced cases where there is activity of the infective agent.

(6) Sufficient vaccine should be injected to produce a reaction on the part of the patient.

(7) At least five injections should be given, even/

even though the infection is apparently checked after the first or second injection.

(8) Although the reaction is uncomfortable for the patient, it is not associated with danger.

(9) The mechanism of the reaction is probably the general stimulation of the whole defensive forces of the body.

(10) It does not produce amelioration or cure in every case.

A P P E N D I X.

SERIES I.

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Case II. H.T. Male. Age 28. Admitted 1st Feb., 1921.

History:- On January 27, 1921, he began to suffer from pain in both thighs and behind both knees. Next morning, he was unable to get out of bed, because of severe pain all over the body. The pain was at first general, but finally settled in the elbows, knees, and ankles. These joints became swollen and tender so that he was hardly able to move.

Previous History:- He states he has always enjoyed perfect health.

Condition on Admission:- Both elbows, wrists, knees, and ankles are swollen, and the skin over these joints is slightly reddened. Pain is severe on movement or handling of the joints. The temperature is 100°F. He is sweating profusely. The perspiration is acid in reaction and has a rank sourish smell. The heart is normal and the other systems of the body appear unaffected. No focus of infection can be discovered.

Treatment:- The picture presented by this case was that of acute rheumatism, and accordingly salicylic treatment was immediately instituted, 20 grains of sodium salicylate being administered every four hours. The condition did not respond to this treatment, and after 10 days the temperature was still elevated, and the joints were still swollen and painful. There was an effusion into the right knee-joint. Synovial fluid drawn from this joint was found to be sterile. A blood culture made at this time showed no growth after 9 days.

The dose of sodium salicylate was increased to 30 grains every four hours, and in 24 hours the temperature fell to normal. During the next few days there was considerable improvement in the joint condition, and for 10 days all went well. When the amount of salicylate was reduced, the temperature became irregular and rose to 101° 2 F., while the affected joints became again swollen and painful. Increase in the dosage of salicylate was followed by improvement, but 14 days afterwards, when the dose was reduced to grains 15 thrice daily, there was a recrudescence of the original symptoms.

It was obvious that, in this case, the infective agent could not be destroyed by salicylic treatment, and accordingly it was decided to try the effect of protein shock therapy. The/

The administration of salicylates was stopped, and 100 million typhoid organisms were injected intravenously. The patient had a very marked reaction, the temperature rising to 104° 5 F. and returning to normal in 24 hours. During that time he complained of increased pain in the affected joints, but at the end of 48 hours this had passed off, the swelling had disappeared, and he complained only of stiffness.

During the next three days he felt some pain in his joints, but his temperature remained normal. 150 million typhoid organisms were then injected. Again there was a marked reaction, the temperature rising to 104° 2 F. Two days afterwards, the pain had gone from all his joints, which were now freely moveable.

Five more injections were given intravenously in doses of 150, 200, and 250 (on three occasions) million typhoid organisms. Consequent on the injection of the last two doses, the reaction was slight compared with that of the previous occasions. After the fourth injection, the patient could be fairly described as "well."

After History:- This patient was able to resume his employment a few weeks after his discharge from hospital, and when seen in November, 1923, 2½ years after treatment, his joints were normal.

Remarks:- Though this case cannot strictly be regarded as belonging to the group of chronic non-suppurative arthritis, it illustrates a point of great interest. The infective agent could not be quelled by salicylic treatment, but it disappeared completely after the intravenous injection of a foreign protein.

Case IV. J.C. Girl. Age 14. Admitted 8th Feb., 1921.

History:- Illness began in June, 1920, when she felt pain in her ankles on walking. A few days afterwards, her wrists, ankles, shoulders, and back, became so painful that she was forced to go to bed. After 14 days the pain became less, and she was able to walk about, though with difficulty. Since that time she has been crippled with pain and swelling of the toes, ankles, wrists, and fingers.

Previous Health:- She has always had good health.

Condition on Admission:- Her general health is good. The teeth, nasopharynx and digestive system are in excellent condition. No focus of infection is discovered. Heart and/

and lungs are normal.

There is some thickening of the synovial membrane and periarticular tissues of both wrists, which are very tender on pressure. Movement of these joints is limited by pain.

The interphalangeal joints of both hands are not affected, but there is thickening of the metacarpophalangeal joints, especially those of the little fingers.

Both ankle joints are stiff and painful, with some thickening of the synovial membrane. There is a doughy feeling over the metatarsophalangeal joints of both feet, and pressure over these joints causes considerable pain.

Treatment:- During the first 7 weeks of her stay in hospital, she was treated with intramuscular injections of Intramine (in doses up to 4.5 c.c.) and Collosol Iodine (1 fl.drachm thrice daily) by the month. There was no apparent alteration in the condition of the hands and feet.

She was then given 100 million typhoid organisms intravenously, which was followed by a smart reaction and transient increase of pain and stiffness in the affected joints. Four more injections were given in doses of 150, 150, 200, and 250 million organisms, respectively. After each injection, there was increased pain in her joints for 24 hours, and this was followed by some improvement in her condition. A further injection of 250 million organisms was given, and on this occasion there was a very marked reaction, the temperature rising to 104° 6 F., and returning to normal in 24 hours. The next day she developed a follicular tonsillitis and the temperature rose again to 103° 2 F. but fell to normal in 36 hours.

After this, her joints improved quickly and a week later, when she was discharged from hospital, the following note was made "Movements of fingers are complete in range and are not associated with pain, though the metacarpophalangeal joint of the left little finger is still slightly swollen. The movements of the wrists and ankles are still associated with some pain, though of full range. There is still considerable tenderness on pressure over all the metatarsophalangeal joints of both feet. She requires massage but she is anxious to leave hospital."

After History:- Patient seen in March, 1923. "Since discharge from hospital she has remained fairly well.
No/

No other joints have become affected. There is still thickening of the wrists and ankles and, from time to time, patient feels them stiff and painful.

1st March, 1924. Since last note, there has been a relapse. The right elbow-joint is now swollen and tender. Her wrists and ankles are the same as they were a year ago.

Remarks:- In this case the activity of the infective process was checked for a period of 18 months, when it broke out again.

Case VIII. T.N. Male. Age 33. Admitted 25th April, 1921.

History:- Illness began in 1915 with pain, stiffness, and swelling of all the joints of the toes. The condition spread to the ankles. He was treated at various times with drugs, alkaline baths, diet, etc., and occasionally there was some improvement. But the disease process gradually advanced; first the right hip-joint was affected, then the right knee, right wrist, left elbow, and small joints of the fingers in turn. Movement of these joints became affected and finally he could move them only with the greatest difficulty.

Previous Health:- In 1909 he suffered from acute nephritis, but he states he recovered completely from this disease.

Condition on Admission:- He lies comfortably in bed and appears well nourished. Examination of his urine shows that it contains albumen and a trace of blood; microscopically there are granular casts present. This indicates that he did not recover completely from the attack of acute nephritis in 1909, and that his kidneys are diseased. His blood pressure is 160 m.m. of mercury, and there is some hypertrophy of the left ventricle of the heart. The temperature is 98° 2 F. and pulse 70 per minute.

The toe-joints are not now affected and movements thereof are quite free and not associated with pain.

The right knee is markedly swollen, due to thickening of the synovial membrane and to the presence of an effusion. No organisms can be found in film or on culture in the fluid obtained from this joint.

All the metacarpo-phalangeal and proximal inter-phalangeal joints of the fingers of both hands show synovial thickening, and there is limitation of movement.

Both/

Both wrists are swollen, stiff, and painful, due to thickening of the periarticular tissues.

The left elbow is fixed in a position of partial flexion. No bony outgrowths can be felt in this joint, but there is thickening of the capsule of the joint. X-Ray examination shows that changes have taken place in the cartilages and bones of this joint. For the bones show some degree of thinning and the joint cavity is obscured.

Treatment:- This patient received 8 injections in doses rising from 100 to 250 million typhoid organisms. After each injection, there was a definite rigor and the usual train of symptoms. The temperature always returned to normal in 24 hours. The blood and albumen in the urine always increased the day following the injection, but rapidly returned to what might be described as the "normal" amount. Steady improvement was shown in his joint condition, and in July, 1921, he expressed a desire to leave hospital. His condition on discharge was "Trace of blood and albumen in urine. The finger-joints are now normal. There is still some thickening of the periarticular tissues of both wrists, but there is now no pain or tenderness, and movement is practically normal. There is no pain in the left elbow, and it can now be moved through an angle of 45°. The right knee is free from pain, and range of movement is practically normal, but there is still considerable thickening of the synovial membrane and a little fluid is present in the joint."

Although there had been very marked improvement in this case, it was felt that he had not been cured, for the presence of even a little fluid in the right knee-joint was disturbing. He was eager to get out to try to work, and indeed for the next six weeks he was able to do so without much inconvenience. In September, 1921, however, the right knee-joint became more swollen and he was re-admitted to hospital. The urine showed the presence of blood and albumen; there was marked swelling of the right knee, and he had fleeting pains in his other affected joints, though they retained their mobility and did not become swollen as they had been on his previous admission.

Four further injections were given and the knee-joint was tapped of its fluid, but no improvement took place in it. Repeated tapping of the joint always resulted in the joint filling up again. Meantime, there was marked increase/

increase in the thickening of the synovial membrane.

The conclusion was reached that, in this case, the focus of infection was the knee-joint itself, and accordingly Mr Taylor was asked to remove the thickened synovial membrane.

The synovial membrane was found at operation to be enormously thickened and oedematous. It was removed and examined microscopically. It showed the usual appearances of chronic inflammatory changes.

Attempts were made to grow organisms from scrapings of the membrane, but with negative result. It was found further, that the cartilages of the joint were ulcerated, but the process did not extend into the bone. These ulcerated patches were scraped. The wound was closed and the leg put up in a ~~Wiston~~ splint.

Consequent on the operation, the patient showed marked improvement. He ceased to have pain in the other joints of the body, and his general condition improved, though he still had some albumen and a trace of blood in his urine. Unfortunately, however, he developed a pressure sore on the leg from the splint. This became septic and he died of acute septicaemia.

Remarks:- In this case there seems no doubt that the chief focus of infection was in the right knee joint. The effect of the non-specific protein reaction was to quell the infection in all joints except the right knee, but here it appeared to be very resistant to treatment.

Case VIII. M.L. Female. Age 36. Admitted May 4, 1921.

History:- Illness commenced three years ago with swelling and stiffness of the joints of the hands and feet, and with pain on movement. In a few weeks the ankles became swollen and painful. At the end of a year, the condition spread to the left knee; then the right knee, right elbow, and left elbow became in turn affected, and finally both shoulders. She states that she experienced a sense of chilliness and general malaise as each new joint was affected.

Previous History:- She had typhoid fever when 17 years of age, a nervous breakdown at the death of her husband when /

when she was 26, and neuritis of the lumbar region when she was 31 years of age.

Condition on Admission:- The muscles of the arms and legs are atrophied and flabby. Apart from that, the patient is well nourished and well developed.

The proximal inter-phalangeal joints and the metacarpophalangeal joints of all the fingers are swollen, doughy, and tender to the touch, and painful on movement. The hands can be closed completely but the grip is very weak. The fingers cannot be completely extended and the hand thus remains in a state of semi-flexion.

The synovial membrane of both wrists is considerably thickened; there is fibrous tissue creaking on movement, and the fingers of the right hand show ulnar deviation. All movements of the wrists are limited, extension being possible only through an angle of 35° , and flexion through an angle of 45° .

There is thickening of both elbow joints, and contracture of the biceps muscle on both sides. The right forearm cannot be extended beyond an angle of 100° with the upper arm, and the left, beyond an angle of 90° . Supination and pronation are only half the normal range.

There is fibrous ankylosis of both shoulders, so that the arms can be abducted only to an angle of 60° with the body.

There is thickening of the periarticular tissues of the ankle joints, and extension and flexion are only about half normal.

The left knee is fixed at an angle of 90° , while the right is flexed at an angle of 130° but can be almost fully extended passively. There is considerable thickening of the synovial membrane of both joints which are tender and painful.

There is partial ankylosis of the temporo-mandibular joints so that, with the mouth open to its utmost, the upper and lower teeth are only about 1 inch apart.

No foci of infection can be discovered, and the heart, lungs, and genito-urinary systems are normal.

Treatment:- Two injections of 100 million typhoid organisms were given, and each time the patient reacted briskly, had increased pain in the joints followed by

a/

a period when the joints felt easier.

A few days after the second injection, she developed a dry pleurisy at the base of the left lung, and it was thought better to discontinue intravenous injections.

She had then four injections of normal horse serum subcutaneously in doses of 5, 10, 10, and 10 c.c. and 24 hours after each injection she complained of her joints being more painful and stiff. This was followed by a period when there was less pain.

There was no permanent improvement, and she left the hospital in much the same condition as she entered, though she said she felt less pain.

Remarks:- There is very little likelihood that any improvement would have resulted even if she had received more injections of a foreign protein. It will be clear that permanent changes had taken place in many of the joints, and that the case was hopeless from the beginning.

Case IX. M.M. Female. Aet. 42. Admitted 23rd May, 1921.

History:- On 15th May, 1921, she complained of severe headache and a general feeling of malaise. On May 17, she had an attack of vomiting, which recurred at irregular intervals for the next three days. On May 19, both knee joints became swollen and intensely painful, and her temperature rose. She was ~~then~~ treated by her doctor for the next four days with salicylates in large doses, but there was no improvement, and she was then admitted to the Western Infirmary.

Previous History:- For a number of years she had suffered from obscure gastric trouble, vomiting with occasional haematemesis being the salient symptom. That the condition was obscure is shown by the following series of operations which had been performed on her from time to time:- (1) Laparotomy for alleged gastric ulcer in 1914 (2) Nephropexy in 1915 (3) Gastro-enterostomy and removal of appendix in 1915 (4) A second Laparotomy because of haematemesis in 1919 and (5) Colectomy in 1920. It is difficult to conceive any pathological condition which would give rise to the necessity for such a formidable list of operations, and one is justified in concluding that the real cause was that she was intensely neurotic, was absolutely intolerant of pain and discomfort, and/

and consequently exaggerated her symptoms.

Condition on Admission:- Her position in bed shows evidence of extreme discomfort. The body is twisted, the head lying over the side of the bed, and the legs being constantly changed in position to give her ease. Her expression is anxious and indicative of severe pain. She is very excited and nervous, is constantly calling out to be relieved of her agony, and in general exhibits marked intolerance to pain. Her temperature is 99° .8 F.

The only joints affected are the knee-joints which are swollen, tender to touch, and very painful. There is fluid present in both knees, and the synovial membrane is also swollen. Outside the joint there are several very tender areas over the head of each tibia, due to the presence of localised periostitis. There is already marked atrophy of muscles on the inner aspect of the thighs.

Progress:- Fluid was drawn from both knee-joints and was found to be semi-purulent. There were great numbers of leucocytes present, but no organisms were found in film or on culture. There was present a slight whitish discharge from the vagina, but on examination of smears from the cervix uteri and the urethra, no gonococci were found. Blood culture revealed no growth after 5 days at 37°C. and the Wassermann reaction was negative.

Treatment:- During the first six days in hospital, measures were taken to quieten her and to give relief from pain by the exhibition of bromides and analgesics. During this time, the temperature varied between 100° F. and 102° .4 F. 100 million typhoid organisms were then injected intravenously. This had the effect of increasing the pain in her joints for 24 hours, but the aggravation of symptoms was followed by a period ~~which~~ during which the joints felt much easier. The temperature became regularly intermittent, the highest rise being 103° .2 F. A second injection of 150 million organisms was given and was followed by a similar train of symptoms, but the temperature did not settle and the condition progressed. A third injection of 200 million organisms was given and following this, the temperature rose to 103° .2 F., came down to normal in 24 hours, and for the next week did not rise above 99° .4. After a fourth injection the temperature came down to normal and remained there for the next ten days.

During this time there was a certain amount of improvement of the joint condition. The fluid disappeared from the knees but she still complained bitterly of pain, and/

and ~~and~~ the slightest pressure over the thickened synovial membranes and over the areas of periostitis of the head of each tibia apparently caused exquisite pain. This led to what can only be described as a disaster.

The extraordinary importance of taking early measures to counteract the tendency to muscular contractures and the consequent deformities, was well recognised. But every attempt made to do this was utterly defeated by the patient. When even the lightest splints were applied, she shrieked with pain. She would allow no one to attempt to move her joints, and the inevitable result followed. By the time her temperature was normal and her general condition much improved, both knees were bent to a right angle.

She remained in hospital for the next three months and during that time received two more injections. The temperature occasionally rose a little above normal but, during the last two months of her stay, remained on or below the normal line. She was obviously much improved but would still allow no one to move her affected joints. She said that there was little spontaneous pain in her joints, but when the least pressure was applied over them or over the heads of the tibia she complained of great pain. The muscles of the thigh and calf were markedly atrophied and there was marked contracture of the flexor groups controlling the movement of the joints.

Remarks:- In this case it is exceedingly difficult to assess the effect of non-specific protein therapy. From the fall in the temperature to normal, the disappearance of fluid from the knee-joints, and the general improvement of the patient's condition, it might be held that it was of considerable value. But pain, and especially tenderness, persisted, and the further injections which were given did not influence the latter in any way. It could be argued that the chief effect of the treatment given, was to lessen the activity of the infecting agent, but that it still remained in and around the joints and exhibited its presence by keeping up the pain and tenderness. That is a point which no amount of discussion can settle, but my conviction is that, had the patient been less intolerant to pain and had allowed her knees to be kept straight, moved, and massaged, she would have left hospital comparatively well instead of, as she did, a cripple.

Case /

Case XII. W.R. Male. Age 47. Admitted 4th July, 1921.

History:- In December, 1918, he had an attack of pain in the right wrist which became red and swollen. This lasted for only 3 days when it passed off leaving the joint, he stated, unaffected. In December, 1919, he had an attack of pain and swelling of the proximal interphalangeal joint of the left thumb, which continued for several months but did not inconvenience him very much. In November, 1920, the right wrist became swollen and painful, and the skin over the swollen joint was red. Since then, the wrist affection has prevented him from working. Pain in the affected joints was continuous but not great, and was habitually worse at night. Occasionally there was exacerbation of the symptoms.

Previous History:- He had typhoid fever when a young man but was otherwise healthy. There was no history of venereal disease.

Condition on Admission:- He is thin and not well-developed but looks healthy. He perspires considerably even when at rest.

The inter-phalangeal joint of the left thumb is painful on movement, and there is distinct grating when the two phalanges are rubbed against each other. The joint is unduly mobile from side to side, showing that the ligaments have become stretched. A radiogram shows roughening of the articular surfaces and thinning of the bone.

The right wrist is spindle-shaped because of the thickened synovial membrane. There is a localised fluctuant swelling on the palmar aspect of the wrist between the tendons of the brachio-radialis and flexor carpi radialis muscles. Active movement of the joint is possible both in flexion and extension to an angle of 45° with the forearm. On movement of the joint, fibrous tissue creaking can be elicited. He complains of constant pain in the joint, and there is tenderness on pressure over the thickened synovial membrane.

Heart and lungs are normal. No septic foci can be found.

Treatment:- Three injections of 100, 150, and 250, million typhoid organisms were given. In each case there was considerable temperature reaction. (to 103° F.) Following the first injection, the pain and tenderness in the/

the right wrist were diminished and movement was more free. After the third injection, the pain left the affected thumb joint. There was no pain or tenderness of the wrist. Only a little swelling remained on the anterior aspect of the joint, and movement was very nearly normal. He was discharged on July 28, well.

He reported again on September 22, and stated that he had returned to work but that, when he used a hammer, the jarring of the wrist on striking caused him some pain. This was considered to be due to an adhesion which had formed in the joint and this was broken down by a sharp movement of the wrist.

March 1924. Since date of last note this man has remained well.

Case XIII. M.R. Female. Age 27. Admitted 15th July, 1921.

History:- Illness began when the patient was 10 years old, with pain and swelling in the left ankle. Gradually the other joints became affected, both elbows became ankylosed, and the wrists and ankles were partially fixed. She was admitted to the Western Infirmary in 1917 when it was considered that nothing could be done for her. In 1918, the right elbow joint was excised to give some mobility to her right arm and enable her to feed herself. During the past two years, the condition slowly spread to the knee-joints and she was readmitted for treatment.

Condition on Admission:- She is well developed and well nourished. The right knee is in a position of slight flexion as a result of contracture of the ham-string muscles. There is marked limitation of movement of this joint, and the right hip is partially ankylosed. The left elbow and the left ankle are quite fixed and the tissues round these joints are extremely hard and sclerosed. There is swelling of the 2nd and 3rd metacarpophalangeal joints of the left hand but movement is good. She does not suffer from pain in these joints, which is in striking contrast to her condition when in hospital in 1917.

Treatment:- It was quite obvious that, in this case, the infection had burnt itself out but, in doing so, had left behind permanent sequelae, which only orthopaedic measures could remedy. She received six/

six injections of typhoid vaccine intravenously but, though she reacted well after each injection, there was no alteration in the joint manifestations. By dint of slow extension by splints, there was some improvement in the movements of the knee. It was not thought advisable to have the left elbow-joint excised, and she was discharged from hospital in statu quo.

Case XIV. H.H. Female. Age 23. Admitted July 27, 1921.

History:- Illness commenced in June, 1920, with pain and swelling in the right wrist. The disease soon spread to the joints of the fingers, the left wrist, both knees and ankles. Occasionally there was a slight improvement in the condition, but the pain and swelling always recurred, and gradually the patient became more crippled.

Previous History:- She had "rheumatic fever" when 11 years of age and she states that, resulting from this, the left ankle was always a little stiff and its movement impaired.

Condition on Admission:- Her general health is good. She does not suffer severe or constant pain and feels quite comfortable in bed. Both wrists show thickening of periarticular tissues and increase of synovial membrane. They are tender on pressure and all movement of these joints is limited. A good deal of pain is caused when attempts are made to increase movement. The synovial membrane of the proximal interphalangeal joints of the index fingers and middle fingers of both hands is thickened, so that these joints present a spindle-shaped appearance though there is no limitation of movement. There is some hypertrophy of the synovial membrane of both knees but flexion and extension of these joints are possible without pain or discomfort. Both ankle joints are tender to pressure and there is slight limitation of movement of the left ankle. Heart and lungs are normal. No focus of infection can be discovered.

Treatment:- Six injections were given in doses rising from 100 to 250 million typhoid organisms. After each injection there was considerable reaction, the highest temperature rise recorded being 103°F. The usual increase of /

of pain and stiffness occurred in the affected joints after each injection, followed by a diminution of the symptoms.

Steady improvement was shown. Swelling of the wrist-joints diminished; they became less tender on pressure, and movement became nearly normal. Thickening of the interphalangeal joints remained, but these could be moved without pain. Both knees and ankles became less stiff but, when she was discharged on 17th September, there was still present some thickening of the periarticular tissues of these joints. She could however walk about quite freely.

March 8, 1924. This patient was seen to-day. She has been at work for the past 21 months. There is still thickening of the wrists, knees, and ankles, but these joints are not tender or painful. She can use her hands quite freely, and can walk 5 miles without causing more than a little stiffness of the ankles and knees.

A P P E N D I X.

SERIES II.

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Case XVII. J.P. Male. Age 22. Admitted 30th Jan., 1922.

History:- Illness began in July, 1921, with pain and swelling of the right ankle. The affection spread to the knees, and stiffness in the morning was a marked symptom. He managed to carry on at work because he found that the pain and stiffness diminished with movement during the day, but by the middle of November, the wrists, fingers, and elbows were affected to a considerable extent. He was treated with salicylates but no improvement resulted.

Previous Health:- In 1920 his tonsils, which were hypertrophied, were removed, but since then he has always had the feeling of wanting to cough to get rid of phlegm from the throat.

Condition on Admission:- On account of pain, he cannot lie in one position for any length of time. The knees have to be supported on a pillow. He is thin and anaemic. The skin is moist and there is some fever. The tonsils have not been completely removed at the operation two years ago, and the remains of the tonsils are septic. The pharynx shows dry catarrh, and the nasal sinuses are septic.

There is swelling of the metacarpophalangeal joints and of the proximal interphalangeal joints of the index and middle fingers of both hands. The latter are markedly fusiform because of the synovial thickening. The 2nd interphalangeal joint of the left forefinger is swollen and red. Both wrists are swollen with thickened synovial membrane, very tender to touch, and movement is limited. Both elbows are swollen and thickened. There is considerable atrophy of the muscles of the arms and of the intrinsic muscles of both hands.

Both knees are much swollen and tender. There is effusion into the joints, as well as periarticular thickening. No organisms are found in film or culture from the joint fluid. Movement of these joints is very limited. There is slight thickening, tenderness, and limitation of movement of both ankles.

Treatment:- During the first 12 days of his stay in hospital, he was given potassium iodide grains, 20 thrice daily by the mouth, and carbolic oil dressings were applied to the joints. There was no alteration in his joint condition/

condition and the temperature remained elevated. 100 million detoxicated typhoid organisms were then injected. There was no rigor, no headache, and no increase of pain in the affected joints, with only a slight elevation of temperature. There was no alteration in the joint condition.

The nasal sinuses were washed out and the remains of the tonsils removed, but no alteration in the joints took place. Three more injections of detoxicated vaccine were then given in doses of 100, 200, and 300 million organisms, and after the last two there was some reaction. This was followed by considerable clinical improvement, the fluid disappeared from his knee-joints, and finally he left hospital apparently well.

After History:- He remained well for 6 months after discharge from hospital, when the disease returned.

Remarks:- It is possible that in this case the improvement resulted from the removal of septic foci, for the reaction following the injection of vaccine was in each case slight.

Case XVIII. M.S. Female. Admitted 9th February, 1922.

History:- In 1920 she began to complain of pain in both shoulders. This persisted for a year, and in January, 1921, both wrists became suddenly painful, swollen, and stiff. Three months ago, the feet and ankles were affected in a similar fashion.

Present Condition:- The ~~left~~ shoulder joint is swollen and painful. There is thickening of the synovial membrane and periarticular tissues of both wrists, of all the metacarpophalangeal and interphalangeal joints of the fingers, and of both ankle-joints. All these joints are stiff, and movement causes considerable pain.

Previous Health:- She has always enjoyed good health.

Treatment:- Five injections of detoxicated typhoid vaccine were given in doses from 100 to 200 million organisms. After each injection there was a rigor and the usual malaise, but the highest temperature response recorded was 102°F. There was some, but not marked, improvement. The pain in the affected joints diminished considerably, but the swelling, thickening and stiffness remained. On discharge, her greatest difficulty was in/

in walking, owing to stiffness of the ankles and metatarsophalangeal joints.

After History:- 20th February, 1924. Since discharge from Hospital, there has been no spread of the disease to other joints nor have the affected joints become worse. But the patient is still very stiff and requires massage. She can walk farther than she could before treatment.

Remarks:- The infective process has been stopped. This case illustrates the necessity for carrying on vigorous massage long after the infection has been checked.

Case XXII. M.S. Female. Aet 34. Admitted 29th April, 1922

History:- In February, 1922, the toes, ankles, fingers and wrists became swollen and painful. The lumbar region of the spine was stiff and painful, and mastication caused severe pain in both temporo-mandibular joints. She recovered partially from this attack but at the beginning of April, 1922, there was a recrudescence of the condition.

Condition on Admission:- There is tenderness and thickening of the periarticular tissues of the ankles and of the metatarso-phalangeal joints of both feet. The feet are sweating and the skin over them is glazed.

The finger and wrist joints are similarly affected. The movement of the left shoulder is limited; the arm cannot be abducted to more than a right angle. There is tenderness and rigidity of the lumbar region of the spine. No focus of infection is discovered.

Treatment:- Four injections of detoxicated vaccine were given in doses of 100, 200, 200 and 300 million organisms respectively. Each injection was followed by shivering, headache, nausea, and a rise in temperature. After each injection, the affected joints became less painful and more supple. She was massaged, and passive movements were employed to increase the range of movement of the left shoulder joint. She left hospital well.

After History:- March 1924. This patient has been able to carry on her occupation since discharge from hospital. Her only complaint now is that her ankles become stiff after she has been standing all day.

Case /

Case XXIII. M.McW. Female. Aet 42. Admitted 13th May, 1922.

History:- In December, 1920, she began to feel the toes and ankle of the left foot stiff. Later on, these joints became painful and swollen so that she could hardly walk. Some months afterwards, the fingers and wrists of the left hand became affected in a similar way, the right elbow was attacked, and 2 months before admission the condition began to spread to the right wrist and fingers. At that time, pain and swelling in the left foot and ankle became very much less and she could walk about in greater comfort. The condition of the other affected joints has varied a great deal in intensity from time to time, but has never shown any signs of improvement in spite of treatment with salicylates and vaccines.

Previous Health:- She has always had very good health up to August, 1920, when, she states, she suffered from stone in the bladder. This stone was passed in the urine, and since then she has had no further trouble.

Condition on Admission:- She is well developed and her general health is good. She has very little pain except when attempts are made to move the affected joints, when she exhibits a marked degree of nervousness.

The right elbow is very much swollen and the skin over it is slightly red. The synovial membrane of this joint is very much hypertrophied, and there is thickening of the periarticular tissues and some fluid in the joint. The elbow cannot be extended or flexed except through a very small angle. Supination and pronation are impossible and there is considerable wasting of the muscles of the arm.

Both wrists show thickening of the synovial membrane, are tender on pressure, and have practically no mobility. (due to adhesions).

The metacarpophalangeal and interphalangeal joints of both hands are slightly swollen but there is no pain and very little loss of mobility. The hands sweat very freely.

The feet appear normal, the left foot having become quite well during the past 2 months. The other joints of the body are unaffected.

Circulatory, respiratory, and other systems are normal, and /

and no focus of infection can be discovered.

Treatment:- Before treatment was commenced, an attempt was made to secure greater mobility of the left wrist by breaking down the adhesions which had formed. This was done by sharply bending the wrist when the patient was off her guard. The joint certainly was made mobile, but next day it was so painful and tender that she could not bear to have it touched, and in a week's time it was nearly as stiff as ever.

This illustrates the folly of breaking down adhesions rapidly, either with or without an anaesthetic, in these particular conditions. For, if this be done, there is so much pain in the joint afterwards, that the patient will not allow further movement and the adhesions will form again. It is far better, if there is the slightest suspicion of any active process being present, that the adhesions should be gradually stretched and greater mobility produced in this way.

In this case the patient received five injections of 200 million detoxicated typhoid organisms. Following each injection there was a rigor, the patient had headache, some nausea and occasional sickness. There was always considerable rise in temperature, settling to normal in 24 hours, but the most marked feature was the very definite focal reaction. After each injection there was marked increase of pain and tenderness in all the affected joints.

Consequent on the first injection, the right elbow became less painful and tender, power of flexion and extension increased, and pronation and supination became quite good.

The condition of the joints gradually improved, and on discharge from hospital on July 20, 1922, the following note was made "There is still considerable thickening of the synovial membrane of the right elbow joint, which limits the movements of flexion and extension of the forearm. She can now, however, raise her hand to her mouth and to the back of her head. The joint is now **not** painful and is only slightly tender to touch. The fingers are now normal. The wrists have become more mobile but there is still considerable limitation of movement."

After History:- March 20, 1924. This patient was seen to-day. Since discharge from hospital she has remained well. She can perform all her household duties and do the hardest work without any inconvenience. There is still thickening of the periarticular tissues of the right elbow and of/

of both wrists, but these joints are neither painful nor tender. The infection has been quelled.

Case XXIV. M.M. Female. Age 24. Admitted 5th June, 1922.

History:- Near the end of 1918 the patient suffered from ulceration of the throat and tonsils which apparently became quite well after treatment. In March, 1919, pain developed in her right knee, and, during the summer, the left knee, the wrists, the finger joints, elbows, shoulders and ankles became swollen and painful. This condition continued during two years, the joints being at times fairly well and at other times very painful and swollen. In 1920 the arms became flexed and fixed at a right angle. In November, 1921, walking became difficult because of the pain and swelling in the knees, and since that date she has been confined to bed. The knees gradually became flexed and in March, 1922, she was admitted to Mr Taylor's ward. Extension was applied in an attempt to straighten the legs, she was treated with massage and her tonsils were removed, but without any improvement. She was admitted to Dr Stockman's ward in June.

Previous Health:- She was always enjoyed good health until the beginning of this illness in 1918.

Condition on Admission:- Both elbows are flexed at a right angle because of contracture of the biceps muscles. All the muscles of the arms and hands are markedly atrophied. X-Ray shows atrophy of ~~humerus~~ bone and blurring of joint cavity.

The wrist joints are swollen and fixed, and X-Ray shows fusion of the bones of carpus. Any attempt to move these joints causes much pain.

The proximal interphalangeal joints of the 2nd and 3rd fingers of the right hand are swollen.

There is marked muscular atrophy in the legs and thighs, the quadriceps muscle being almost wasted away.

The synovial membranes of both knees are swollen and doughy to the touch. The ham-string muscles show marked contracture, and the knees are fixed at a right angle and are tender and painful. She is very nervous and excitable and, when any attempt is made to move the knees, she weeps and/

and cries out. X-Ray does not show the bones to be affected. The other systems are not affected.

Treatment:- Four injections of detoxicated vaccine were given in doses of 100, 200, and 300 million organisms. There was very slight reaction in each case. No improvement in the joint condition was observed.

Case XXV. A.W. Female. Aet 48. Admitted June 13, 1922.

History:- The disease began in 1908 with pain in the right shoulder after a "chill." This lasted for a few days and then passed off. Six months afterwards, the wrist, finger, and ankle-joints became swollen and stiff. From that time onwards until 1918, there was gradual and increasing disability resulting from the condition of the joints, though at times she felt fairly well. In 1918 she was treated in the Western Infirmary with massage and received considerable benefit.

For a short time after she left hospital in 1918, she remained fairly well and comfortable, but at intervals after that she had bouts of pain and swelling of the affected joints. She gradually became worse and was re-admitted to the Infirmary for further treatment.

Condition on Admission:- There is swelling of all the proximal interphalangeal joints of the fingers which are fusiform and limited in movement. There is ulnar deviation of the fingers of both hands.

The periarticular tissues of both wrists are thickened and tender to the touch. Movement of these joints is limited. The shoulder joints are apparently unaffected and movements are normal. Around these joints there is considerable thickening of the subcutaneous fibrous tissue which is tender on pressure.

She complains of pain in the region of the knees but this is due to panniculitis on the inner aspect of the joint. The ankles are swollen as a result of thickening of the capsule of the joint. Hallux valgus is present on both sides and all the toes are held in a flexed position. There is a bunion on the great toe of each foot.

Heart and lungs are normal. No septic focus is discovered.

Treatment:- Two injections of detoxicated vaccine were given/

given in doses of 200 million organisms. There was very little reaction, and no improvement in the joint condition. For private reasons she had to leave Hospital.

After History:- March 1924. Since leaving hospital, ~~the infection~~ has spread to other joints and she is now worse than she was in 1922.

Case XXVII. M.C. Female. Age 18. Admitted 1st July, 1922.

History:- In the spring of 1921, both knees and the right elbow became swollen and painful. A few weeks afterwards there was distinct improvement. She remained comparatively well until April, 1922, when there was an exacerbation of symptoms and as a result she could walk only with difficulty.

Condition on Admission :- The patient does not hear well. This is due to impacted cerumen in the external meatus of the left ear and to an indrawn membrane in the right ear. There is no evidence of perforation or cicatrix of this membrane.

There is thickening of the synovial membrane and periarticular tissues of the right elbow, and movement of that joint is limited.

Both knees are swollen, and the right joint contains a small amount of fluid. The fluid is purulent, but no organisms can be discovered in film or on culture.

The right ankle is swollen and painful.

Treatment:- Two injections of 200 million detoxicated typhoid organisms were given, and, following each, there was only a slight reaction. A third injection of 400 million organisms was given, but again there was little reaction, and no improvement was shown in the condition of the joints. It was then decided to give ordinary typhoid vaccine in a dose of 100 million organisms. There then ensued a marked reaction which was followed in a few days by very marked benefit. In fact, 5 days afterwards, she insisted that she was well and left hospital.

After History:- March, 1923. This patient wrote to say that she had remained well since she left the Infirmary.

March, 1924. She wrote saying that in June, 1923, the left /

left knee had become again swollen and painful and that she had been forced to remain in bed for two months.

Case XXVIII. R.C. Male. Age 52. Admitted 26th June, 1922.

History:- Nine weeks before admission, the patient caught a "chill" and began to reel both heels painful. Soon, both knees became swollen and painful, and afterwards both shoulders. After four weeks, there was some improvement which lasted only 14 days. The condition then became worse and both ankles became swollen, stiff, and painful. He was treated with salicylates without benefit.

Condition on Admission:- There is no history of gonorrhœa and no evidence that he ever suffered from this disease. No septic focus can be found.

The right knee is very much swollen, tender, and very painful on the slightest movement. The left knee shows some thickening of the synovial membrane and is tender on pressure. The right ankle is swollen and painful.

Both wrists are stiff but not painful. There is thickening of the periarticular tissues of the left elbow which is tender on pressure, and movement is possible only through an angle of 90°. Both acromioclavicular joints are tender on palpation and the arms cannot be abducted beyond an angle of 90° with the body.

Treatment:- To begin with, detoxicated vaccine in doses of 200 million organisms was used. Four injections were given. The reaction was fair and there was slight improvement. No further injections were given during the next four weeks, and the patient gradually became worse. Then 2 injections of ordinary vaccine in doses of 100 and 200 million organisms were given. In each case there was a marked reaction and this was followed by marked improvement.

After History- March, 1924. The patient writes to say that he has been back at work for the last 14 months. He is in good health and complains only of a little occasional tenderness in his heels.

Case XXIX. C.McI. Female. Age 25. Admitted 19th July, 1922.

History- During the past 6 months her back has gradually become stiff and weak.

Condition/

Condition on Admission:- All movements of the head, - rotation, flexion, and extension, - are very limited. Flexion of the trunk is fairly good, but lateral movements and rotation are very limited. There is marked rigidity of the spine in the lower dorsal and lumbar regions. X-Ray examination does not show bony changes in the vertebral column.

Treatment:- Three injections were given, the first two of detoxicated and the last of ordinary vaccine. There was little reaction after the first two, and considerable reaction after the last injection. Improvement manifested itself only after the last injection. She was given exercises and on August 27, left hospital very much improved.

After History:- March 1924. This patient writes to say that she is in excellent health, has carried out all her duties since she left hospital, and has improved very much. There is still some limitation of the lateral movements of the spine.

Case XXX. H.B. Female. Age 50. Admitted 28th July, 1922.

History:- Sixteen years ago, the joints of the hands and feet became swollen, painful, and gradually deformed. Eighteen months ago, the right ankle swelled up, became very painful, and the patient was forced to stay in bed for about three months. Since then, she has had constant pain and stiffness in the joints of the hands and feet, and in her knees and ankles.

Condition on Admission:- Nearly all the metacarpophalangeal and interphalangeal joints of both hands are swollen and stiff. There is considerable deformity of the hands. The ankles and joints of the feet are affected in similar fashion. There is well marked hallux valgus on each foot. There is present generalised panniculitis.

Treatment:- Two injections of detoxicated typhoid vaccine in doses of 200 million organisms were given. There was no reaction and no alteration in the joint condition. Thereafter she was given three injections of ordinary typhoid vaccine. Each was followed by considerable general reaction with increase of pain in the affected joints. The pain gradually diminished, and after receiving massage/

massage she left hospital practically free from pain, though the deformity remained.

After History:- 11th March, 1924. There is still present deformity of varicous joints but it is much less than before treatment. She can walk with comfort, and use her hands. Her chief complaint is pain in the shoulders, which is due to fibrositis of the fascia of the trapezius muscle on each side. The infective process has been checked.

A P P E N D I X.

SERIES III.

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Case XXXI. M.K. Female. Age 38. Admitted 5th Sept. 1922

History:- The disease process started in 1908 when many joints of the body became swollen and painful. Since that time she had received Hospital treatment on two occasions, in 1908 and again in 1914. Since discharge from Hospital in 1914, she has been able to do her housekeeping, although she has always been a little stiff and lame and cannot raise her arms above her head. In July 1922, she began to have pain in her hands with some swelling of the joints, and acute pain in the right knee.

Condition on Admission:- There is thickening of the wrists and of the metacarpo- and interphalangeal joints of the fingers of both hands. These joints are tender, and the grip is very weak. There is ~~contraction~~ ^{contracture} of the biceps muscle on each side so that the forearms cannot be extended beyond an angle of 135° with the arms. The movements of flexion, pronation, and supination are very limited. There is partial fibrous ankylosis of both shoulders. There is fibrositis present in the trapezius and deltoid regions on both sides.

The right knee is partially flexed, and cannot be fully extended. The patella is scarcely moveable. The left knee can be fully extended but it is swollen and painful on pressure. It cannot be fully flexed. Both ankles are swollen, the left being very stiff and limited in movement.

Treatment:- One injection of detoxicated typhoid vaccine provoked no reaction, and there was no improvement. 8 injections of ordinary vaccine were given in doses rising to 250 million organisms. To begin with, there was considerable reaction, which was followed by some improvement in the pain and stiffness of the joints, but later on the reaction became very slight. She was given massage, and splints were used in an attempt to straighten the legs. She left hospital improved as far as it was possible, in view of the marked alteration which had taken place in the joints.

After history:- This patient remained comparatively well for a year, when the left knee again became painful and prevented her from walking.

Case XXXII. J.D. Female, Age 28.

Admitted Sept. 21st., 1922.

History:- In March 1921, the patient had all her teeth extracted, and shortly afterwards both wrists became swollen, red, stiff, and painful on movement. The knees and shoulders were next affected, and in September 1921 the condition spread to the ankles. She lost her appetite, became thin, and the condition gradually advanced. Hot soda baths, salicylates and various vaccines have been exhibited in the treatment of the condition but they did not yield even temporary improvement.

Previous History:- She has always had good health until the onset of this disease.

Condition on Admission:- The wrist joints are swollen with synovial thickening, and there is a little fluid present in each joint. Movement of these joints is accompanied by pain.

There is swelling of the first and second metacarpophalangeal joints, and the proximal inter-phalangeal joints of the ring finger of each hand. There is some atrophy of the muscles of the fore-arms and hands.

Movements of the shoulders are painful but there is no swelling of the joints.

The ankles are swollen as a result of synovial thickening and are painful and tender to touch. There is some thickening of the capsule of both knee-joints and wasting of the muscles above and below each joint. She has difficulty in walking because of pain.

She has twinges of pain in the right temporo-mandibular joint and in the cervical vertebrae.

All the other systems of the body are healthy and no focus of infection can be discovered.

Treatment:- Four injections of ordinary typhoid vaccine in doses of 100, 200 and 250 million were given. After each injection there was a decided reaction, the temperature rising in one instance to 104 $\frac{1}{2}$, with increase of pain in the affected joints. Improvement was evident, and she was dismissed on Oct. 20th., 1922, in the following condition. "Patient can walk quite easily. The swelling of the wrist-joints is much less than on admission though there is still some thickening and tenderness present." She was advised to continue massage.

After history:- Recurrence 6 months after discharge from hospital.

Case XXXIII. M. J. Age 34. Admitted Oct. 13th., 1922.

History:- Twenty-one months before admission, the patient began to have pain, first in the inter-phalangeal joints and later in the metacarpo-phalangeal joints of both hands. The pain was accompanied by swelling of these joints and, at a later date, the condition spread to both wrist-joints. No other joints were ever affected.

Previous History:- She has always had good health.

Condition on Admission:- The hands are moist with sweat and considerably deformed. Both wrists are much swollen, due to synovial thickening: they are painful on movement and tender on pressure. There is marked limitation of movement of both wrists.

There is considerable thickening of the capsule of the joints of the index and middle fingers of each hand, and palpation over these elicits fibrous tissue crepitus. There is slight ulnar deviation of the fingers of both hands.

Heart and lungs are normal. No septic focus can be discovered.

Treatment:- Five injections were given in doses rising to 250 million organisms. Each injection was followed by a decided reaction, but in this case the focal reaction was only of the slightest. In the end, there was considerable diminution in tenderness of both wrists, and the movement became increased, but there was only slight diminution in the synovial swelling. The active process appeared to have come to an end and accordingly she was dismissed on November 22nd..

1st March, 1924. Her doctor informs me that the improvement has been maintained since her discharge from hospital. There is still present a thickened synovial membrane in both wrists, but the condition has not spread to any other joints, and he regards her as fit for work.

Case XXXIV. M.C. Female. Age 33. Admitted 3rd Oct., 1922

History:- Illness began 2½ years ago, with pain and swelling of the joints of the fingers of both hands. The condition slowly progressed, involving the wrists, knees, and left shoulder. She continued at work until May, 1921, when the pain and swelling of the knees forced her to give up. Since then, the joint-condition has become gradually worse.

Previous History:- Her previous health has always been good.

Condition on admission:- Both knee-joints are swollen and painful, the left much more than the right. There is some thickening of the capsule of the right knee with pain on movement. The synovial membrane of the left knee is very much swollen, doughy to the touch, and very tender. Movement of this joint is very much limited because of the extreme pain. There is also some contracture of the ham-string muscles, which prevents the leg from being completely extended at the knee.

There is marked panniculitis present on the inside of the thighs and legs.

Both wrist-joints exhibit thickening of the periarticular tissues, and movement is very much limited. A similar state of affairs exists in the metacarpophalangeal joints and inter-phalangeal joints of both hands, and, as a result, the power of grip is decreased especially in the right hand.

There is panniculitis of the shoulders and upper arms, which causes a good deal of pain and tenderness.

Heart, Lungs, and other systems are quite healthy and no septic focus can be discovered.

Treatment:- 5 Injections were given in doses rising to 250 million organisms. In each case there was marked reaction. A modified Turner's Splint was used to straighten the left leg, and, on discharge from Hospital, she could walk up and down stairs, and suffered very little pain. There was, however, still very marked thickening of the synovial membrane of the left knee-joint.

After-history:- March 1924. No other joints have become affected, but the left knee-joint is still very painful and cripples this patient.

Case XXXV. M.S. Female. Age 25. Admitted 3rd November, 1922

History:- In 1918, the patient was engaged in munition work which involved much standing in the open air, and often in very wet weather. She complained then of pain in both feet, especially in the toes. The knees were next affected and then the shoulder-joints. Later, the wrists and inter-phalangeal joints of the fingers became affected, have remained swollen, and are often very painful. She received various forms of treatment, her tonsils, adenoids, and some decayed teeth were removed, all without any effect on the condition of the joints.

Previous History:- She has always enjoyed good general health.

Condition on Admission:- There is thickening of the capsules of the proximal inter-phalangeal joints of both hands, which are therefore swollen. These joints are, however, painless. A few of the metacarpo-phalangeal joints are similarly affected. There is some wasting of the intrinsic muscles of the hands.

There is peri-articular thickening of both wrists, but movement is good and is only painful on extreme flexion and extension.

Each knee-joint shows some thickening of the capsule but movements are of full range, though stiffly performed.

There is considerable deformity of the toes of both feet, several being of the hammer-toe variety, and there is thickening and tenderness on pressure of the meta-tarso-phalangeal joints.

All other systems are healthy, and there is no focus of infection.

Treatment:- 3 injections in doses of 100, 150, and 200 million organisms were given, and she was massaged. There was marked improvement, and though there was still some thickening of the affected joints, she left hospital well.

After history:- March, 1924. The patient states that she has been able to carry on her work for the past year, though the finger-joints are still swollen. No other joint has become affected. The infective process has ceased.

Case XXXVI. M.S. Female. Age 32. Admitted October 19, 1922.

History:- In March, 1922, she noticed that her right shoulder joint was stiff. This stiffness passed off for a short time, but soon recurred and spread to the other joints of her body, so that in July she could not kneel. Later on, the joints of her hands became swollen, and stiff, but not painful, and her wrists and knees became much more swollen. She was treated without resulting improvement.

Previous History:- She has always enjoyed good health.

Condition on Admission:- The proximal interphalangeal joints of the fingers of both hands are swollen, giving to the fingers a fusiform appearance. They are not painful on pressure or on movement. There is thickening of the capsule of the metacarpo-phalangeal joints. The intrinsic muscles of both hands are atrophied. There is thickening of the periarticular tissues and limitation of movement of both wrists.

There is marked thickening of the periarticular tissues and synovial membrane of both knees, which limits movement. The ankles are similarly affected.

There is generalised panniculitis, affecting chiefly the legs, which causes her considerable pain.

Heart, lungs, and other systems are healthy. No septic focus can be discovered. Temperature is above normal.

Treatment:- Six injections were given. After each, there was a marked reaction and it was not necessary to raise the dose above 150 million organisms. The temperature did not settle completely until after the 5th injection. There was considerable improvement in the shape of diminished pain and increased mobility of joints, but the thickening persisted, and on discharge from hospital her joints were stiff.

After History:- March, 1924. She writes to say that no other joints have become affected, but that she is crippled by the stiffness and deformity of the fingers, ankles, and knees.

Case XXXVII. T.D. Male. Age 43. Admitted 26th Dec., 1922.

History:- In 1904, his left knee became suddenly swollen and painful, and, very soon, both elbows became similarly affected. The latter were more painful than the knees, but less swollen, and they soon became so stiff that he could move them only with difficulty. For a number of years the condition of his knees and elbows varied. Later, the shoulders, wrists, and the metacarpophalangeal joints, became painful and swollen. He was able to move about until 13 weeks before admission, when the right/

right knee became very painful, the swelling increased, and he was forced to go to bed.

Condition on admission:- Both shoulder-joints are ankylosed. Both elbow-joints are fixed at a right angle. There is marked contracture of the biceps muscle on each side, and marked wasting of all the muscles of the arm. Both wrists are fixed and swollen, and any movement causes pain. The interphalangeal joints are fusiform in appearance and, on moving them, a creaking leathery feeling is experienced. The metacarpo-phalangeal joints are thickened. There is some limitation of movement of the fingers which are painful.

The Left knee-joint is quite fixed. There is very little pain in it, and, round about the joint, little irregularities and projections of bone can be felt.

The right knee-joint is swollen and very tender, due to the thickening of the synovial membrane. There is contracture of the ham-string muscles, and the knee cannot be fully flexed and extended.

Both ankles and toes are swollen and very stiff. Movement is limited and painful.

Treatment:- No improvement resulted from treatment with typhoid vaccine intravenously, although five injections were given and the patient reacted moderately well.

Case XXXVIII. A. McC. Female. Age 52. Admitted 16th Jan. 1920.

History:- In January, 1918, the left knee became painful, and she was easily tired on walking. In 1919, the right knee became so painful that, for a time, she could not move about. In 1920, both shoulders became involved, with pain in the arms, hands, and fingers, so that she was unable to wash her face. During the past year, the jaw has become stiff, and the neck can be moved only with difficulty.

Condition on Admission:- The patient lies rigid in bed. The right shoulder droops, the head being slightly turned to the left. The arms are held flexed at the elbows, and both knees are drawn up. She is unable to do anything for herself. There is marked fibrous periarticular thickening of both wrists and elbows and of the proximal-phalangeal joints of the fingers of both hands. The biceps are contracted on both sides. There is wasting of the pectoral, deltoid, and scapular muscles. Lateral movement of the mandible is impossible. There is tenderness over the nuchal ligament and adjacent muscles. Both knee-joints were thickened and doughy, and there is slight contracture of the ham-string muscles.

There is marked limitation of movement of all affected joints, especially of the right elbow and both shoulders. Flexion of the vertebral column at any point is impossible. X-ray examination shows no changes in the bones of the spine. Most of the affected joints are painful, and any attempt to increase the range of movement causes considerable pain.

Treatment:- Five injections were given in doses rising to 200 million organisms. There was a marked reaction in each case. Definite improvement was obtained. The thickening of her joints remained, but she was able to get up, to walk up and down stairs, and to pick up objects from the floor, while she became quite free from pain.

After history:- March 1924. For 3 months after discharge from hospital, this patient remained well and was able to carry on her work. Then the stiffness and pain in the affected joints returned, and she is now unable for her duties.

Case XXXIX. A.M.M. Age 26. Admitted 19th January, 1923.

History:- 16 months before admission, the patient had pain and stiffness in the joints of the arms. In March 1922 the ankles became swollen, and the disease spread to the elbows, fingers, shoulders, and knees. From September until December 1922, she received hospital treatment, but on leaving the Infirmary she could hardly walk. She states that occasionally she is feverish.

Condition on Admission:- There is thickening of the periarticular tissues of both wrists which are painful and tender, and movement is limited. The left is worse than the right. The interphalangeal joints of both hands are thickened, and there is present slight Dupuytren's Contracture. There is periarticular and capsular thickening of both elbows, but movement of these joints is not restricted.

Both ankles are markedly swollen, and movement of these joints causes considerable pain. No septic focus is discovered. There is marked sweating of the hands and feet.

Treatment:- 5 doses of ordinary typhoid vaccine were given, followed in each case by considerable reaction. Three days after the first injection, there was very much less sweating of the hands and feet. She improved rapidly and, on discharge, the movements of all joints, especially of the ankle joints, were greatly improved, and she could walk fairly comfortably. There was now no evidence of active infection.

After History:- March 1924. This patient writes to say that no other joints have become affected. The sweating of the hands and feet has not returned. She still complains of stiffness and tiredness in her feet and ankles.

Case XL. N.McC. Female. Age 32. Admitted 23rd Jan. 1923.

History:- Illness commenced in August, 1920, with swelling, stiffness, and a little pain in the finger-joints of both hands. Since then, the condition has persisted in spite of various forms of treatment. She was a patient in The Royal Mineral Hospital at Bath from October till December 1922, but received no benefit. Near the end of December, the left ankle became swollen and painful on walking.

Condition on Admission:- The proximal inter-phalangeal joints of the 1st and 2nd fingers of the left hand, and of the 1st, 2nd, and 3rd fingers of the right hand, are markedly fusiform, due to thickening of the synovial membrane. They are tender on pressure, and the patient is unable to close her hands.

The left ankle is swollen. There is thickening of the synovial membrane, tenderness on pressure, and limitation of movement. There is marked generalised panniculitis. No focus of infection is discovered.

Treatment:- Massage and four injections of ordinary typhoid vaccine in doses up to 250 million were given. The swelling of the fingers diminished and the movements of the joints became more supple. On discharge, she could close her fingers easily, and the swelling and tenderness of the left ankle had gone.

After history:- 27th Feb., 1924. This patient was seen to-day. The ankle-joints are normal. There is still some thickening of the periarticular tissues of the inter-phalangeal joints of the fingers, but much less than on admission. She can close her hands perfectly, and has been at work since discharge from hospital. She suffers no pain. The infective process is completely stopped.

Case XLI R.B. Female. Age 27. Admitted 15th Feb., 1923.

History:- Five years ago, the proximal interphalangeal joints of the right hand became swollen, and gradually the condition spread to the same joints of the other hand. At this time, she only felt stiffness but, 2 years ago, the joints became painful. Eight months ago, both ankles became swollen and painful.

Condition on Admission:- There is considerable thickening of all the proximal interphalangeal joints, left wrist, and both ankles. These joints are tender on pressure and are limited in their range of movement. There is marked generalised panniculitis. No focus of infection is discovered.

Treatment:- 5 Injections were given, and she was massaged. She improved in that the synovial membrane of the affected joints became softer, less tender, and less painful. The infective process had apparently ceased, and she was dismissed with the advice to carry on massage treatment for the panniculitis.

After History:- 1st March, 1924. This patient was seen to-day. The affected joints are still swollen but they are not painful and there has been no exacerbation of the condition since discharge from hospital. She still has marked generalised panniculitis and requires prolonged massage.

Case XLII. C.McP. F Age 26. Admitted 16th Feb., 1923.

History:- Illness began in Oct. 1922, with severe pain and swelling of the right wrist. The right hip next became painful, and she was forced to go to bed. While there, it was found that she had some fever. The knees, and then the elbows and shoulders, became affected in the same way. In January 1923, the pain and swelling in these joints diminished, but all the affected joints remained stiff and tender.

Condition on Admission:- There is swelling of the periarticular tissues of the proximal interphalangeal joints of both hands, and some wasting of the ~~interosseal~~ muscles. Both wrists are thickened, tender, and very painful on forced flexion and extension. Both shoulders are tender all over on pressure, but especially in front, over the capsule of the joints, and movement is limited by pain.

There is pain in both knees which are slightly thickened, and the ankles and toes are slightly swollen and painful.

The temperature is elevated and the patient sweats a good deal. No focus of infection is discovered.

Treatment:- Four injections in doses rising to 250 million organisms were given. After the third injection, the temperature settled to normal and did not rise again. There was very marked improvement, and, on discharge, she could use all her joints perfectly, without pain, and only a slight degree of thickening remained in the fingers and wrists.

After History:- This patient emigrated to Canada in August, 1923. In February 1924, she wrote to say that she was perfectly well and able to do the hardest work without any inconvenience.

Case XLIII. C.McM. Female. Age 49. Admitted 17th Feb. 1923.

History:- Pain and swelling commenced in both wrists three years ago. Sometime afterwards, her feet and ankles became painful. In July 1922, she went to Strathpeffer for treatment, but during the first three weeks was confined to bed and her temperature was elevated. During the next six weeks, she received the baths and massage and felt much better. Since then, however, she has lapsed to her former condition.

Condition on admission:- The 2nd and 3rd metacarpophalangeal joints of the left hand are swollen with periarticular thickening.

The 2nd and 3rd metacarpophalangeal joints and the proximal interphalangeal joints of the 4th and little finger of the right hand are fusiform. The interphalangeal joints of the little finger are completely ankylosed.

Both wrists show thickening of capsule, and there is considerable pain, tenderness, and limitation of movement. The interossei muscles are wasted and the grip is poor.

The right elbow shows some periarticular thickening, and movements of flexion and extension are limited. The patient cannot raise the right hand to the head. The left shoulder joint is very painful and tender, and the patient cannot raise the arm above the level of the shoulder.

She has pain in the knees and hips, and cannot rise from a chair without help. There is thickening and tenderness on pressure over the metatarsophalangeal joints. Marked generalised panniculitis is present.

Treatment:- Four injections of hyphoid vaccine were given, and each was followed by marked reaction and some improvement. On discharge, the movements of the wrists and fingers were much freer, and the grip was increased in power. The fibrous thickenings had not altered to any appreciable extent, but she could walk with comfort.

After History:- This patient continued to improve until December, 1923. At that time, the panniculitis from which she suffered became worse and still troubles her. No other joints have become affected.

Case XLIV. F.R. Female. Age 49. Admitted 23rd March, 1923.

History:- Illness commenced in December, 1921, with severe pain in the temporo-mandibular joint so that she could not eat. At that time, according to her doctor, she showed signs of mitral insufficiency. Gradual improvement took place for a few weeks, and then the left shoulder became painful. The disease spread to her hands, the right in particular being affected, and in February, 1922, the interphalangeal joints and wrists were much swollen and tender. After this, there was considerable improvement, but in January, 1923, the condition lit up again. The hands and wrists became much worse, and the knees became so painful and swollen that she could not walk about. Since the beginning of March, the pain has been very severe, confining her to bed for 10 days before admission.

Condition on Admission:- The temporo-mandibular joints show crepitation on movement, and there is thickening of the fibrous tissue of capsule. Fibrositis is present in the deltoid and trapezius regions, causing limitation of movement of/

of the shoulders. There is fusiform swelling of the interphalangeal joints of both hands and thickening of the joint structures of the wrists, hindering movement especially on the right side, and the hands cannot be closed tightly. The ankles are not much affected, but there is fibrous thickening at the base of the toes, and painful fibrous tissue around both knee-joints. The range of movement of the knee-joints is complete. There is generalised panniculitis present. The heart sounds are weak, but otherwise there is nothing abnormal. No focus of infection can be found.

Treatment:- Three injections of ordinary vaccine were given, and she reacted well. Considerable improvement resulted from this treatment. The following was her condition on discharge from hospital "The ankle and knee joints are practically free from swelling and pain, and movement is now complete. The movements of the left wrist are also complete in range, but there still remains slight thickening of the periarticular tissues of the proximal interphalangeal joints of the left hand, which interferes slightly with the closing of the hand. The movements of the right wrist have increased in range, and the swelling of the synovial membrane and periarticular tissues has diminished. The thickening of the interphalangeal joints remains, but movements are freer and not associated with pain. There is still some fibrositis on both shoulders."

After History:- Soon after discharge from hospital, this patient had an operation for hernia, and then her appendix was removed. She was thus confined to bed for a considerable time and unable to take exercise, and in March, 1924, she wrote to say that she has become very stiff and has difficulty in walking.

Case XLV. C.S. Female. Age 20. Admitted 24th March, 1923.

History:- Three years ago, the right knee became swollen and painful. Then the wrists and fingers were affected, and the process has gradually spread until practically all joints are affected.

Condition on Admission:- There is marked thickening of the periarticular tissues of the knees, ankles, wrists and right elbow. All these joints are tender on pressure and there is limitation of movement. There is thickening of the inter-phalangeal joints of the fingers and she has great difficulty in closing her hands. There is generalised panniculitis present.

Treatment:- Massage was begun, and she was given four injections of ordinary typhoid vaccine. The pain and tenderness of the affected joints rapidly diminished and, though the thickening remained to a considerable extent, she could, on leaving hospital, close her hands, and walk without any pain or inconvenience.

After History:- 2nd Feby., 1924. This patient was seen to-day. There is still thickening of the periarticular tissues of the affected joints but, since discharge from hospital, she has been able to carry on all her duties without inconvenience. The infective process has been checked.

Case XLVI. J.J. Male. Age 43. Admitted 7th April, 1923.

History:- Towards the end of 1922, he felt aching and fatigue in both feet. Soon afterwards, the finger-joints of both hands became swollen and painful, and then the wrists, shoulders, ankles, and knees were similarly affected.

Condition on Admission. General health is good. No focus of infection is discovered. All the proximal interphalangeal joints of the fingers of the left hand are swollen and painful. Only those of the middle and ring fingers of the right hand are involved. There is thickening of the periarticular tissues of both wrists which are tender and painful on movement. There is slight thickening of the right knee-joint, and the tissues round the left knee are markedly thickened, with increase in the fluid of the joint. In this fluid, short gram-positive bacilli of diphtheroid type are to be found in films and on culture. The ankles are not thickened, but he states that occasionally they are painful. There is present fibrositis of the buttocks and shoulders.

Treatment:- Three injections of typhoid vaccine in doses of 100, 150 and 200 million organisms were given. Each injection was followed by considerable reaction and after the 3rd, all joints were normal except the left knee where there was still some fluid present. This joint proved very resistant to treatment and five more injections of 200 million organisms were given before the fluid disappeared. On discharge, there was still some thickening of the periarticular tissue of this joint, but otherwise he was well.

After history:- March, 1924. This patient has remained well.

Case XLVII. E.Y. Female. Age 46. Admitted 9th April, 1923.

History:- Seven years ago, she experienced pain and discomfort at the base of the toes, and later, pain developed in the wrists and shoulders. After a year, she was treated at Harrogate for 3 weeks and improved to some extent. Since then, however, her ankles have become painful, and during the past 2 years she has found it more and more difficult to carry on her work. Since the summer of 1922, her hands have become so painful that she is unable to knit or sew.

Condition on Admission:- She is pale and anaemic. There is thickening of the right elbow, and pain and limitation of movement. Both wrists are very much thickened, tender, and painful. There is a ganglion present on the radial aspect of the dorsum of the left wrist. The 1st and 2nd metacarpo-phalangeal joints of both hands are thickened and painful.

The ankle joints are stiff and painful, and there is considerable pain and tenderness over the metatarso-phalangeal joints of both feet.

Treatment:- 4 injections in doses rising to 200 million organisms were given, and she was massaged. On discharge, she had no pain in any of her joints, the thickenings had diminished, and there was only slight tenderness on pressure over the wrists and the metatarso-phalangeal joints. She was very much improved.

After History:- 27/2/24. This patient was seen to-day. The joints of the hands are normal. There is a little swelling of the left wrist near the root of the thumb (ganglion). The feet are normal, but patient states that she has a tired feeling in the arch of the foot after walking long distances. The infective process is completely stopped.

Case XLVIII. M.W. Female. Age 53. Admitted 13th April, 1923.

History:- Four years ago, the joints of her feet became swollen and tender, and, a year afterwards, the wrists and fingers became affected in the same way. She continued her household duties, though partially crippled, but in Sept. 1922, the swelling and pain increased, her shoulders became affected, and since December, 1922, she has been confined to bed.

Condition on Admission:- She cannot walk, and has to be fed by a nurse. The shoulders are so tender that she will not allow/

allow anyone to touch them, and there is marked limitation of movement.

Both wrists are swollen and painful. The right wrist cannot be moved, and the left wrist can only be slightly pronated and supinated. The metacarpo- and inter-phalangeal joints of both hands are affected and she cannot close them.

There is thickening of the synovial membrane of both knees which are painful and tender on pressure. Full flexion of the knees causes great pain. No focus of infection is discovered.

Treatment:- Four injections of ordinary vaccine were given in doses of 100, 150 and 200 (twice) million organisms. There was very remarkable improvement and, on discharge, (12th May) she could walk freely without pain, feed herself, close her hands tightly, and move her arms freely. There was still limitation of movement of the left shoulder, and some thickening of the wrist and knee joints remained.

After History:- 27/2/24. This patient was seen to-day. She can now raise her arms above her head. The movements of both elbows are perfect. There is still some thickening of both wrist-joints, but movement is really normal. She can now walk without discomfort.

Remarks:- This case showed very remarkable improvement.

Case XLIX. J.A. Female. Age 15. Admitted 21st April, 1923.

History:- Illness began in February, 1922, with stiffness in hands and feet, causing lameness. Shortly afterwards, the joints of the hands and feet became swollen, painful, and tender. From that time until February, 1923, the condition gradually got worse, and both knees became swollen and stiff.

Condition on Admission:- There is marked thickening of the synovial membranes and periarticular tissues of both wrists which are tender and limited in their movement. The proximal interphalangeal joint of each middle finger is thickened and slightly tender. Similar changes are observed in the right ankle-joint and in the metatarso-phalangeal joints of the feet.

Both knees are markedly swollen. The synovial membrane is thickened and each knee contains excess of fluid. The synovial thickening is very marked in the left knee where synovial fringes can be palpated between the patella and tibia.

The sediment of the fluid drawn from the left knee-joint is abundant, and consists mainly of polymorphs. No organisms/

organisms are found in film or on culture. No focus of infection is found.

Treatment:- This case proved very resistant to treatment. Seven injections of ordinary vaccine were given, and in each instance there was a good reaction. But the condition of her knee-joints did not improve to any great extent, and after the last injection there was still fluid in the right knee-joint. This gradually disappeared but she could not be regarded as well when she left hospital.

Remarks:- This appeared to be a case where, in spite of the reaction of the body to a foreign protein, the infective agent could not be inhibited.

Case L. J.H. Female. Age 44. Admitted 21st April, 1923.

History:- In 1916, she suffered from some disease of the left knee-joint. This joint was excised at that time, and the leg fixed in the straight position. In March 1922, the right knee-joint became gradually swollen and painful, and in January, 1923, there was an exacerbation of symptoms which persisted until date of admission.

Condition on Admission:- The left leg is fixed at the knee as the result of the operation. There is marked general thickening of the periarticular tissues and synovial membrane of the right knee-joint. There is tenderness on pressure over this swelling, and also over the tibia just below the knee, where there is pitting on pressure. She suffers considerable pain in this joint which is practically fixed in a position of slight flexion. X-Ray examination shows no bony changes in the right knee-joint.

Treatment:- 7 Injections of ordinary typhoid vaccine were given. As a result, there was considerable general reaction, but little focal reaction. The thickening of the joint persisted, but the pain and tenderness became very much less and she was able to walk fairly well.

After-History:- 27/2/24. This patient was seen today. There is still marked enlargement of the synovial membrane of the right knee, but it is only slightly painful. There is not the slightest sign of activity of the infective process, and the disability is due solely to the increased synovial membrane.

Case LI. A.F. Female. Age 50. Admitted 30th April, 1923.

History:- Illness commenced 18 months ago, with pain and swelling of the joints of the fingers, ankles, and wrists. She received treatment and some improvement was obtained, but, during the past two months, the condition has become more acute and the pain and stiffness have increased in severity.

Condition on Admission:- There is thickening and tenderness of the inter-phalangeal joints of both hands, and of the wrists, ankles, and shoulder joints. She suffers pain in these joints and, resulting from this, there is considerable limitation of movement. There is present a mitral systolic murmur.

Treatment:- 4 Injections of ordinary vaccine in doses of 100, 150, and 200 million organisms were given. The patient showed steady improvement; the pain and tenderness in her joints disappeared, though the joint thickening persisted, and she was discharged on 25/5/23 very much improved.

After-History:- March 1924. This patient writes to say that she has been able to carry out all her duties since she left hospital, but that during the past month she has not been so well. She does not give details of her complaint.

Case LII. G.P. Female. Age 52. Admitted 10th March, 1923.

History:- Illness commenced three years ago with pain, stiffness, and swelling of the right knee. This gradually got worse so that walking was difficult. A year later, both elbows became similarly affected, and then both wrists and ankles. During the past 7 months she has not been able to do her work, and can walk only with the aid of two sticks.

Condition on Admission:- She is very thin and suffers considerable pain in the affected joints. The muscles of the limbs are atrophied. The right knee is slightly flexed; it is swollen as a result of the thickened synovial membrane, and periarticular tissues. Flexion is possible from 140° to 110° with the thigh. The left knee is ankylosed (fibrous) at an angle of 160° .

There is limitation of movement of both elbow joints which are thickened and sclerosed. Hard fibrous nodules are present over both elbows. The wrists are stiff, painful, and thickened. The fingers are flexed at the meta-carpo/

meta-carpo-phalangeal joints and cannot be extended.

Treatment:- 4 Injections were given, and each was followed by considerable reaction. The amount of pain she suffered was much diminished, but there was no alteration in the condition of her joints.

After History:- March, 1924. This patient writes to say that no other joints have become affected, but that she is still crippled with pain and stiffness of her joints.

Case LIII. J.R. Female. Age 20. Admitted 28th June, 1923.

History:- In March 1920, she had an attack of pain, stiffness, and swelling of the fingers, wrists, knees, and ankles, with elevation of temperature. She was confined to bed for 9 months, recovered to some extent, and at the end of a year was able to walk about. She kept fairly well until about 3 months ago, when she had a fresh attack affecting the left knee, and can now only get about with the aid of sticks.

Condition on Admission:- The left wrist is practically ankylosed. Flexion and extension of the right wrist is possible only through an angle of 25°. There is thickening of these joints and also of the interphalangeal joints and both elbows.

The left knee is swollen, painful, and contains free fluid. No organisms are found in film or on culture from this fluid. There is thickening of the synovial membrane, and the range of movement is limited. There is wasting of the thigh muscles. No focus of infection is discovered.

Treatment:- Four injections of ordinary vaccine were given. There was considerable improvement, the fluid disappearing from the left knee, all the affected joints becoming less painful, and the range of movement markedly increased.

After History:- 4th March, 1924. This patient was seen to-day. The wrists are still thickened, but the movement of the right wrist is of full range and not associated with pain. The finger and elbow-joints are now normal. There is still thickening of the left knee-joint but there is no tenderness on pressure over the joint. She can now walk several miles.

Case LIV. G.S. Male. Age 49. Admitted 3rd July, 1923.

History:- In 1916, while at Salonika, he suffered from bacillary dysentery. While in hospital, he developed "synovitis" in both knees, was sent home, and was discharged from the Army in December, 1916. About that time his knees and other joints began to get stiff. In 1919, he was treated with "ionisation" and afterwards in Strathpeffer, but without improvement. He has never had severe pain in his joints. In the winter of 1922-1923 his feet became swollen.

Condition on Admission:- He has now no signs of dysentery. He cannot fully flex the fingers of both hands. Both wrists can move only through an angle of 35°. The right elbow will not extend beyond an angle of 135° with the arm, but the left elbow is not involved. There is thickening of all these joints.

Both knees are kept flexed at about 115°. The left knee is completely fixed, and the right only moves through 15°. There is considerable thickening of the periarticular tissues of both knee-joints.

Marked creaking can be elicited on movement of all affected joints. He suffers very little pain.

Treatment:- 3 injections of typhoid vaccine were given, with considerable reaction but with no clinical improvement, and he was discharged.

Remarks:- In this case the infection had died out, and he really suffered from the permanent sequelae of the disease.

Case LV. C.S. Female. Age 55. Admitted 9th July, 1923.

History:- In January 1921, she began to suffer from pain in the shoulders, hands, and feet. The condition gradually got worse. One year ago, both knees began to swell. After this, she had her teeth extracted but there was no alteration in the joint condition.

Condition on Admission:- Both knees are very much thickened, painful, and tender. There is considerable limitation of flexion, and patient is unable to walk. Both wrists are swollen and painful, as a result of periarticular thickening. The proximal interphalangeal joints are similarly affected, and the hands are considerably deformed. No focus of infection is discovered. There is present generalised panniculitis.

Treatment:- 5 injections of typhoid vaccine were given, and she received massage and passive movements. The pain diminished, the swelling of the affected joints became less, and she had greater freedom of movement. She could walk, but required the support of a stick.

After History:- March, 1924. Since discharge from hospital, she has had no increase in pain and the disease has not become worse or spread to other joints. She is at times, however, very stiff as a result of the associated panniculitis and fibrositis. This infection appears to have ceased.

Case LVI. N.G. Male. Age 46. Admitted 10th July, 1923.

History:- 15 months before admission, he had pain in the right wrist and right elbow. The disease then spread to the shoulders and to the joints of his feet. 6 months before admission, his teeth were extracted on medical advice, but there was no improvement. The affected joints became swollen and his movements were hindered.

Condition on Admission:- The patient walks with the aid of sticks because of pain in his feet and knees. There is slight thickening of the tissues round the knee and ankle-joints, and especially of the metatarsophalangeal joints which are tender on pressure. Several of the metacarpophalangeal joints of both hands are swollen and painful. The right fore-arm cannot be fully extended, and the right arm cannot be raised above the head. He has fibrositis of the muscles of the shoulder girdle.

Treatment:- Three injections of typhoid vaccine were given. After each, there was a marked reaction and this was followed by improvement of the joint condition. He received massage for the fibrositis of the shoulders and, on 28th July, was dismissed "well."

After History:- March 1924. Since discharge from hospital, this patient has remained well.

Case LVII. M.P. Female. Age 47. Admitted 13th July, 1923.

History:- Illness commenced 2 years ago with pain in both arms. The fingers became stiff and swollen, and grasping movements were painful. The stiffness and pain extended to the wrists and then to the ankles and feet. Three months before /

before admission, the knees became affected and afterwards the shoulders and hips.

Along with the pain and stiffness there was some swelling of the joints, which so affected the feet and ankle joints that for 15 months she has been unable to walk.

Condition on Admission:- There is thickening of the metacarpophalangeal and interphalangeal joints and of the wrist joints of both hands. She is unable to close her hands completely. She cannot fully extend her forearms nor can the arms be raised above the head. The knees, ankles, and metatarsophalangeal joints are all swollen and painful. Movement of these joints is limited. No focus of infection is discovered.

Treatment:- Three injections were given without producing much improvement beyond some diminution in the pain of the affected joints. She received massage, and after a few weeks was able to walk though stiffly.

After History:- March, 1924. This patient writes to say that her condition has not altered since her discharge from hospital. She cannot be regarded as cured.

Case LVIII. A.F. Female. Age 53. Admitted 30th July, 1923.

History:- Illness of 20 years' duration.

Condition on Admission:- There is marked swelling of the inter-phalangeal joints of both hands. There is ulnar deflection of the fingers. The wrists show considerable thickening and are completely fixed. The elbows are not markedly affected.

The toes are deformed in all directions, and she has had one amputated for comfort. There is thickening of the knee joints. She has fibrositis of the shoulders and hips.

Treatment:- Three injections were given. After each, there was marked reaction. There was no apparent change in the affected joints, but she felt less pain and stiffness and could walk about more easily.

Remarks:- This is the most that was to be expected in such a case, where the disease had lasted for 20 years and had caused so much deformity.

Case LIX. A.McM. Female. Age 32. Admitted 3rd August, 1923.

History:- The disease commenced five years ago with pain and swelling of both ankles. In turn, the shoulders, knees, and, more recently, the hips became affected. Pain was severe on movement, and she was incapacitated completely at intervals. In 1922 there was some improvement, but in April, 1923, the condition increased in severity.

Condition on Admission:- Both ankle joints and those of the fingers are swollen and acutely painful, and movement is very limited. There is marked tenderness on pressure over the metatarsophalangeal joints. The wrists and knees show slight thickening of the capsule, and movement is limited. The hips, elbows, and shoulders are not affected. There is generalised panniculitis. No focus of infection is found.

Treatment:- Three injections of ordinary typhoid vaccine were given, and she was massaged. There was very marked improvement, and though some thickening of the joints remained, the pain and tenderness diminished and, on discharge, was almost gone.

After History:- March, 1924. This patient writes to say that she has been very well since she left hospital and can carry out all her duties. She has now no pain or stiffness in the joints which were affected.

Case LX. J.R. Male. Age 52. Admitted 27th August, 1923.

History:- 15 years ago, the patient had an attack of severe pain and swelling of his hands, wrists, and feet. He did not recover completely, and, 11 years ago, his ankles became affected. His elbows, and hips were never involved, but, during the past 3 weeks, his knees became affected and the joints of the fingers became swollen and painful.

Condition on Admission:- Both wrists are completely ankylosed. There is considerable thickening of the finger joints which are painful and tender on pressure. There is fibrositis of the deltoid and trapezius region on each side, limiting movements of the shoulders.

The toes of both feet are stiff, swollen, painful, and tender and there is slight thickening of the periarticular tissues of both knees which are tender on pressure.

Treatment /

Treatment:- Three injections of typhoid vaccine were given. In each case, there was a marked reaction, the temperature in one instance rising to $104^{\circ}.6$ F. The pain, stiffness, and swelling in the affected joints disappeared and, though his wrists were ankylosed, he was able to move about quite freely and to use his hands. He was discharged on September 14.

After History:- 25/2/24. This patient was seen to-day. He can walk quite freely and has been at business every day since he left hospital. Both wrists are fixed. He states that, in cold wet weather, he feels some aching in the joints of his fingers and toes, but that otherwise he suffers no inconvenience.

Case LXI. W.R. Male. Age 49. Admitted 11th May, 1923.

History:- Illness began in 1920 when his fingers became painful, stiff, and swollen at the inter-phalangeal and metacarpo-phalangeal joints. Since that time, the swelling has persisted. In May, 1922, there was an exacerbation of the disease and nearly all the joints of the body became stiff and painful. The pain ceased in all joints except those of the fingers, wrists, and big toes. In December, 1922, the right knee became swollen and painful, and since then he has been confined to bed. In April, 1923, the right elbow and then the left elbow became painful and swollen.

Condition on Admission:- Both elbows show marked thickening of the synovial membrane. In each case there is contracture of the biceps muscle so that the arms cannot be completely straightened. Movements of pronation and supination are limited. Both wrists are swollen, tender, and stiff. There is marked thickening of the metacarpophalangeal and proximal interphalangeal joints and he cannot close his fingers completely.

There is marked thickening of the synovial membrane of the right knee with a small excess of synovial fluid in the joint. It can be extended completely, but cannot be flexed through more than 120° .

Treatment:- Seven injections of ordinary typhoid vaccine were given. Although he reacted very well, there was little or no improvement in the joint condition, and he was discharged in statu quo.

Case LXII. J.T. Female. Age 41. Admitted 25th September, 1923.

History:- Four years ago, the patient experienced pain in the finger joints and in the balls of the toes. At this time the swelling was slight. In slow progression the wrists, elbows, and/

and shoulders became involved. The knees were then slightly affected, but, during the past two months, there has been an exacerbation of symptoms, and she has pain in her jaw on eating and talking.

Condition on Admission:- She is well nourished and looks healthy. The little finger of each hand is partly flexed and fixed. The 2nd and 3rd metacarpophalangeal joints of the right hand are swollen and tender. There is thickening of both wrists and limitation of dorsiflexion. The elbows are slightly thickened, and the movements of the shoulder joints are limited by fibrositis in the deltoid and trapezius regions. She has generalised panniculitis.

The knees and ankles show thickening of the synovial membranes and periarticular tissues, are tender on pressure, and movement is limited. She has difficulty in walking and in rising up and sitting down.

Treatment:- Four injections were given and she was massaged. She showed considerable improvement. On her discharge from hospital, the arms could be raised completely above her head, the finger joints were normal, and the wrists were not painful or tender. The knee joints and ankle joints were normal. There was slight tenderness on pressure over the metatarsophalangeal joints of both feet. She still had fibrositis and panniculitis in various parts of the body, and was advised to continued massage.

After History:- March, 1924. This patient writes to say that she can now walk quite freely. She complains of pain in her shoulders and neck - due to the panniculitis from which she suffers.

Case LXIII. A.S. Female. Age 51. Admitted 15th October, 1923.

History:- Three years ago, both elbow joints became painful and swollen, and later they became stiff. Then the knees, wrists, and fingers were affected but not to the same extent. Two years ago, the knees became very much more swollen and painful and the left ankle was affected. She was confined to bed from January until May, 1922. Since then, she has been able to walk only with great difficulty with the help of sticks.

Condition on Admission:- Patient is stout and looks healthy. Both knee joints are much swollen and movement is limited. The same periarticular thickening is present in the left ankle and in both elbows, and the movement of these joints is markedly limited. She has generalised panniculitis and fibrositis of the shoulder region, which limits movement of these joints. The temperature is elevated. No focus of infection is discovered.

Treatment/

Treatment:- Six injections of typhoid vaccine were given, and she was massaged. After the third injection, the temperature became **normal**. She showed considerable improvement and, on discharge, could walk without the aid of sticks. The movements of both knees and of both elbows were practically complete, and the left ankle was normal. There was still present panniculitis, but not so marked as on admission.

After History:- March, 1924. The patient writes to say she can still walk without sticks. No other joints have become affected, but she says that her back is still sore and stiff.

Case LXIV. R.D. Male. Age 21. Admitted 19th October, 1923.

History:- Three years before admission, his back was stiff in the morning, but this stiffness passed off during the day. Later on, he developed pain in his hips, and two years ago the left knee became stiff and painful and occasionally swelled up. $1\frac{1}{2}$ years ago, his shoulders were affected in the same way.

Condition on Admission:- There is marked limitation of movement of the vertebral column and consequently he cannot stoop to pick up anything from the floor. He cannot sit up in bed unless the legs are allowed to hang over the side. There is slight scoliosis, with the convexity to the right, in the lower dorsal and upper lumbar regions. X-Ray examination shows no bony changes in the vertebral column. The left knee is tender on pressure and some fibrous tissue creaking is present. There is stiffness and pain on moving the shoulder joints. Fibrositis is present in the fascia lata of each thigh and at the attachment of the adductor muscles to the pubic bone. No focus of infection is discovered.

Treatment:- Five injections of ordinary typhoid vaccine were given, and each was followed by a marked reaction. He was treated with massage and exercises, and on discharge he could walk freely without the aid of a stick, and indeed could run. The range of movements of the spine had increased markedly. He could bend down and touch the floor if he was allowed to bend his knees a little. His knees were normal and his general health was good.

After History:- March 1924. This patient writes to say that he keeps well, has dispensed with his walking stick and has only slight difficulty in stooping to pick up objects from the floor. The infective process has ceased.

Case LXV. R.S. Male. Age 34. Admitted 12th November, 1923

History:- During the past year his fingers and wrists have become gradually swollen, stiff, and slightly painful. Otherwise he has been in perfect health.

Condition on Admission:- The proximal interphalangeal joint of the middle finger of the left hand is very much swollen, and elastic in consistence. It is tender on pressure and there is pain on complete flexion.

Both wrists are thickened and tender, and the proximal interphalangeal joints of the little finger and index finger of the right hand are affected in the same way.

Treatment:- Four injections of ordinary typhoid vaccine were given, and each was followed by a definite reaction. In this case, there was produced very little improvement in the affected joints which remained swollen and stiff.

After History:- March, 1924. This patient writes to say that the condition has spread to his left knee and ankle.

Case LXVI. C.L. Female. Age 26. Admitted 5th Sept., 1923

History:- Several days before admission, this patient had acute pain in her wrists and knees. This continued, and she was sent into hospital as a case of acute rheumatism.

Condition on Admission:- There is swelling and tenderness of both wrists, the right ankle, and both knees. The temperature is elevated.

Treatment:- She was given 20 grs. of sodium salicylate every four hours, and in 48 hours the temperature came down to normal and the joint symptoms cleared up. During the next five weeks, whenever any attempt was made to diminish the amount of salicylate, the temperature rose and the joint manifestations returned. It was therefore decided to try the effect of protein shock therapy. Three injections of ordinary typhoid vaccine were given, each followed by considerable reaction. The temperature came down to normal, and the joint condition cleared up. She was discharged well.

After History:- 13th March, 1924. This patient was seen to-day. She is well.

Case LXVII. I.D. Female. Age 38. Admitted 22nd Oct., 1923.

History:- Illness commenced three months ago, with aching and stiffness in the knees, ankles, and feet. Shortly afterwards, several of the joints of the fingers became swollen, painful, and so stiff that she was unable to close her hands completely, and consequently was prevented from working.

Condition on Admission:- There is marked thickening of the periarticular tissues of the metacarpophalangeal joints of the fore-finger and middle finger of the left hand. The joints of the left little finger are not swollen, but she complains of pain all along the finger.

The distal interphalangeal joint of the right thumb is markedly thickened, tender to touch, and the patient can hardly move it.

There is some thickening and tenderness of the knees, ankles, and metatarsophalangeal joints.

There is marked panniculitis of the legs, thighs, and abdomen.

Treatment:- Five injections of ordinary typhoid vaccine were given intravenously. Each injection was followed by a definite reaction and considerable improvement followed. The following was her condition on discharge from hospital. "The knees, ankles, and feet are now normal, and she can walk easily. There is still some panniculitis of the legs and thighs. Both hands can be closed easily and completely, and the thickening of the finger-joints is much less than on admission. These joints are still a little tender on hard pressure, and the patient still complains of stiffness in the movements of the left little finger."

After History:- March, 1924. "Improvement maintained. The disease has not affected any other joint."

Case LXVIII. DD. Male. Age 47. Admitted 13th November, 1923.

History:- In August, 1921, the patient experienced pain, gnawing in character, at the 3rd metatarsophalangeal joint of the left foot, and over the left ~~skin~~ bone. Shortly afterwards, there appeared swelling over the ~~skin~~, on the dorsum of the foot, and behind the left ankle. He could not wear boots, and the pain and swelling became worse when he walked. On account of the swelling and pain over the tibia, a diagnosis of syphilitic periostitis was made, and, in spite of the fact that/

that his blood was negative to Wassermann's test, he received energetic antispecific treatment, but without improvement.

In May, 1922, a portion of the tibia was gouged out for histological examination. It showed merely ill-defined chronic inflammatory changes.

Since then his condition has become worse.

Condition on Admission:- He walks with the aid of a stick. The left leg, especially on the anterior aspect, is swollen, very tender, and painful. The dorsum of the foot is swollen and painful, and there is marked tenderness on pressure over the metatarsophalangeal joints. He describes the pain as burning in character. There is slight oedema over the anterior aspect of the leg and the dorsum of foot. The left foot sweats profusely. There is thickening of the capsular ligaments of the ankle and toe joints.

Treatment:- Seven injections of ordinary vaccine were given, and each was followed by considerable reaction. The oedema disappeared gradually and the tenderness diminished considerably, but slight pain persisted. On discharge from hospital, no swelling or tenderness was present, and he could walk much more easily, but he still complained of pain in the anterior aspect of the leg.

After History:- March, 1924. This patient was seen to-day. The improvement has been maintained, but he states that he has still pain when he walks.

Case LXIX. E.T. Female. Age 52. Admitted 20th November, 1923.

History:- Four years ago, she felt slight pain and stiffness in both knees on getting out of bed in the morning. Shortly afterwards, these joints became swollen, and since then they have become gradually worse, though at times they were less painful and more supple. In July, 1923, there was fluid in both knee joints and, on six occasions, they had been tapped. The only other joint affected was the right elbow.

Condition on Admission:- There is considerable thickening of the periarticular tissues and synovial membranes of both knee joints. The tissues have a coarse fibrous feel, and are very tender on pressure. There is fluid present in both joints. No organisms are found in film or on culture from this fluid. The legs cannot be fully flexed at the knees.

The periarticular tissues of the right elbow joint are thickened and tender. There is some contracture of the biceps muscle. No focus of infection is discovered.

Treatment/

Treatment:- Six injections of typhoid vaccine were given. After the second injection, the knees became more swollen, but, following the third dose, the swelling receded and movement of the joints improved. On discharge, there was still thickening of the synovial membrane of the knee joints, but the swelling was much less than on admission and she could walk very well. She suffered no pain.

After History:- March, 1924. The patient writes to say that, since discharge from hospital, she has remained in good health and is able to carry on her ordinary duties. No other joints have become affected but she still feels stiff when getting up in the morning.

Case LXX. J.G. Female. Age 45. Admitted 19th January, 1924.

History:- Illness began in January, 1923, with pain in left elbow joint. A week afterwards, the left shoulder was affected and the condition then spread to the finger joints which became painful and swollen. In May, 1923, the right knee became affected, and since then the disease has spread to the ankles and toes.

Condition on Admission:- She is well nourished and looks in good health. No focus of infection is discovered. The proximal interphalangeal joints of the middle, index, and little fingers of both hands are fusiform, due to increase in the periarticular tissues. These joints are painful and tender. There is slight thickening of the tissues round both elbow joints. The right knee is very much thickened and painful. It contains excess of **synovial** fluid. Both ankle joints are swollen and painful, the left being worse than the right. There is slight thickening of the metatarsophalangeal joints of some of the toes of both feet and these are tender on pressure.

Treatment:- Two injections of 100 and 125 million organisms were given. After each, there was considerable reaction, and this was followed by marked improvement in the condition of the joints. Four days after the second injection, she developed a small boil on the right arm and, after the 3rd injection of 150 million organisms, there developed a spreading cellulitis with this boil as centre. This subsided under appropriate treatment, and she was given a final dose of 200 million organisms. On discharge, she could move all the joints of her body without pain. She could walk very well, but there was still some thickening of the periarticular tissues of the right knee.

Remarks:- This case is of interest in that a small septic focus became very acute after the injection of a foreign protein. The focus, however, bore no causal relationship to the disease of the joints.

Wife of

George Robinson

J. Robinson
70, Market St.
Glasgow

Glasgow

Scotland

1841

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1843

1844

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John Robison
1846

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1849

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1851

George Mitchell
28, Great Street,
Glasgow

Printed by J. G. ...

ROBINSON

GEORGE MITCHELL'S BOMING TAPER

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P A R T II.

A STUDY ON IONIC MEDICATION.

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A STUDY ON IONIC MEDICATION.

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In the course of the investigation discussed in the first part of this thesis, it was found necessary to test the efficacy of a form of therapy known as iontophoresis, ionization, or ionic medication. The basic idea underlying this special therapeutical measure is, that drugs in their ionic state are driven through the skin or a mucous membrane by means of an electric current, and exert their effect on the underlying tissues. In the treatment of rheumatoid arthritis, a few writers have claimed that they have been able to obtain complete cure in this way. Others, recognising that the disease is the result of a general infection, and therefore not likely to be cured by local treatment, have stated that, by ionic medication, they were able to remove the thickened fibrous tissue of the affected joints, and to dispel the associated fibrositis and neuritis in other parts of the body. They have even claimed that a joint which has become ankylosed can recover its mobility rapidly and completely, if treated in this way. It appeared to me, therefore, to be of great practical importance to put this form of treatment to the test of actual practice, for, if the claims made for it could be substantiated, the/

the solution of the orthopaedic problems of rheumatoid arthritis, which ordinarily present great difficulty, would become comparatively simple.

The method employed was as follows. The current was obtained from the ordinary electric-lighting mains, and, to lower the voltage and regulate the current so that it could be used with safety to the patient, there was inserted in the circuit a shunt resistance. In this way the current could be raised or lowered very gradually and evenly. A milliampèremeter was placed in the same circuit as the patient to measure the current actually passing. Flexible zinc electrodes of different sizes (8" x 5" and 5" x 3") were used, and between these electrodes and the patient's skin, were placed pads consisting of sixteen layers of lint. These pads were soaked in solutions of various electrolytes, and thus served as reservoirs from which the ions were to be driven through the skin. In order to increase the concentration of the current at, and limit it to, the affected part, the smaller electrode was used in this region. The other, or indifferent, electrode was placed at some convenient part of the body, and here the larger of the electrodes was used to reduce the concentration of the current by diffusing it over a wider area. The pad under the indifferent electrode was /

was soaked in a normal saline solution, while the pad under the electrode covering the affected part was soaked in a 2% solution of sodium salicylate or potassium iodide, which are the two drugs most extensively employed in the treatment of medical conditions by ionization. The latter pole was made the negative pole, so that, when the current passed, the salicylic or iodine ions, being anions, would move to the positive pole and therefore into the skin. As a general rule, currents up to 100 milliamperes for 30 to 45 minutes were employed. In a few cases, a current of 200 milliampères was reached during the last ten minutes of a thirty minute period of treatment.

In this way fifteen cases were treated, some with the iodine ion, others with the salicylic ion, but generally with both at different times. Treatment was repeated frequently, as soon as the effects of the irritation of the skin following each application had passed off. Cases of fibrositis of the lumbar and other regions, and cases of sciatica, were treated in a similar fashion. The results can be briefly summarised. In no case was cure obtained. I failed completely to observe the so-called "lytic" effect on the pathological fibrous tissue underneath the skin. The fibrous thickenings did not appear to be affected in any way, and, in consequence, there was /

was no increase in mobility of joints which were ankylosed. The only benefit which was observed to accrue to the patient was a temporary relief of pain. This persisted for several hours after the process of ionization, but in every case the pain returned, though in a few cases not to the same extent. The diminution of pain could in no way be ascribed to the introduction of the iodine or salicylic ions, for, when the current was reversed and therefore no iodine or salicylic ions were being introduced, the same relief followed. Similarly, when a pad soaked in a solution of sodium chloride was used over the affected part, exactly the same result was obtained.

The failure to obtain the beneficial results reported by other observers led me to examine closely the theory of ionic medication. I found, on perusing the literature of the subject, that the theory was based on the results of a few experiments on animals, and that, though much work had been done on the practical application of this theory in the treatment of disease, there existed no exact records of experiments on human beings, which had any direct bearing on the theory itself. I decided, therefore, to make a number of experiments which will be described later, and I propose in this part of the thesis to/

to use these experiments and my clinical observations as the basis for a critical examination of the whole subject.

The initial difficulty is the exact meaning of the term "ionic medication." According to those who speak with authority on the subject, the term embraces (1) the introduction of drugs into the body through the skin or a mucous surface, by means of an electric current, and (2) the modification of the chemical composition of parts of the body, by the setting up of chemical changes throughout the tissues. (1) If the second part of the definition means that the chemical composition of the tissues is modified by the drugs introduced, then it is understandable. If, however, as is generally held, it means that this modification is the result of the passage of an electric current through the body, without any reference to the drug introduced, it is very difficult to see how the process can be termed "medication." It is obvious, in any case, that the two parts of the definition involve quite different conceptions, and will require to be considered separately.

The first question therefore which has to be considered is: Can drugs be introduced through the skin by means of an electric current? The answer to that question/

question is undoubtedly in the affirmative. The original experiments of Leduc showed that it was possible to introduce, in this way, strychnine ions through the skin of a rabbit. ⁽²⁾ Finzi proved that the ferri-cyanide ion could be carried through the skin of a monkey. ⁽³⁾ Inchley repeated these experiments on cats, rabbits, and guinea pigs, and showed further that it was possible to introduce electrically a number of other alkaloids, some metals, and certain negative ions. ⁽⁴⁾ In the case of the human subject there are, as has been indicated, no exact records of experiments, though a number of writers have mentioned that it is possible to prove the penetration of the iodine ion. In my experiments I have been able to confirm this, and further, I have been able to demonstrate quite conclusively the presence in the body of another anion, the salicylic ion, and of two kations, pilocarpine and atropine, after they have been carried through the human skin by a current of electricity.

The question then arises: Has the ion thus introduced into the body any special pharmacological action in virtue of the manner of its introduction? If we are to believe the ionic theory of the action of drugs - namely, that soluble salts exist in the body mainly as ions, and that each ion possesses an independent pharmacological action - then we must believe that the method of administration will make /

make no difference to its intrinsic action. That this is so, has been shown by the experiments on animals by Leduc and Inchley. The strychnine ion introduced electrically exhibited its ordinary action on the spinal cord and caused convulsions, while the atropine ion exhibited its ordinary action in producing paralysis of the cranial autonomic nerves. In the case of man, it can be shown very clearly by using a solution of pilocarpine nitrate under the positive pole. After the current has passed for some time, the individual under experiment exhibits salivation, sweating, and disturbance of vision - in other words, the ordinary signs of the action of the pilocarpine ion introduced in any other way. It may seem that I elaborate this point somewhat unnecessarily, but the suggestion has frequently been made, or at any rate implied, that, when an ion is introduced through the skin by means of an electric current, it is thereby endowed with some peculiar properties. That this is not so, is obvious. The essential pharmacological action of any particular ion is the same whether it be passed through the skin into the body by inunction, a hypodermic needle, or an electric current.

If that be so, the critic will very naturally ask: Wherein lies the particular merit of this method of introducing drugs into the body? The technique is expensive/

expensive, complicated, and wasteful of valuable drugs, compared at anyrate with the hypodermic needle or inunction. What advantages does it possess to compensate for these very obvious drawbacks? The answer is given that "in treatment by ionization a cloud of ions is introduced into the place where the disease exists;"⁽⁵⁾ that the ions are limited to the diseased region, and that therefore the local concentration is high. As a result, the action is more intense, and the effect consequently greater.

In order to examine these statements we must enquire: (a) what quantity of drug can be passed through the human skin by means of the electric currents used for therapeutic purposes? (b) What evidence is there of a local concentration of the drug after it has passed through the skin? (c) How deeply can the drug be made to penetrate in this way?

I investigated the first question with special reference to the iodine and salicylic ions, which, as has been indicated, are the two remedies most extensively employed in the treatment of medical conditions by ionization. The method adopted was that already described - a 2% solution of potassium iodide or sodium salicylate being used to soak the pads under the negative electrode. The process was continued for a period of thirty/

thirty to forty minutes with currents ranging from 25 to 200 milliampères, and the urine was collected for analysis during the twenty-four hours following the experiment. Kendall's method⁽⁶⁾ was employed to estimate the amount of iodine present in the urine, and the amount of salicyl bodies was estimated by the method described by Thoburn and Hartzlik⁽⁷⁾. The following table gives the results when potassium iodide was used.

Current in milliampères	25	50	100	200
Milligrams of iodine in 24 hours' urine.	30	55	96	146

It must be pointed out that it is not possible to raise the current all at once to the amperage indicated. For the comfort of the patient that has to be done gradually, and accordingly the currents noted in the table were not acting during the whole period of the experiment. The rapidity with which the current could be raised varied with different individuals, but the quantities of iodine given in the table were the maximum found for each particular current.

In the case of the current of 200 ma. the duration of /

of the experiment was 40 minutes, the current being raised from 100 to 200 ma. during the last thirty minutes of the period. The duration in the other cases was thirty minutes.

The following pages contain the protocols of the experiments.

Experiment 6.

Subject: D.C. Electrodes 8" x 5".

Positive Electrode on posterior aspect of left thigh. Pad under electrode soaked in normal saline solution.

Negative Electrode on posterior aspect of right thigh. Pad under electrode soaked in 2% solution of potassium iodide.

<u>Time.</u>	<u>Current.</u>
4.10 p.m.	0 milliampères.
4.11 p.m.	10 do.
4.12 p.m.	20 do.
4.13 p.m.	25 do.
4.31 p.m.	25 do.

Current stopped.

Slight reddening of the skin underneath the electrodes.

Total amount of iodine in 24 hours urine = 30 milligrams.

Experiment 10.

Subject: J.T. Electrodes 8" x 5".

Positive Electrode on posterior aspect of left thigh.

Pad under electrode soaked in normal saline solution.

Negative Electrode on posterior aspect of right thigh.

Pad under electrode soaked in 2% solution of potassium iodide.

<u>Time.</u>	<u>Current.</u>	<u>Remarks.</u>
3.28 p.m.	0 milliampères.	
3.29 p.m.	15 do.	Collection of Saliva begun.
3.30 p.m.	30 do.	
3.31 p.m.	50 do.	
3.44 p.m.	50 do.	Collection of saliva ended.
4. p.m.	50 do.	

Current gradually reduced. There is distinct reddening of the skin underneath the electrodes.

Saliva tested for presence of iodine by the following method:

To 5 c.c. of saliva is added 5 drops of a 1% solution of sodium nitrite and a few drops of concentrated sulphuric acid. The iodine liberated, when extracted with chloroform, gives a beautiful pink colour.

Result of test - very faint pink colour.

Total amount of iodine in 24 hours urine - 54.98 milligrams.

Experiment 13.

Subject: J.T. Electrodes 8" x 5".

Positive Electrode on posterior aspect of left thigh.

Pad under electrode soaked in normal saline solution.

Negative Electrode on posterior aspect of right thigh.

Pad under electrode soaked in 2% solution of potassium iodide.

<u>Time.</u>	<u>Current.</u>	<u>Remarks.</u>
11.25 a.m.	0 milliampères	
11.26 a.m.	15 do.	First collection of saliva begun.
11.27 a.m.	25 do.	
11.28 a.m.	35 do.	
11.29 a.m.	50 do.	
11.30 a.m.	80 do.	
11.31 a.m.100 do.	
11.40 a.m.100 do.	First Collection of saliva stopped.
11.56 a.m.100 do.	Second Collection of saliva stopped.

Current gradually reduced to zero.

There is marked reddening of the skin under the electrodes.

1st Specimen of Saliva tested for iodine...Positive (faint).

2nd Specimen of Saliva tested for iodine...Positive (distinct)

Urine passed at 12.15 p.m. tested for iodine..Positive "

Total amount of iodine in 24 hours' urine = 96 milli-grams.

Experiment 16.

Subject: D.B. Electrodes 8" x 5".

Positive Electrode on lumbar region. Pad under electrode soaked in normal saline solution.

Negative Electrode on posterior aspect of left thigh. Pad under electrode soaked in 2% solution of potassium iodide.

<u>Time.</u>	<u>Current.</u>	<u>Remarks.</u>
4.10 p.m.	0 milliampères	
4.11 p.m.	10 do.	First collection of saliva begun.
4.12 p.m.	20 do.	
4.13 p.m.	30 do.	
4.15 p.m.	40 do.	
4.16 p.m.	60 do.	
4.19 p.m.	80 do.	
4.20 p.m.	100 do.	
4.23 p.m.	120 do.	
4.25 p.m.	130 do.	
4.27 p.m.	140 do.	First collection of saliva stopped.
4.29 p.m.	150 do.	Second collection of saliva begun.
4.30 p.m.	160 do.	
4.32 p.m.	180 do.	
4.34 p.m.	190 do.	Irritation under negative electrode greater than positive electrode.
4.38 p.m.	200 do.	
4.51 p.m.	200 do.	Second collection of saliva stopped.

Current gradually reduced. There is marked reddening of the skin, particularly underneath the negative electrode.

1st specimen of saliva tested for iodine - Positive (faint)

2nd specimen of saliva tested for iodine - Positive (distinct)

Urine passed at 5 p.m. tested for iodine - Positive.

Total amount of iodine in 24 hours' urine = 146 milligrams.

It is known that from 60 to 80 per cent or more of the amount of iodine taken into the body by any channel, is excreted in the urine in 24 hours. From the figures given it is possible to estimate approximately the amount of the iodine ion which entered the body. Taking even the lowest percentage, the maximum amount of iodine which was introduced into the body by each current was 50, 92, 160 and 243 milligrams respectively. In other words, it will be seen that, with the ordinary currents used in therapeutics, and for the ordinary duration of treatment, the total amount of iodine introduced was not greater than 0.77 grain, 1.4 grains, and 2.46 grains. Even with the huge current of 200 milliampères the amount was only 3.74 grains. It is probable that in each case it was very much less.

When sodium salicylate was used, the amount of salicyl bodies excreted in the urine, after the employment of ordinary currents, was so small that it could not be estimated with any degree of accuracy. Using a current rising to 170 milliampères during a thirty minute period, the total amount of salicyl bodies found in the urine was only 9 milligrams. It is of interest to note that this result coincides with that of Inchley, using a cat as the subject of experiment. (4) He found only very small amounts of salicyl bodies in the urine, and comments on the fact that the salicylic ion is not carried through the skin to the extent that enthusiastic writers on the subject would lead one to suppose.

Objection may be taken to this process of reasoning, for it may be argued that the amount of any ion excreted in the urine gives no true indication of the quantity passed through the skin. The objection has really very little weight, but it can easily be overcome by considering the results when pilocarpine nitrate and atropine sulphate were used. The following are records of typical experiments.

Experiment 20.

Subject JT.

Positive Electrode 3" x 2" on left thigh. Pad soaked in 1% solution of pilocarpine nitrate.

Negative Electrode 5" x 3" on right thigh. Pad soaked in normal saline solution.

<u>Time.</u>	<u>Current.</u>	<u>Remarks.</u>
3.34 p.m. . . .	1 milliampère	
3.35 p.m.12 milliampères	
3.37 p.m.15 do.	
3.38 p.m.23 do.	
3.39 p.m.33 do.	
3.41 p.m.38 do.	
3.43 p.m.42 do.	
3.45 p.m.43 do.	Slight salivation.
3.47 p.m.45 do.	Feeling of increased warmth.
3.48 p.m.46 do.	Sweating begins.
3.50 p.m.47 do.	Salivation & sweating distinct.
3.52 p.m.48 do.	Salivation & sweating distinct.
3.54 p.m.50 do.	Salivation & sweating distinct.

Current stopped. Marked reddening of the skin under electrodes.

3.55 p.m. - Far vision slightly blurred - Pupils reacted to light.

3.58 p.m. - More blurring of far vision.

5.50 p.m. - Salivation and sweating practically ceased. Far vision is now normal.

Experiment 24.Subject: D.C.

Positive electrode 3" x 2" on anterior aspect of right forearm. Pad soaked in 1% solution of atropine sulphate.

Negative electrode 5" x 3" on anterior aspect of left forearm. Pad soaked in normal saline solution.

<u>Time.</u>	<u>Current.</u>	<u>Remarks.</u>
4.12 p.m.	1 milliampère	Pulse 78 per minute.
4.13 p.m.	3 milliampères	
4.16 p.m.	5 "	
4.20 p.m.	5 "	Flushing of face. Pulse 80 per minute.
4.30 p.m.	5 "	Flushing of face. Pulse 92 per minute.
4.35 p.m.	5 "	Dryness of mouth. Pulse 126 per minute.
4.36 p.m.	5 "	Feeling of fulness in head. Pulse 135 per minute and of low tension.
4.42 p.m.	5 "	Disturbance of near vision. Mouth very dry. Pulse 140 per minute.

Current stopped. Skin under electrodes very red and tender.

4.44 p.m.	Pulse 126.	
5. "	Pulse 120.	Very marked dryness of mouth and throat. Pupils dilated and glancing. Eyes cannot accommodate for near vision.

At 12 noon the next day:- Vision for near objects still affected slightly.

Four days after this experiment the skin which had been under the positive electrode was still red, and showed a tendency to peel.

From these experiments it will be seen that, with pilocarpine nitrate, using a current rising to 50 milliampères over a period of twenty minutes, there was produced in the subject of the experiment salivation, sweating, and slight disturbance of vision. All these effects could be produced on the subject, and to a slightly greater degree, by injecting 1/5th grain of pilocarpine nitrate hypodermically. In the case of atropine sulphate, it was not considered advisable to use large currents because of the poisonous effects of very small quantities of that drug. But, using a current of 5 milliampères for thirty minutes resulted in sufficient atropine being introduced to produce a rapid pulse (140 per minute), marked dryness of the mouth and throat, wide dilatation of the pupils, and paralysis of accommodation lasting for 20 hours. All these symptoms and signs could be produced on the same subject by injecting hypodermically 1/30th of a grain of atropine sulphate. In these experiments, the amount of the drug introduced into the body was estimated, not from the quantity excreted, but by its physiological action, and in each case it will be observed that this amount was small. It will be noted, further, that the action of/

of these drugs, when administered electrically, differs in no way from their action when given hypodermically.

While the salient feature of the experiments described is that the amount of drug introduced is very small, there is another feature which is of considerable importance, and which bears on the question of local concentration. It will be seen that, in "ionizing" a patient with potassium iodide, it was possible to demonstrate iodine in the saliva collected during the first fifteen minutes of the period of treatment. Again, in the case of pilocarpine nitrate, salivation made its appearance twelve minutes after the current was started; practically the same time as after slow hypodermic injection of the drug. Similarly, the effect of atropine was noticed eight minutes after the commencement of the experiment. Where, then, is the evidence of local concentration? It must be quite obvious that, as soon as the ion is carried through the skin, it is whisked off in the blood stream, and that therefore no local concentration ever takes place. Otherwise, how is it possible to explain its appearance so quickly in parts of the body so far removed from the seat of entry, and in such amounts as to produce its physiological action on these parts?

The/

The next question to consider is the depth of penetration of the ions. In man, it is difficult to produce any experimental evidence to bear on this question, but the discussion in the previous paragraph throws some light upon it. If the ions introduced through the skin appear so rapidly in distant parts of the body, it must be obvious that they are set free from their function of carrying the electric current as soon as they pass through the skin. That they penetrate deeply is therefore unlikely. It should be noted further that, until it passes the barrier of the skin, the current can be conveyed only by the ions of the solutions underneath the electrodes. But, as soon as this barrier is passed, the current will be carried by the enormously greater numbers of the ions of the body fluids, and the relatively much smaller number of ions introduced will be relieved of their task. That fact renders even more unlikely deep penetration of the foreign ions introduced. In most of the text-books on ionic medication, several experiments are related to prove that ions penetrate deeply. These experiments are, however, useless for this purpose. They only show that it is possible for considerable penetration to take place in dead or isolated/

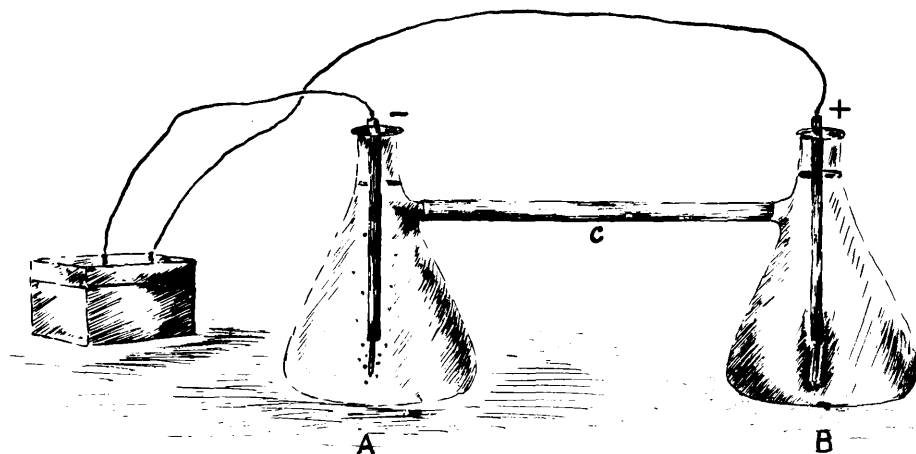
isolated tissue and in parchment. In the living body there is quite a different state of affairs.

In the few cases where attempts have been made to show deep penetration of ions in man, they have signally failed. Finzi claimed that he had been able to obtain penetration of the ferri-cyanide ion into the knee-joint of a monkey. ⁽³⁾ Grave doubt has to be cast on this experiment, because of the possibility of the ferri-cyanide ion found in the joint being carried there by diffusion after the animal was killed. Finally, Inchley, repeating this experiment on a rabbit, found that there was no deeper penetration into the joint than could be obtained by simple injection of the drug under the skin covering the joint. ⁽⁴⁾ The whole weight of experimental evidence goes to show that the penetration of ions is not deeper than the subcutaneous tissue.

It would appear, therefore, that the following statements are true:

- (1) The amount of any drug introduced in an ionic state into the body by currents which can be used therapeutically, is very small.
- (2) The drug, as soon as it is carried through the skin, is swept away in the blood stream and produces its specific effect on the system generally. There is therefore no local concentration.
- (3) There is no evidence of deep penetration. On the contrary, in animals the experimental evidence is all against the drug penetrating further than the subcutaneous tissue. In man, it seems to be quite clear that a similar state of affairs exists.

We have now to examine the second part of the definition - namely, that in the process of ionization, chemical changes are set up in the tissues, and that the resulting modification of the chemical composition of the body produces a therapeutical effect. That statement, as will be obvious, has really nothing to do with medication, but is a claim for the action of a constant current of electricity. An example of this is the claim that there is a "lytic" action underneath the negative electrode, and that this "lytic" action affects principally exudates and recently formed bands of lowly organised tissue. (8) It is quite true that, when an electric current is passing through the body fluids, there will be movement of anions towards the positive pole and of kations towards the negative pole. But it does not follow that any chemical changes are set up in the tissues between the poles. Faraday demonstrated long ago that, when a current is passed through a solution of an electrolyte, no apparent change occurs in the fluid, and that chemical changes take place only at electrodes. The truth of this can be shown beautifully by the following experiment.



A and B are conical flasks connected by a piece of glasstubing, C. A, B, and C, are filled with a solution of potassium iodide and into A is put the negative electrode and into B the positive electrode. When the electric current flows through the solution, the iodine ions begin to move towards the positive pole and the potassium ions to the negative pole. When the iodine ions reach the positive pole, they gave up their electrical charges and, becoming iodine atoms, can be seen streaming away from the pole. If starch solution is present in both flasks and in the connecting tube, it is only the solution in flask B which becomes blue, and, at first, only around the electrode.

When the potassium ions reach the negative pole, they give up their electrical charges, become potassium atoms, and combine with water to form a caustic alkali. No chemical change takes place in the connecting tube C.

In ionic medication, therefore, the potassium or sodium ion will give up its electrical charge at the negative/

negative electrode, become a potassium or sodium atom, and, combining with water to form a caustic alkali, will act on the tissue in contact with the electrode, - that is, the skin. To suggest that any ion of the body fluids can produce a "lytic" action on the tissues underneath the skin before it has reached an electrode is manifestly absurd. There can be no "lytic" action except on the skin underneath the negative electrode. Further, it is difficult to conceive, and there is no evidence to suggest, that the mere migration of an ion, which is normally a constituent of the body fluid, to another part of the fluid, can cause any chemical change which would have a therapeutical effect.

Certain authorities, recognising the difficulty of explaining their therapeutical results on the basis of chemical changes in the tissues, have claimed that it is the movement of the ions which is the important factor. They suggest that there is a bombardment of millions of tissue ions on the affected part, and that this "ionic massage" may be of benefit. In the present state of our knowledge of the forces bound up in matter, it is hardly worth while discussing such a hypothesis. Two facts, however, are, from the purely mechanical point of view/

view, worth mentioning: (1) Though the number of ions set in motion must be enormous, the total mass of ions acting on any part is, as I have shown, very small; (2) the greatest migration velocity of any ion, - the hydrogen ion, - with a potential gradient of one volt per centimeter⁽⁹⁾ is only 0.0032 c.m. a second. It is difficult to see how a "bombardment" carried on by a small mass moving so slowly, can have much effect. It can be in no way comparable to massage at the hands of a well trained and intelligent expert.

It will now be clear that no real and permanent benefit can reasonably be expected in the treatment of rheumatoid arthritis by ionization. For iodides and salicylates can be administered by the mouth in doses sufficient to produce a continuous concentration of iodine or salicylic ions in any part of the body, far greater than can possibly be produced by ionization. Further, very much greater quantities of salicylic ions can be passed locally through the skin by applying methyl salicylate, and much greater quantities of iodine ions by applying iothion (di-iodhydroxypropan), an oily liquid having the chemical formula $\text{CH}_2\text{I}, \text{CHOH}, \text{CH}_2\text{I}$. Yet none of these methods of treatment is of the slightest use in rheumatoid arthritis. Again, it has been shown quite/

quite clearly, that the passage of an electric current through the body can produce no "lytic" effect on the new formed fibrous tissue under the skin. It is therefore useless to expect that this form of therapy will be of value in increasing the mobility of an ankylosed joint.

There was, however, as has been indicated, a temporary relief of pain following the process of ionization. It would be of interest to enquire as to the particular factor to which this is due. It has been shown conclusively that it is not due to the specific action of any ion. It must be due, therefore, to the galvanic current. Two different factors will thus require to be considered: (1) the current passing between the electrodes and (2) the action of the current at the electrodes. Turrell suggests that the action of the current passing between the electrodes has the effect of generating an appreciable increase of temperature in the tissues under the skin, and to this increase of temperature he ascribes the beneficial results which follow. ⁽¹⁰⁾ It is true that Joule's law applies to electrolytes, and that, therefore, all the energy of the current spent when traversing the electrolyte is used simply in the production of heat, and/

and not in causing chemical changes. But the most of the heat produced in this way is on the skin, where the resistance to the current is greatest, while that produced in the tissues underneath the skin is small, is slowly evolved, and is dissipated quickly throughout the body. The experiments Turrell brought forward in support of his view, merely showed an increase of the surface temperature of the limb to which the electrodes were applied, and that could quite easily be caused by dilatation of the cutaneous vessels. He admitted further that the more powerful heat-producing action of the diathermy current was not nearly so good as the ordinary galvanic current. His attempt to explain this obvious difficulty is not convincing.

It has to be admitted that the passage of an electric current through the tissues will have a general stimulating effect on them, which may be of some benefit. But to me it seems clear that it is the action of the current at the electrodes which is the chief factor in the relief of pain. In every case treated in this way, there is some irritation of the skin under the pads, which is evident from the sensations of the patient and from the marked hyperaemia of the skin seen when the pads are removed. This irritation is produced partly by the products of the electrolysis of the substances in the/

the solution employed to moisten the pads, and partly by the heating effect of the current on the skin where the resistance to its flow is greatest. In some cases it is sufficient to cause a tender part of the skin to remain red for several days. Nor is it necessary to use very large currents to produce this irritation; for, while the amount of irritation varies directly as the amount of current, it varies inversely as the size of the electrode. It is possible, therefore, to get a considerable amount of irritation, even with small currents, if small electrodes be used. Here, then, is the ordinary counter-irritant action. It is difficult to account for the manner in which counter-irritants produce their beneficial effect, but that they do relieve deep-seated pain, at any rate temporarily, is undeniable. It seems to me, therefore, that while it is possible that the interpolar current has some slight general stimulating effect on the tissues underneath the skin, the great factor in producing temporary relief of pain is the counter-irritant action on the skin underneath the electrodes.

So far, only the medical aspect of ionization has been discussed. As far as its surgical application is concerned, those who practise this method in the treatment of many varieties of septic sinuses, lupus nodules, and septic diseases of the vagina and uterus, claim/

claim that the results obtained are excellent. I have had no practical experience of its use in these conditions, and can therefore offer no opinion as to its therapeutical efficacy. But, as far as the theory is concerned, attention may be drawn to the following facts. Zinc is the ion which is used in practically all cases. A number of electro-therapeutists use simply a zinc probe, which is put into a sinus, or a zinc sound which is passed into the uterus, the metal forming in each case the positive electrode. When a current is passed, the metal has a destructive action on any tissues with which it is in contact. The chlorine ions of the tissues move to the zinc electrode, give up their electrical charges, and the chlorine atoms thus set free combine with the zinc of the electrode to form nascent zinc chloride. This substance will produce its well recognised caustic action on the tissues, and its antiseptic action against any organisms which are present. But that is not "ionic medication." It is simply a method of producing nascent zinc chloride electrolytically in a place where its action may be of value. In the same way, when an electric current is passed through a zinc rod placed in a septic cavity filled with a solution of zinc sulphate, there is constantly being produced, electrolytically, nascent zinc sulphate by the sulphuric ions of the solution moving to the zinc electrode, giving up their electrical charges/

charges, and the atoms thus formed combining with the metal. In addition, the irritation of the tissues under the electrode causes an increased blood supply to the part, which, in the chronic conditions in which ionization is employed, will be of some benefit. That there is any deep penetration of zinc ions is impossible, and indeed undesirable, in view of the powerful coagulating effect which zinc ions have on the albumen of the tissues. It appears to be entirely unnecessary to invoke the conception of the deep penetration of zinc ions in order to explain the therapeutic results which follow ionization. The combined action of the compounds formed electrolytically at the zinc electrode, and the irritation of the tissues, is quite sufficient to produce all the effects which have been described.

In conclusion, it will be obvious that, if the argument presented above is accurate, there is very little scientific basis for the theory of ionic medication, and - as far, at any rate, as the medical aspect is concerned, - for the practice thereof. To those who strongly support this theory, I may appear guilty of an excess of zeal in attempting to undermine their hypothesis. In defence, I can only draw their attention to the words of Claude Bernard: "In science, the word criticism is not synonymous with the word disparagement; to criticise means to seek the truth by distinguishing what is true from what is false."

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