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THE TREATMENT OF INFECTIVE ARTHRITIS WITH SPECIAL REFERENCE TO HYPERTHERMIA

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The term, infective arthritis, is applied to a group of diseases in which there are inflammatory changes in one or more joints of the body, known to be, or believed to be, due to a systemic infecting agent. In some of these the specific infecting agent is known; in others it is unknown or of a doubtful nature.

The material presented in this study is not a representative cross-section of such joint infections as they occur in the ordinary population or even among the personnel of the Armed Forces. Our work is concerned with the diagnosis and treatment of the venereal diseases and, as might be expected, patients with arthritis who are sent to us for treatment or who are found by us in the routine of ordinary practice, are those with gonorrhoea, those who have a history of past gonorrhoea or those who present evidence of some other infection of the genito-urinary tract. Yet there were cases in our series in which the evidence of genital infection was obtained only by specialized examination, and which in other hands might certainly have received the diagnostic label, "rheumatoid arthritis". In undertaking the treatment of such patients, we were fortunate in that many of them came under our care earlier in the course of the disease than might be expected in civil life, in which the premium on absolute physical fitness is less and force of economic circumstances may delay the application of in-patient treatment.

Rheumatoid arthritis

The subject of the disease, or group of diseases, which is known as rheumatoid arthritis and by other names, is not one upon which we can claim expert knowledge, and is therefore uncertain ground upon which we are unwilling to linger. It is, however, a subject which touches the fringe of venereology, leaving a "no man's land" of some doubt and difficulty. Study of some of the recent literature of the subject does little to clarify the problem. Sclater has analysed the case records of 388 cases of rheumatoid arthritis which occurred in Scotland. He gives the criteria on which the diagnosis was made as follows.

(1) The presence of persistent swelling of the periarticular tissues in the region of more than one joint.
(2) The involvement, either primarily or subsequently, of the wrist, metacarpophalangeal joints, or interphalangeal joints.
(3) The presence of muscular wasting.
(4) Radiological evidence compatible with a diagnosis of rheumatoid arthritis.
(5) The absence of evidence that the arthritis is specific (for example, tuberculous or gonococcal) in origin.

Concerning the first point, the polyarticular nature of the disease, Sclater himself states that the disease may remain monarticular for some months before other joints become affected. On the second point, that wrists or hands are involved either primarily or subsequently, in his own cases the knee joint was the first to be affected in 21 per cent of the cases as compared with involvement of the fingers in 35 per cent, of wrists in 13 per cent, feet in 11 per cent and ankles in

* An address to the Medical Society for the Study of Venereal Diseases, 26th May 1945.
10 per cent. On the other hand, Fingerman and Andrus, in a postmortem study of 61 cases of rheumatoid arthritis, found involvement of knees in 42 cases, hands in 34 cases, feet in 20 cases and ankles in 15 cases. On the third point, the rapid occurrence of muscular wasting, both local and general, is also a characteristic feature of gonorrhoeal arthritis. With regard to the fourth, the radiological picture, here again the evidence is inconclusive and the words of Camp may be held to reflect the general indecision; he states that "the roentgenologist cannot differentiate the atrophic arthritis seen in some cases of mild but moderately advanced gonorrhoeal arthritis from the atrophic arthritis of infectious (p无意)ferative or rheumatoid) arthritis". Sclater's final criterion, that of absence of evidence of a specific infection such as gonorrhoea, will carry little weight unless an expert and systematic search for such infection is carried out in all cases.

Even the commonly accepted clinical view that rheumatoid arthritis is primarily a disease of young women does not always stand up to the criticism of statistical analysis. Of Sclater's cases, 30.5 per cent were males; in females he found the incidence of the disease between the ages of 55 and 64 years to be almost as great as in either of the age periods, 15-24 or 25-34 years. McCrae, of the Johns Hopkins Hospital, found equal distribution of the sexes in 110 cases.

This discussion could be prolonged, but as it is very controversial and in the main irrelevant to the purposes of this paper, there is no intention to pursue it. It may be concluded with the statement of a personal conviction that, in the diagnosis of cases of infective arthritis of obscure origin, there is no justification for failure to exclude the presence of genital infection by means of full and systematic examination and tests. The fact is that this precaution is often disregarded owing to ignorance on the part of the physician, to the social status of the patient or to a perverted sense of chivalry.

The diagnosis of gonorrhoeal arthritis

The diagnostic methods by which the presence of genital infections may be established have been reviewed by one of us (King) and are too well known to require detailed emphasis. Reference may be made again to certain points which are often neglected. The patient's history is apt to be unreliable but may be given in good faith. The symptoms of gonorrhoea or other genital infection may be so slight in the female, and even in the male, that they fail to attract the patient's attention. In cases of doubt both a smear taken before the first morning micturition and the first morning specimen of urine should always be examined. Harkness has again drawn attention to the value of these simple tests in the diagnosis of gonococcal arthritis, and the importance of them is difficult to overemphasize. First-class standards of technique in cultivation of the gonococcus and in the complement fixation test for gonorrhoea are vital to such investigations.

Harkness, who is very sceptical of the value of the complement fixation test in its general application, states that the test was positive in 77 per cent of his 336 cases of gonococcal arthritis. Culp applied the test in 100 of his 200 cases of gonorrhoeal arthritis and found that in 90 of them it was positive. Orpwood Price and King investigated 14 cases of joint, connective tissue and uveal tract infections in which there was no prima facie evidence of gonorrhoeal infection, but in 10 of which there was a history of past gonorrhoeal infection. In 5 of these, vesiculo-prostatic cultures grew the gonococcus and the complement fixation test for gonorrhoea was positive; in 8 the serum test was positive and the culture was negative, and in one the culture was positive and the serum was negative. All therefore showed direct or indirect evidence of gonorrhoeal infection.

### Table 1—Aetiological Classification of Cases of Infective Arthritis

<table>
<thead>
<tr>
<th>Designation of group</th>
<th>Basis of classification</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Gonococcal infection</td>
<td>65</td>
</tr>
<tr>
<td>B</td>
<td>Past gonorrhoea; no present evidence of gonococci</td>
<td>48</td>
</tr>
<tr>
<td>C</td>
<td>No past or present evidence of gonococci</td>
<td>65</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>...</strong></td>
<td><strong>178</strong></td>
</tr>
</tbody>
</table>

...
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Analysis of cases

The present series consists of cases treated during the four-year period from March 1940 to March 1944. Numerous cases of arthritis have passed through our hands since that time. It was part of our purpose, however, to try to assess ultimate standards of fitness as well as immediate response to treatment, and it was therefore decided to set this arbitrary limit of time to the scope of the report.

There were 178 patients of whom 174 were men and 4 were women. These were divided into three groups: the first (group A), 65 in number, in which gonococci were found in the secretions; the second (group B), 48 in number, without present evidence of gonococci in the secretions but with the history of past gonorrhoea; and the third (group C), 65 in number, without evidence of present or past gonococcal infection. In the last group 14 patients gave the history of a previous attack of non-specific urethritis and one of non-specific cervicitis. This classification is shown in Table 1.

Most of the cases in the second and third groups showed some evidence of the presence of infection of the genito-urinary tract, such as urethral discharge, pyuria or excess of leucocytes in the prostatic secretion. Such evidence was present in 45 cases out of 48 in group B and in 60 cases out of 65 in group C.

It will be noted from Table 2 that the majority of patients with gonococcal arthritis were in the age group 20-24 and 25-29, but that in the case of non-specific metastatic infections there were rather more patients in the fourth decade of life.

Table 3 shows the frequency with which individual joints were involved and indicates the number of cases in each group in which the infection was restricted to one joint. There were 29 cases of monarticular infection, fairly evenly distributed between the three groups. In 142 cases the infection was polyarticular. In the remaining 7 cases the infective condition was limited to soft tissues. A number of cases with arthritis showed involvement of soft tissues also. The instances in which the plantar fasciae were involved are included in the group labelled "Heels." In Table 3 special reference is made to cases which showed characteristic involvement of the Achilles tendon (tendo calcaneus) and to one case of sciatica. The knee joints were affected most commonly and next the feet and ankles. There appeared to be no significant difference of involvement of particular joints in the gonococcal and non-specific cases. Keratoderma blennorrhagica and circinate balanitis occurred in all groups but were more common in the proved gonococcal cases. The two conditions were present together in some instances: 5 in group A, 2 in group B and 5 in group C.

Table 4 is included in order to illustrate some interesting points regarding the incidence of infection in the joints most frequently involved. In all groups both knees were more commonly affected than was one or the other knee, and when one knee was involved it was more commonly the left. In the case of the ankles there was less consistency about the distribution of infection. In arthritis of the
feet involvement of the metatarsophalangeal joints was very characteristic and by far the most common finding.

Methods of treatment

The opinions here expressed on the value of the less radical forms of treatment, such as urethral irrigations and the administration of sulphonamides, are based on impressions and have not the support of figures. Many patients were transferred to us after several methods of treatment had been tried, and in our own cases it was clearly the correct policy, from the patient’s point of view, to use more drastic methods of treatment if the less drastic methods were not immediately successful. Indeed, we have come to regard the more severe forms of infective arthritis as emergency conditions to be treated by emergency measures. Too often the persistence of symptoms indicates the presence of progressive damage to the joints, and sometimes the damage is far more serious than the severity of the symptoms would suggest. Almost all our cases, therefore, were treated by a

<table>
<thead>
<tr>
<th>JOINTS AFFECTED (171 cases)</th>
<th>POLYARTICULAR (142 cases)</th>
<th>MONARTICULAR (29 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Knees</td>
<td>44</td>
<td>24</td>
</tr>
<tr>
<td>Feet</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Ankles</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Shoulders</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Wrists</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Heels</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Elbows</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Toes</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Spine</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fingers</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hands</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Sacro-iliac joint</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hips</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Sterno-clavicular joint</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Acromio-clavicular joint</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Temporo-maxillary joint</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Ribs</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONCOMITANT AFFECTION OF SOFT TISSUES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendo calcaneus affected</td>
</tr>
<tr>
<td>Sciatica</td>
</tr>
<tr>
<td>Iritis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Keratodermia blennorrhagica</td>
</tr>
<tr>
<td>Balanitis cirrhinata</td>
</tr>
</tbody>
</table>

*Present without arthritis in 7 cases

multiplicity of methods. There are, however, two sharply divided groups: (1) those treated with hyperpyrexia induced by physical means, henceforward in this paper briefly to be described as hyperthermy (130 in number); (2) those in whom the most radical treatment gave took the form of one or more injections of intravenous anti-typhoid-paratyphoid (T.A.B.) vaccine (48 in number).

An adequate comparison between these two groups is not possible, unfortunately, because the latter group comprised our own patients treated by us from the
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beginning of the metastatic infection, and the cases were, in a considerable proportion, of slight or moderate severity. On the other hand, most of the patients treated with hyperthermy represented the failures of other treatments (including intravenous vaccine) and had been transferred to us weeks or even months after the onset of metastatic infection. In some of these cases severe and irreparable joint damage had already occurred; consequently the aim in treatment was to

limit further progression and to give the patient the best chance of returning to civil life as a useful citizen. In discussing the results obtained with hyperthermy, this should be regarded as a preliminary report. Many of our patients were treated in the early days of inexperience when there were sometimes grievous faults in both judgment and technique. For this reason it is probable that results obtained at a later date will prove to be superior.

The assessment of the results of treatment in conditions of this kind is particularly difficult. The variations in scope and intensity of clinical manifestations are very great indeed, and depend upon two very variable factors, namely, the virulence of the infection and the reactive powers of the patient. Add to this variation the uncertainty as to causation in many cases and the known fact that patients with gonococcal and other forms of arthritis sometimes recover completely without treatment of any kind, and it is then clear that assessment is prone to become a matter of opinion based on an aggregate of impressions. In the present instance we have tried to improve our basis of assessment by attempting to gauge the present degrees of fitness and capacity of individual patients, 1–5 years after the completion of treatment. This has involved an arduous and complicated system of follow-up, which would probably be impossible in civil life and has its difficulties and failures under war-time conditions in the armed Forces. Each man has been followed to his present station through the appropriate Records Office, and the Medical Officer of his unit has been asked for a report on his medical category and present condition. Those who have returned to civil life have been traced and asked for a personal report. Replies from the latter source have varied in their value. Some patients have expressed themselves cautiously, perhaps with an eye to some future possibility that the matter of pension might be reopened; others have given detailed and helpful information. In addition to British Army and Royal Air Force personnel, some of whom, at the time of writing, are serving in distant theatres of war, patients treated for arthritis included naval ratings, Australians, New Zealanders, Canadians, United States Army personnel and some members of European Allied Nations. It is not surprising, therefore, that there are some gaps in our information.

General measures of treatment

Patients should be given absolute rest in bed in all cases, whether there is fever or not, and whether or not the weight-bearing joints are involved. The infection is systemic and movements may aid dissemination and precipitate further complications. In severe cases sedatives are required, especially at night, and should
be given unstintingly in the period of delay before radical treatment is instituted. Acutely infected joints should be protected from the weight of the bedclothes by bed-crades or similar devices. The local application of heat, by means of kaolin or Antiphlogistine poultics or of a radiant heat cradle, will often give temporary relief. Counter-irritation, by the application of 5 per cent iodine, Scott’s Dressing (compound mercury ointment) or some other local irritant, to affected joints may be of assistance sometimes. Splinting or the application of plaster should be avoided if possible owing to the danger of fibrous ankylosis. If splints are applied as emergency relief measures, they should be retained in use for as short a time as possible. All such measures should be used temporarily only until more radical specific therapy can be undertaken. Certain specific general methods of treatment will be considered independently.

Urethral irrigation

This form of treatment has fallen into general disuse, if not discredit, with the advent of newer remedies. Nevertheless it was the standard treatment for gonorrhoea and urethritis for many years and in careful hands produced many good results. A number of experts who practised urethrovessical irrigations— and gave them personally—in the days before sulphonamides were available, claim that it was almost unknown for metastatic lesions to develop in patients under their care; there is reason to believe that this treatment is a good preventive measure if carried out skilfully. Weak and warm potassium permanganate solution still seems to be the irrigating fluid of choice, and the procedure remains an excellent secondary method of elimination of a recalcitrant focus of urethral infection. Skilful and careful technique is, however, essential. Many metastatic infections have been precipitated by trauma to the posterior urethra, resulting from unskilful urethrovessical irrigations.

Prostatic massage

In most cases of metastatic arthritis evidence can be found of chronic infection of the prostate gland and seminal vesicles. It is probably unwise to examine these organs in the acute or subacute stages of metastatic infection, for even minor trauma may cause extension of the disease. In the stage of recovery, drainage of the glands may be promoted and benefit may result from gentle digital massage once weekly, especially if the symptoms suggest ‘‘pocketing’’ of infection or if microscopical examination of the prostatic fluid shows clumping of the leucocytes. There is no doubt that harm results from over-treatment of these glands, and digital massage of the prostate should always be used with restraint. Culp treated 22 cases of gonococcal arthritis, of which 13 had reached the chronic stage, with prostatic massage, but without obvious benefit.

Sulphonamides

Evidence on the value of the sulphonamides in the treatment of metastatic arthritis is conflicting. Early reports on the use of sulphanilamide in the treatment of gonococcal arthritis claimed results which varied from the satisfactory to the spectacular. The drug was generally regarded as a potent agent in preventing metastatic spread of infection and in treating metastasis when established.

Colston, Dees and Harrill claimed excellent results in 10 cases. Culp treated 22 patients with gonorrhoeal arthritis with sulphanilamide and claimed that about two-thirds of the number were cured or markedly improved; there were no complete failures. An American committee under the chairmanship of Jordan, in a report entitled ‘‘Primer on Arthritis’’, regarded the sulphonamide compounds as specific agents in the treatment of gonococcal arthritis, causing decided improvement in most cases within 24–72 hours.

Harkness stated that the unaided use of the sulphonamides, in many cases of synovitis and arthritis due to gonorrhoea, gave results which were no better than those obtained with the orthodox treatment of the past. In his cases there was no evidence that treatment with sulphonamides prevented extension of the infection to other joints.

In 1942 one of us (King) stated that the results obtained by the administration of sulphonamides in metastatic cases had been unimpressive. Of 61 cases under review at that time all but 6 had received one or more courses of sulphapyridine, the amount given varying
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from 18 to 49 grammes and the period of administration varying from 3 to 14 days; 8 patients had received a course of sulphamethaizone in addition. There was no very notable improvement in any of these cases, and when improvement did occur, the extent to which sulphonamide administration contributed to this was difficult to assess.

Since that time other sulphonamides, such as sulphathiazole and sulphadiazine, have become freely available and have been used by us in the treatment of cases of arthritis. Those patients who were transferred to us almost invariably had had considerable doses of these compounds before transfer. This further experience has given us no cause to revise our earlier opinion: the sulphonamides alone are not regarded as effective agents in the treatment of infective arthritis.

Sulphonamides combined with pyretotherapy

The question as to whether or not the combination of fever therapy with sulphonamides gives better results in the treatment of arthritis than does fever therapy alone is a more difficult one to answer. The results which we obtained in the treatment of sulphonamide-resistant gonococcal urethritis from the combination of hyperthermy and sulphonamides were greatly superior to those obtained with hyperthermy alone, and this fact has led us to use this combination in the majority of our cases of arthritis. Of the 130 patients treated with hyperthermy, 34 received 6 grammes of sulphathiazole and 60 received 8 grammes during the 12 or 16 hours preceding the beginning of the fever sessions.

Nicol found that intravenous T.A.B. vaccine seemed to give the best results in cases of arthritis occurring during or after a course of sulphapyridine. Simpson, Rose and Kendall first suggested in 1941 the combination of fever with sulphonamides in the treatment of resistant gonorrhoea, and they probably have more experience than has anybody else in the various modifications of this procedure. So far as we can trace, however, they have expressed no views as to the value of combined therapy in the treatment of gonococcal arthritis.

There is no doubt that hyperthermy, with or without chemotherapy, produces good results in the treatment of gonococcal arthritis; but the standards of assessment are too uncertain and our cases without adjuvant chemotherapy are too few for it to be possible to express a firm opinion on the possible advantages of combining fever with sulphonamides. To state an impression, it has seemed that little was gained by adding sulphonamides to hyperthermy in the treatment of gonococcal or non-specific infective arthritis, so far as the joint infections were concerned. Nevertheless, there has been evidence of beneficial effect on the accompanying infection of the genital tract, and the use of sulphonamide therapy has been continued for that reason.

Penicillin

The cases under review were treated before penicillin was available, and no assessment of the value of this substance in the treatment of arthritis can be attempted. It is, however, worth while to record that in recent months all the cases of resistant arthritis transferred to us for hyperthermy had received generous amounts of penicillin by intra-muscular injection (in addition to other treatments) before transfer. Some patients had received more than 1,000,000 Oxford units. As the result of this treatment some had had temporary improvement in symptoms, but there appeared to be no lasting benefit. It is hoped that detailed facts and figures can be given in a subsequent report.

Pyrexia produced by intravenous vaccine therapy (T.A.B. vaccine)

Of the methods for the treatment of acute and subacute infective arthritis which are easily available and easily applied, this has been by far the most effective. Many pyrogenic agents have been used for this purpose and most clinicians have their own personal choice. In the past we have used with success commercial vaccines made from the Ducrey bacillus and from Bacillus coli.

In the present series T.A.B. vaccine has been used because it was effective and available. Most of the cases were treated by the "divided dose" method of injection first introduced by Nelson in 1931. The technique described by Nicol
in 1942 continues to give satisfactory results. We give 25,000,000 organisms intravenously followed by a further 25,000,000 after an interval of 4 hours, by which time the temperature has begun to rise as the result of the first injection. By this method a relatively small dose of organisms produces a satisfactory and prolonged level of pyrexia without severe toxic effects. The temperature level varies from 102° to 104° F. and the period of pyrexia at this level is prolonged for 4 hours or more. There are, of course, individual variations and in some cases these levels of temperature are not attained or are exceeded. In the event of relative failure of response, the individual doses are increased; in the event of undue pyrexial response to the first injection, the second injection is withheld.

It should be emphasized that intravenous vaccine therapy, like most other drastic treatments, has its dangers; fatalities have been reported. It is important to be satisfied with the general fitness of the patient, especially as to cardiac and vascular function, before the treatment is applied. Patients who undergo this treatment must be watched carefully and nursed skilfully. The toxic effects, which Nicol has described in full, are not negligible, and the complications (to which some reference is made below) are comparable with those which may follow the more radical procedure of hyperthermy.

We have no experience of Typhoid H. vaccine, as used by Kulchar and Card, nor of the continuous administration of T.A.B. vaccine, introduced by various workers in America and used in the treatment of resistant gonorrhoea by Cronin. With the dosage employed, the latter procedure is probably not without danger.

It is noteworthy that Culp speaks with some enthusiasm of the value of 1 per cent mercurochrome solution, given intravenously, in the treatment of cases of acute and subacute arthritis, most of which were gonorrhoeal in origin. He treated 29 patients of whom 20 were either cured or showed marked improvement. He describes the recovery as remarkable in some cases and states that often one or two injections were followed by complete cures. This treatment is said to have been introduced in 1925 by Young, Hill and Scott and to have enjoyed a considerable vogue for the treatment of arthritis and other conditions. Judging by the description of some of Culp’s cases, the benefit derived was probably due to pyrexial reactions. We have no experience of this treatment, but it would be interesting to have more evidence as to its value and the reasons why it has passed into obscurity.

In 48 of our cases, intravenous T.A.B. vaccine was the only form of pyretotherapy used; these cases are analysed in Table 5, in which are shown the immediate results obtained according to the assessment of the condition of the patients at the time of discharge from hospital. It will be seen that the considerable majority showed full recovery, whereas others showed a measure of recovery which enabled them to return to duty in a lower medical category. Of the 48 patients, only 4 were classed as failures and discharged as unfit for further service.

Table 6 shows the late results in the same 48 cases assessed 1–5 years after treatment was completed. Those who are still serving and those who were discharged as unfit but subsequently recovered may be claimed reasonably as successes of treatment. Thus of the total of 48 cases, in 37 treatment is known to have been successful.

Most of these patients were treated at a time when hyperthermy was not available. They were cases which occurred in the routine of ordinary practice in venereal diseases and were not specially selected because of lack of severity of

### Table 5—IMMEDIATE RESULTS OF T.A.B. VACCINE THERAPY IN 48 CASES

<table>
<thead>
<tr>
<th>Results recorded</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category unchanged ... ...</td>
<td>15</td>
<td>14</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Category reduced ... ...</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Discharged unfit ... ...</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Proportion of full recovery ...</td>
<td>94%</td>
<td>87%</td>
<td>69%</td>
<td>83%</td>
</tr>
</tbody>
</table>
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symptoms. On the other hand, in most of the cases this treatment was applied from the very onset of the metastatic signs and they do not represent, as do those of the hyperthermy group, the results of failure in treatment and of delay in transfer. Of 130 patients treated with hyperthermy, 43 had some intravenous T.A.B. vaccine, given by ourselves or others, before hyperthermy was undertaken. Of these patients, 24 had been treated with T.A.B. vaccine on one occasion, 10 on 2 occasions, 6 on 3 occasions and 3 on more than 3 occasions. It would perhaps be justifiable to regard these as failures of intravenous T.A.B. vaccine therapy, but it is not possible in such cases to set so rigid a boundary between success and failure. To obtain success with this treatment it must be applied early and applied often. The patient must be treated with vigour and boldness and his pyrexial reactions must be made to follow one close upon the other with no more than one or two days' rest between injections. Dosage must, if necessary, be increased to the limit consistent with safety. In the series which we have described the patients were not treated according to any set pattern in frequency and intensity of therapy; rather, the procedure in individual cases was based on observation of day-to-day progress. The results appear to justify the vigour of the methods used.

Hyperthermy

The value of mechanically induced hyperpyrexia in the treatment of gonorrhoeal arthritis is said to have been discovered accidentally by Simpson in 1932 as a result of a fever session given for coexisting syphilis. The early claims for success made by some workers seem to have been based on immediate symptomatic improvement and were preferred in terms more glowing than the tests of time and experience would seem to warrant. The handicap of early overstatement is one from which many valuable treatments have suffered, including the sulphonamide therapy of gonorrhoea and, perhaps, the penicillin therapy of gonorrhoea and of syphilis.

At the Fifth Annual Fever Conference in 1935, Hench and Popp, of the Mayo Clinic, summarized the previous reports on the treatment of gonococcal and chronic infective arthritis by hyperthermy, and also described their own experience.

The 15 reports which Hench and Popp analysed covered most of the early experimental work, in which greatly varying temperatures were used for greatly varying periods of time, and in which numerous different techniques for the induction of fever were employed. Such an analysis has obvious difficulties, but the end result was that in 147 cases of chronic infective (rheumatoid) arthritis treated by these methods there was notable improvement in 35 per cent, whereas 22 out of 24 cases of gonococcal arthritis were markedly or completely relieved.

Their own cases included 16 with gonococcal arthritis; 9 were acute cases and of

### TABLE 6—LATE RESULTS OF T.A.B. VACCINE THERAPY (1–5 YEARS AFTER TREATMENT)

<table>
<thead>
<tr>
<th>Personal history</th>
<th>Military or civil status</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Serving, killed in action, missing, wounded or prisoner of war</td>
<td>Category unchanged</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Category raised</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Category lowered</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Discharged as unfit (6 for other causes)</td>
<td>With subsequent recovery</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Light work only</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Totally incapacitated</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>No details available</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No information</td>
<td>Untraced</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
these 7 were promptly cured or almost cured. Seven patients had chronic gonococcal arthritis and of these 4 were cured or almost cured and an additional 2 were markedly relieved. The combined total was 69 per cent cured or almost cured. The length of time which elapsed before ultimate assessment was not stated. Sixty patients with rheumatoid arthritis were treated and the majority received 4–6 fever sessions of 5 hours at 104°F to 105°F; these were rectal temperatures. Assessment 8–11 weeks later showed that 37 patients felt that they had experienced little or no improvement. Duration of infection had been important in relation to the benefit received; satisfactory improvement occurred in 50 per cent of those whose arthritis was of one year or less in duration as compared to 25 per cent of those who had had arthritis for 2 years.

It is interesting to note that the height of rectal temperature recommended by Hench and Popp in cases of gonococcal arthritis (and used in their series) is from 106°F to 106·8°F or 107°F, whereas the temperature level recommended for non-specific cases is considerably lower. It seems that the early workers in this field were obsessed with the importance of hyperpyrexia as an agent for the direct destruction of the gonococcus; they aimed, therefore, at a level of temperature in the patient which laboratory experiments had shown to be most lethal to the organisms, namely 106–107°F or 106–108°F. In our own early work we maintained such temperatures but later, upon advice, reduced this temperature level to between 105·8°F and 106·2°F. (King, Williams and Nicol), obtaining just as good results and greatly diminishing the incidence of complications. Working on the assumption that fever is likely to be a more effective therapeutic agent at the higher levels, up to the limit of safety, we have used the same temperature levels for non-specific as for gonorrhoeal cases. This procedure, together with the circumstance that most of our cases were seen comparatively early in the course of the disease, probably accounts for the fact that our results in non-specific cases were better than those generally reported.

Methods of application.—In the treatment of gonococcal arthritis, hyperthermy has retained through the years an important and well-merited place, although it is clear from reports on the subject that standards of technique vary greatly and that inexperienced workers in this difficult procedure are prone to describe as therapeutic failures those failures which are in truth due to lack of experience and to faulty technique.

Mann employed a six-hour session of fever at 106·5°F, given after two days of sulphanilamide therapy (total dosage 6·6 grammes). This combined treatment proved to be effective in the treatment of uncomplicated sulphonamide-resistant gonorrhoea but was less effective in the treatment of gonococcal arthritis. His experiment was that complete alleviation or improvement usually ensued, but that within a month relapse usually occurred and, to use his own words, "the arthritis became an atrophic type". It seems probable that more and longer sessions of fever were required.

Trautman treated 129 patients with gonococcal arthritis by giving fever at 106°C–107°F in several five-hour or six-hour sessions, or in two or three sessions of 10 hours each, at 105°–107°F. Of 56 patients in whom arthritis had been present for one month or less and who were adequately treated and observed, 53 showed marked improvement or recovery and 2 were moderately improved; 42 patients had arthritis of 1–6 months' duration and of these 35 showed marked improvement or recovery and one was moderately improved. Of 19 patients with arthritis of duration over 6 months, 14 were markedly improved or recovered and 3 were moderately improved. Of the total of 56 patients, 52 who showed marked improvement or recovery were followed up for 1–5 years; all except 2 had maintained this degree of improvement.

Culp treated 19 cases of gonococcal and non-specific arthritis but only about half the number of patients were cured or markedly improved. Most of these had received only five hours of fever at 106°F and some of them less, which must be regarded as inadequate treatment for such conditions. His complaint of "disagreeable" complications and of death in this series probably indicates an inexperienced technique.

In our own series of 178 cases, 130 patients were treated with hyperthermy. The unit of treatment was 8 hours of fever at 106°F—or, to be quite accurate, within the range of 105·8°–106·2°F.—preceded in most cases by sulphonamide administration as described above. Of these patients, 18 received 3 or more full sessions, 35 received 2 sessions, 65 one session; in 14 cases such a full session was not completed for various reasons.

Immediate results of treatment.—The immediate response to this treatment was
HYPERTERMIA IN INFECTIVE ARTHRITIS

usually very notable. Relief from pain was complete in most cases, although there might be recurrence, but of considerably diminished intensity, after a day or two. It was good policy to warn the patient of this possibility. Relief from muscular spasm was usually immediate and the range of movement of affected joints was increased, sometimes quite remarkably. Swelling diminished and restoration of function was usually progressive. Within a matter of days, even in severe infections, the patient was able and willing to bear weight upon the affected joints and he was soon up and about. This rapid restoration of function

was of great value not only in the promotion of physical recovery but in restoration of morale—a quality which tends to decline with rapidity in the average arthritic. In order to hasten the restoration of function, the services of a skilled masseur were important; even more important was the patient's own contribution to his recovery by the expanding range of his movements and by his restored capacity to bear weight. Inevitably, infected joints had sustained some damage which resulted in functional loss. The extent of such damage depended upon the severity and duration of the infection, and upon it depended the length of convalescence and the extent of ultimate disability.

The decision as to whether or not additional sessions of fever should be given in the individual case was often a difficult one. When signs of activity of infection persisted, the matter was not in doubt and second and third sessions were given. In only 4 cases were more than 3 sessions given. It was not always easy to distinguish the evidence of persistent active infection from that of residual disability. Continuing progress towards recovery was evidence which favoured the latter, but it was not uncommon to find that activity persisted in the most severely affected joint whilst the other joints were making rapid progress to complete recovery.

Undoubtedly some patients were undertreated as the result of errors of judgment or because of natural disinclination to submit patients to further strenuous treatment which might not prove necessary, and of pressure of numbers. It is our experience that whenever this treatment becomes available there are more candidates for it than the available organization is adequate to treat. Recent experience is that the best results are obtained by giving 2–3 eight-hour treatments in all cases of more than moderate severity.

As stated above, 130 patients received this treatment. One died as the result of treatment and is therefore excluded from assessment. Table 7 shows the immediate results obtained, as estimated at the time of discharge from hospital.

Disregarding the 4 cases in which the records were mislaid, it may be seen that 71 out of 125 patients (57 per cent) returned to duty in the same medical category after suitable convalescence. In 21 cases (17 per cent) the medical category was temporarily reduced in anticipation of recovery within 3 months; 33 cases (26 per cent) were regarded as failures and the patients discharged as permanently unfit for service. A subsequent follow-up showed that a good proportion of the unfit made an excellent recovery in civil life in periods varying from 3 to 52 weeks. It will be noted that the proportion of immediate successes obtained in group A, in which the gonococcus was found—30 out of 46, or 65 per cent—was greater than in either group B, with a history of gonorrhoea—17 out of 32, or 53 per cent—or in group C, with presumed non-specific infection—24 out of 47, or 51 per cent. The margin of difference was less in the ultimate assessment.

<table>
<thead>
<tr>
<th>Table 7—IMMEDIATE RESULTS OF HYPERTERMIA IN 129 CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results recorded</td>
</tr>
<tr>
<td>Category unchanged</td>
</tr>
<tr>
<td>Category reduced</td>
</tr>
<tr>
<td>Discharged unfit</td>
</tr>
<tr>
<td>No record available</td>
</tr>
<tr>
<td>Total number of cases</td>
</tr>
</tbody>
</table>
Late results of treatment.—Table 8 shows the late results in the same cases, assessed 1-4 years after treatment was completed.

If we regard those who are still serving and those who made a good recovery in civil life to the point of doing heavy work unhampered by sickness as successes, it will be seen that in 85 out of 118 cases (72 per cent) the treatment was effective. This excludes from assessment the 11 cases in which no information could be obtained. Comparison between groups A, B and C shows that the respective figures for successes were as follows.

- Group A—33 out of 42 (or 78.5 per cent).
- Group B—22 out of 30 (or 73 per cent).
- Group C—30 out of 46 (or 65 per cent).

The cases in the group marked "No details available" have been accepted as failures because they are of individuals known to have been discharged from the Forces. The reasons for discharge are not known, and if it was due to arthritis it is possible that some of them recovered subsequently; therefore the true proportion of successes is probably better than it appears to be at present.

Duration of illness in relation to late results.—It was to be expected that the duration of symptoms up to the time at which treatment was undertaken would have a considerable bearing on the ultimate success of treatment. In order to establish this point, the cases were subdivided into (1) those undergoing treatment within the first month of metastatic complications, (2) those in the period 1-6 months after, and (3) those in whom treatment was delayed for more than 6 months. These results are shown in Table 9. One case in group B is excluded from assessment because insufficient information is available.

Erythrocyte sedimentation rate.—This test proved to be a good rough index of the severity of infection. Very high readings are sometimes found in acute cases, both gonococcal and non-specific. In estimations by the Westergren method before treatment it was found that in group A, 11 cases gave readings of more than 50 millimetres in one hour and 2 of more than 100. In group B, 6 cases gave readings of more than 50 and one of more than 100. In group C, 13 gave readings of more than 50 and one of more than 100.

The impression was gained that cases with unexpectedly low readings in this test gave relatively poor immediate clinical response to hyperthermy. In such cases higher readings were sometimes obtained after the first treatment and these gave promise of better clinical response to subsequent fever sessions. A fall in the erythrocyte sedimentation rate occurred after successful treatment in most cases.

Persistently high positive readings indicated the probability of a residual focus of infection in spite of recovery of joint function; in such cases the test could be taken as evidence that further hyperthermy was required.

Technique of treatment with hyperthermy.—Our present technique is substantially the same as that previously described (King, Williams and Nicol) and no further
HYPERTHERMIA IN INFECTIVE ARTHRITIS

detailed description is required. Mention was then made of the practice of maintaining inhalation of oxygen or of an oxygen and carbon dioxide mixture (5–7 per cent) through an oro-nasal B.L.B. mask throughout the period of treatment, whenever patients could be persuaded to endure the extra discomfort involved. It has been found that some patients who receive the oxygen and carbon dioxide mixture have tachycardia, which is relieved by changing to pure oxygen. We do not account for this but it undoubtedly occurs. Present

<table>
<thead>
<tr>
<th>Duration of symptoms before treatment was given</th>
<th>Results of treatment</th>
<th>Number of cases</th>
<th>Comparison of successful results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
<td>24 6 16</td>
<td>46–78 per cent.</td>
</tr>
<tr>
<td>Up to 1 month</td>
<td>Failure</td>
<td>5 3 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No record</td>
<td>1 1 —</td>
<td></td>
</tr>
<tr>
<td>1–6 months</td>
<td>Success</td>
<td>8 10 12</td>
<td>30–68 per cent.</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>4 3 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No record</td>
<td>5 1 2</td>
<td></td>
</tr>
<tr>
<td>Over 6 months</td>
<td>Success</td>
<td>1 5 2</td>
<td>8–57 per cent.</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>— 2 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No record</td>
<td>1 — —</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>49 31* 48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One case in group B was excluded from assessment owing to insufficient information.

practice is, therefore, to give the mixture during the period of induction of fever and for at least 2 hours after treatment is finished. During the eight-hour period of maintenance the patient breathes pure oxygen unless some factor in his general condition, such as marked fall of systolic blood pressure, necessitates temporary reversion to the oxygen and carbon dioxide mixture.

A further modification in technique is that all patients who undergo this treatment now receive as a routine at least 1,000 cubic centimetres of 5 per cent glucose in physiological saline, intravenously, early in the period of maintenance of fever. This measure has led to a general increase in the fitness and comfort of patients during fever sessions.

It may be added that, in general, patients with arthritis are among the most satisfactory and cooperative who undergo this treatment. This is largely a question of attitude of mind. They see the benefit conferred upon others and they are aware of the potential seriousness of their condition as regards future health and earning capacity. In addition, the relief from symptoms is usually immediate and begins within the first hour of treatment. This is a source of great encouragement and induces an attitude of calm and relaxation which makes for smooth and uneventful treatment. It is probably for this reason that the more severe complications of treatment have always been uncommon among patients with arthritis.

The complications of pyretotherapy

These are fully described in the articles to which reference has been made above (Nicol for T.A.B. therapy; King, Williams and Nicol for hyperthermy).

The major complications of hyperthermy have been almost entirely eliminated as the result of improvements in technique and of greater nursing experience. In all 1,869 treatments have now been given to 1,187 patients since November 1941; the 2 fatalities which occurred in the first few months as the result of inexperience, and which have been reported elsewhere (King, Williams and Nicol), remain the only serious catastrophes. There are still critics who ignore the record of the past three years and condemn this treatment as hazardous. Such criticism is based on ignorance and may be discounted. Nevertheless it is important again
to emphasize that hyperthermy is a major undertaking and the technique difficult
and exacting. It is a procedure which should be confined to fully equipped
hospitals and one which requires the highest standards of performance from all
concerned with it.

One observation on patients treated with intravenous T.A.B. vaccine should
be placed on record. The occurrence of liver damage in some of our patients
who had undergone hyperthermy was noted previously (King, Williams and
Nicol). Later the presence of bile in the urine in some patients who had received
intravenous T.A.B. vaccine was observed, and in a few of these patients slight
clinical jaundice developed. Serial estimations of serum bilirubin were made in
some of these cases before and after pyretotherapy; they showed that transitory
liver damage occurred as the result of the intravenous injection of T.A.B. vaccine,
and was similar to, although on the whole less in intensity than that which
occurred after hyperthermy. Such changes are, perhaps, a concomitant of all
fever reactions, however they are caused.

Summary and discussion

Difficulties of diagnosis in cases of presumed non-specific infective arthritis are
discussed, and reference is made to the importance of specialized examination and
of tests for the exclusion of latent gonococcal infection in such cases. The results
obtained in the treatment of 178 cases of infective arthritis occurring in members
of the armed Forces during the period March 1940—March 1944, have been
analysed, and an attempt has been made to assess, by following up the cases,
the end results after 1–5 years. There were three groups of cases: group A,
in which gonococci were found; group B, in which gonococci were not found
but in which there was a history of past gonorrhoea; group C in which, as far
as could be ascertained, the gonococcus had not been present at any time. There
was little to choose between these groups as regards the particular joints affected
or the respective ages of the patients. As regards response to treatment, the
group with evidence of gonococcal infection showed a greater proportion of
successes than did the non-specific group, but the difference was not as great as
that described by other workers. This is attributed to the fact that our patients,
on the whole, were seen earlier in the course of the disease than would be usual
in civil life, and to the fact that in treating them with hyperthermy high levels of
temperature were used, similar to those employed with gonococcal infections.
Pyretotherapy with intravenous T.A.B. vaccine produced excellent results in all
groups when used early and used vigorously. Of 44 patients treated by this
means and subsequently followed up, in 37 the treatment was successful. The
cases treated with hyperthermy were the failures of other methods of treatment
including, in 43 cases, T.A.B. vaccine. Nevertheless, ultimate success was
obtained in 72 per cent, the percentage for the three groups being 78.5, 73 and
65 respectively. The value of accessory methods of treatment is discussed and
reference is made to the technique and complications of T.A.B. vaccine therapy
and of hyperthermy.

Conclusions

1. In the diagnosis of infective arthritis of obscure origin, specialized examina-
tion and tests are required to establish or exclude the gonococcus as the causative
organism.

2. Pyretotherapy is the treatment of choice in gonococcal arthritis and in
other cases in which genital infection is the presumed cause of metastatic infection.

3. Other methods of treatment are of value in prevention and as accessory
measures.

4. The induction of fever by intravenous injection of T.A.B. vaccine produces
excellent results when used early and used vigorously.

5. Hyperthermy is the treatment of choice for the severe and resistant case.
The earlier this treatment is applied, the better are the results. This treatment is
drastic but, given experience and a careful technique, it is not dangerous.
THE LAUGHLEN TEST

Our thanks are due to Brigadier T. E. Osmond for unfailing support and encouragement, to Colonel W. P. Croker for permission to publish these results, to Mrs. A. J. King for an immense amount of clerical work in the follow-up, and to Major H. J. Bell, M.B.E., R.A.M.C., for extracting information as to the total number of patients treated by hyperthermy.

REFERENCES

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THE PRACTICAL ADVANTAGES OF THE LAUGHLEN TEST FOR THE DIAGNOSIS OF SYPHILIS.*

By G. F. LAUGHLLEN, M.D., C.M.
Pathologist, Toronto East General Hospital, Toronto

The Laughlen test for syphilis was developed as the result of a search for a method better adapted to the requirements of a busy hospital laboratory than were those methods which existed in 1935. The particular need was for one that could be completed in a short time to enable a laboratory to rule out syphilis in a blood donor. None of the methods in use at that time could qualify as acceptable for that purpose. The Wassermann reaction was far too complex for any but the largest laboratories, and tests such as the Kahn presented difficulties of interpretation that required the services of expert serologists. It was true that the city and provincial health laboratories provided a very reliable and efficient service, but this was not entirely adequate, because reports could seldom be secured inside of two or three days and often longer. This service did not supply all the needs of city hospitals, and those outside large centres such as Toronto were having even more difficulty in getting quick reports.

Historical note

The Laughlen test was introduced to the medical profession in August 1935 (Laughlen 1). In the original paper the preparation of the reagents and the technique were described in detail, and a series consisting of approximately 1,000 comparative tests was reported. In a second paper (Laughlen 3) some changes in the preparation of the reagents and in the technique were described and a report was made on a series of over 5,000 comparative tests. A series of 63 tests, done on citrated plasma, was also reported; this report showed that if the citrate concentration were kept at a minimum, plasma could be employed with the

* An address to the Annual Meeting of the Ontario Medical Association, 23rd May 1945.