the electron microscope are striking; fibrils show a regular periodic crossbanding at 640Å intervals, with a characteristic complex of intraperiodic sub-bandings. It seems reasonable to expect that this appearance must be modified if disease is located in the fibril itself. So far, however, convincing changes in the fibrils have been demonstrated only in senile skin and in some rare skin conditions (Tunbridge, et al., 1952). Wolpers (1950) encountered non-banded fibrils in rheumatic nodules, but only in the necrotic areas, and considered that the change followed, rather than preceded, the development of the fibrinoid lesion. Recently, however, Rich, et al. (1953) have described markedly abnormal collagen fibrils occurring in experimentally produced local anaphylic skin lesions of the Arthus type, and have pointed out certain technical difficulties in demonstrating their presence. Electron microscopy may have much more to reveal about the fine structure of collagen in health and disease.

The biochemical approach is increasingly relevant to the problems of hypersensitivity and immunology and their relationship to the initiation of the tissue changes which precede the development of rheumatic lesions. Modern methods of microscopy and tissue analysis have contributed much to the understanding of connective tissue structure and function. It is not unreasonable to hope that the elucidation of rheumatic disease lies within the same field.

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MEDICAL TREATMENT OF RHEUMATIC HEART DISEASE

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Widespread interest in the recent important advances in the surgical treatment of mitral stenosis has temporarily transferred emphasis from the medical aspects of the treatment of rheumatic heart disease. It must not be forgotten, however, that no matter how dramatic the improvement which follows operation, the patient still has rheumatic heart disease with myocardial and perhaps other valvular lesions, is still liable to the risks and dangers of that condition and has, indeed, still got mitral stenosis, though often of significantly less severity. The principles of management are not changed, even if the severity of the disease is mitigated.

Asymptomatic Rheumatic Heart Disease

A large proportion of patients with rheumatic heart disease are recognized in the asymptomatic stage; this includes most of those who have had a typical attack of rheumatic fever (about half the cases) and many others whose disease is discovered by mass radiography, by routine examination at school, or examination by National Service Medical Boards, at insurance examinations and during routine examinations during pregnancy.

Amongst such cases children left with a systolic murmur after rheumatic fever form an important group. Too often the physician advises restriction of activity in a misguided attempt to safeguard the
child in case permanent damage to the heart subsequently proves to be present. This leads to two important unintended consequences; the child becomes generally unfit and he is psychologically segregated from his fellows at school, so that he grows up believing himself physically inferior. General physical unfitness limits most of us in sedentary occupations, but a week or two of progressive physical activity on an active holiday restores a degree of physical well-being which greatly adds to our capacity for effort without dyspnoea. If we have no cardiac damage we may be able to get along quite well in spite of moderate unfitness, but the patient whose reserve is impaired by rheumatic heart disease cannot afford this additional limitation. Regular exercise is indispensable for physical fitness. If no permanent lesion does develop in children with systolic murmurs, as is often the case, permanent unfitness both physical and psychological may still cause substantial incapacity and sometimes 'cardiac' invalidism for life. Those robust both physically and mentally will, of course, survive the misguided advice of even the most authoritative physician, but the remainder will pay a heavy price for their doctors' timidity. If, however, we are to encourage activity in these patients with possible or asymptomatic rheumatic heart disease, how are we to know how much exercise is safe? James Mackenzie gave as good guidance as any since his time: 'The conditions which contra-indicate exercise in treatment are acute and progressive affections of the heart, and when heart failure is so extreme that the rest force is being exhausted. All other conditions benefit by exercise judiciously employed, and no abnormal sign should be taken to forbid exercise unless it is accompanied by progressive exhaustion.' Although there is no scientific proof of the truth of this assertion, nor likely to be, it is certain that avoidance of exercise is far more likely to do harm than over-indulgence, except in the conditions which Mackenzie specified. At the very least, if a normal way of life does not evoke symptoms if should always be enjoined, particularly upon sons and daughters of over-fond mothers. Children have a way of stopping when they are tired. One restriction alone is justified—the prohibition of strenuous competitive sports, for it is only in this sort of activity that a keen boy may continue to exert himself to the point of exhaustion.

Occupation. When the child with asymptomatic rheumatic heart disease leaves school, suitable work must be selected. It is wise to bear in mind that the capacity for effort may become impaired later, and consequently to recommend work involving little physical effort. It is regrettable that many of the most suitable clerical posts in large firms and national institutions are closed to patients with slight rheumatic lesions owing to superannuation requirements. In this Department we have investigated the problem of placement of patients with heart disease in industry over some years. We have been impressed by the importance of the tastes and desires of the individual as a major factor in success, and we regard commonsense and personal observation by the doctor as competing very successfully with more scientific methods of assessing both the physical burden involved in the work and the capacity for effort of the individual. Metabolic tests during work and assessment of capacity for effort by exercise tests are more in the nature of offerings on the altar of science than practical aids. Most important of all is the desire of the individual to work—the impulse to become a self-supporting independent member of the community.

Prevention of subacute bacterial endocarditis. This complication is a real danger to patients with rheumatic heart disease and probably at least 15 to 20 per cent will develop it if precautions are not taken. Since the mortality of bacterial endocarditis is still nearly 50 per cent., in spite of adequate penicillin treatment, prevention is obviously important. A considerable proportion of cases arise from injudicious dental management, either from neglect of infected teeth or from extraction. Further, the danger appears to be greatest in those whose heart disease is most trivial, and perhaps the major advantage of recognizing asymptomatic rheumatic heart disease is that it gives the opportunity to instruct the patient upon the importance of a thorough dental overhaul at six-monthly intervals. If treatment or extraction of one or two teeth is necessary, this may be undertaken as an outpatient and penicillin cover by 500,000 units of soluble penicillin one hour before and five hours after operation has proved adequate in some hundreds of our cases. If the patient has been well advised it should not be necessary to remove a large number of infected teeth, but if this has to be done in patients not previously under supervision, it is better to admit to hospital and give 2,000,000 units daily by three-hourly intramuscular injections for two days before and three days after operation.

Rheumatic Heart Disease with Effort Dyspnoea

Patients with effort dyspnoea are particularly prone to the fear that exertion is harmful and, if allowed to do so, may so immobilize themselves that they increase their cardiac disability by the additional incapacity of general physical unfitness. Nor are doctors immune from the criticism that they aid and abet this undesirable attitude. It
should be made quite clear to the patient that exercise which does not provoke dyspnoea is not only free from danger but actually beneficial provided it is regularly taken. Naturally, in the group of patients under consideration no question of heart failure has arisen. Special problems arise in those patients with tight mitral stenosis subject to paroxysmal dyspnoea, due to acute pulmonary congestion or oedema. Such attacks may occur on exertion at first and in these circumstances considerable physical effort is clearly dangerous. The treatment of the attacks with morphia and oxygen, and perhaps venesection, is only palliative; the only satisfactory treatment is by surgery, and this is almost a matter of urgency in this particular group.

Apart from the management of effort, the principal problems of treatment in this group are concerned with the prevention of deterioration and the management of complications.

**Prevention of deterioration.** The capacity for effort of a patient with rheumatic heart disease does not often deteriorate without cause. The seven principal causes are:

1. Onset of an arrhythmia, usually auricular fibrillation.
2. A recurrence of cardiac rheumatism, clinical or subclinical.
3. An acute infection, usually respiratory.
4. A prolonged period of overwork with lack of leisure and regular exercise.
5. The development of anaemia.
6. The onset of subacute bacterial endocarditis.
7. Pregnancy.

If the condition of the patient deteriorates without apparent reason, it is wise to review these possible causes, for adequate treatment depends upon recognizing the cause of the deterioration.

**Onset of arrhythmias.** Although auricular fibrillation is the usual arrhythmia in rheumatic heart disease, its onset is often heralded by frequent auricular premature beats, which in some cases cause distressing palpitation. On occasions, paroxysmal auricular tachycardia occurs in this phase. In all these prodromal manifestations, digitalis appears to be helpful; if a dose of 2 gr. daily is given, digitalization develops slowly over some three weeks. Not only does this ensure that when fibrillation develops the rate will be controlled (and heart failure, which is often due to the onset of fibrillation, may thus be avoided at that time), but also digitalization sometimes controls the premature beats. Sometimes paroxysmal auricular fibrillation with a rapid ventricular rate causes distressing palpitation and heralds the onset of permanent fibrillation. The only satisfactory method of controlling paroxysmal fibrillation is to keep the patient permanently digitalized, for the paroxysms are usually over before the ventricular rate can be controlled by digitalis. On the other hand a paroxysm in an already digitalized patient usually passes unnoticed by the patient because the ventricular rate is slow. Sometimes auricular flutter precedes auricular fibrillation and may prove a much more difficult arrhythmia to control. Digitalis is the most effective drug and the aim is to convert the flutter to fibrillation. When this happens it is worth noting that the ventricular rate is immediately after the appearance of fibrillation is nearly always about 70 to 80 per min. So we may reasonably deduce that the change of rhythm occurs when the patient is adequately digitalized and not before. Most failures to produce fibrillation are due to inadequate digitalization. There is a tendency to be over cautious because digitalization must be 'blind,' that is, we cannot control it by any progressive change such as the gradual fall of ventricular rate of the fibrillating heart. If, however, 3 gr. of the powdered leaf are given eight hourly, full digitalization is nearly always achieved during the fourth day, and if conversion of flutter to fibrillation does not occur by the end of the fourth day a maintenance dose of 2 gr. daily should be substituted for the higher dose. In the fully digitalized patient quinidine (6 gr. two-hourly for six doses) may succeed in controlling the flutter. Quinidine should never be given without previous digitalization because it slows the flutter rate, sometimes to such an extent that the ventricle no longer respond to each flutter wave, and 1:1 auriculoventricular flutter may rapidly lead to heart failure. Digitalization causes enough impairment of auriculoventricular conduction to prevent a 1:1 ventricular response.

**Recurrence of active cardiac rheumatism.** The treatment of active cardiac rheumatism is outside the scope of this article. There is, however, now some reason to believe that grumbling rheumatic activity in the heart may be present without obvious clinical manifestations. For instance, examination of the heart in patients dying of apparently ordinary rheumatic heart failure, where dying during pregnancy, may reveal histological evidence of active inflammatory changes with Aschoff bodies. This is also true in an appreciable proportion of left auricular biopsies taken during mitral valvotomy. During long term follow-up studies of women with chronic rheumatic heart disease in this Department, it has been noticed that in a small proportion of cases progressive deterioration of capacity for effort is accompanied by the gradual development of new valvular lesions over some years. In the majority of cases of rheumatic heart disease deterioration can usually be traced to one of the causes already enumerated. When it is gradual and cannot be ascribed to a known cause
it may be that there is grumbling rheumatic activity going on in the myocardium. In such cases rest may be of great importance, and certainly there should be no encouragement of activity. But at present our views on this subject are necessarily speculative.

Acute respiratory infections. It is surprising how severely an acute respiratory infection can upset a patient with rheumatic heart disease. Usually serious effects are most noticeable in those with chronic pulmonary congestion, and the patient with tight mitral stenosis and considerably raised pulmonary venous and arterial pressures may easily develop acute pulmonary oedema. Often respiratory infections lead to the onset of arrhythmias, especially auricular fibrillation. One unfortunate patient, a doctor’s wife, who was awaiting mitral valvotomy, developed acute bronchitis. Within a few hours the onset of 2:1 auricular flutter had led to acute pulmonary oedema from which she died. Although catastrophe rarely occurs so rapidly, any patient with mitral stenosis and pulmonary congestion should take a minor respiratory infection very seriously, summon their doctor and go to bed until recovery is complete. If auricular fibrillation occurs, rapid control (by intravenous digoxin (1.5 mgm.) followed by oral digitalis) may avert heart failure. Antibiotics, particularly penicillin and chloramphenicol, are much more necessary than in a previously well patient, to whom the infection does not constitute a serious threat. When a true pneumonia occurs, prompt and effective treatment is even more important, but it is not only such major respiratory infections that matter—all are important in patients with chronic pulmonary congestion.

Anaemia. Rheumatic heart disease is commoner in women than men, and women are particularly prone to develop iron-deficiency anaemias. If the condition of such a patient deteriorates without obvious cause, anaemia should always be excluded. If oral iron does not produce a good reticulocyte and haemoglobin response, intravenous iron may be effective and this is particularly true during pregnancy.

Prolonged overwork. Overwork in itself may not be so harmful as the lack of leisure and moderate physical exercise which accompanies it. An unhealthy way of life must be avoided by the patient with rheumatic heart disease. Those in robust health, free from all disease, can perhaps, within limits, afford to ignore the rules, to work, smoke and drink too much, to sleep, rest and exercise too little, but the patient with chronic heart disease must be moderate in all he does and avoid these over-and-under indulgences if he wishes to preserve his capacity for effort. The physician may sometimes feel a little hypocritical when he gives such advice, which he might himself find it hard to follow, but it is his duty to do so none the less.

Subacute bacterial endocarditis. If this complication is to be treated successfully (either from the point of view of preventing death or from the aspect of reducing the damage done to the heart), it must be diagnosed early. This can only be done if it is realized that the early stages of the disease are not marked by any characteristic feature. Our study of the early symptoms in this Department has led us to the conclusion that the four commonest presenting features are asthenia, pains in the limbs, pyrexia without known cause and so-called ‘influenza’ from which the patient does not regain normal health as expected. Rather unexpectedly, only one patient in seven who developed such symptoms waited more than four weeks from the onset before consulting a doctor, so the opportunity for early diagnosis was there, though unfortunately rarely seized. Once the diagnosis is suspected repeated blood culture will establish it in the majority of cases.

Details of the treatment of this complication cannot be discussed here. It is sufficient to note that the usual course of treatment lasts six weeks, two million units of penicillin being given daily. Only rarely does a penicillin-insensitive organism necessitate the use of other antibiotics. If the disease is treated within three months of the onset, the great majority of patients make a satisfactory recovery, but many of those whose infection is not longer standing die of heart failure, although the infection is fully controlled.

Pregnancy. The management of pregnancy in patients with rheumatic heart disease is of major importance, for 90 per cent. of heart disease in pregnant women is rheumatic. In 596 of our recent cases (of which about 10 per cent. should never have become pregnant), the mortality due to the association of pregnancy with heart disease has been 2.5 per cent. Two-thirds of this mortality occurred in the 53 patients in whom pregnancy should not have occurred. The recognition of this group of cases is extremely important. In general we can divide pregnant patients with heart disease into three groups upon criteria which are summarized in Table 1. The outlook in these groups is given in Table 2. In summary, we may say that the risk of pregnancy is not increased in Group I, is little increased in Group II and pregnancy is too dangerous in Group III.

Termination of pregnancy is reasonably safe in the first trimester and should be advised in early pregnancy in Group III and in some of the more severe cases in Group II. After the first trimester termination is not often as safe as allowing the pregnancy to continue. It has been suggested that mitral valvotomy is in suitable cases a means of
allowing pregnancy to continue if it would otherwise be unsafe. That might be true if we could be sure of a good result, but if the result is not good then by the time this is known it will probably be too late to terminate. In the first trimester it seems safer to terminate the pregnancy in such cases and consider valvotomy later. On the other hand, valvotomy in suitable cases may save life if the patient refuses termination and possibly in some cases too late in pregnancy for termination.

In the supervision of pregnancy in these patients the main object is to recognize and treat the very earliest stages of heart failure. In this connection it must not be forgotten that rheumatic heart failure in pregnancy differs in many respects from heart failure apart from pregnancy. The majority of patients who die owing to rheumatic heart failure associated with pregnancy do so because they develop acute pulmonary oedema, whereas in rheumatic heart disease apart from pregnancy acute pulmonary oedema is uncommon and death is usually due to right heart failure. The early signs of failure during pregnancy are not found by examination of the neck veins or ankles but by searching for evidence of increasing pulmonary congestion. The precipitating factors are usually insufficient rest, anaemia, acute respiratory infections, the development of auricular fibrillation and, rarely, the onset of subacute bacterial endocarditis. Treatment follows the lines to be discussed later, but the treatment of the precipitating cause is of paramount importance. Close supervision during pregnancy is essential in order to detect and treat at once the precipitating factors and the failure at the earliest stage. Termination of pregnancy should never be undertaken until the cardiac condition has been improved as much as possible by adequate treatment, and in some cases adequate treatment will so greatly improve the cardiac condition that termination is unnecessary. The majority of patients who develop heart failure in later pregnancy do well and have a normal confinement at term without any trouble from the heart. The earlier the onset in pregnancy the graver the prognosis, and heart failure in the first trimester is an indication for therapeutic abortion after adequate treatment of the cardiac condition. A normal confinement is usually well tolerated by patients with rheumatic heart disease and induction of premature labour for cardiac reasons is now obsolete. Nor is rheumatic heart disease ever an indication for Caesarean section. The danger of labour have been exaggerated in the past. Provided the confinement is skilfully conducted the mode of delivery is less important than the cardiac condition of the patient at term, and that depends largely upon adequate supervision during pregnancy.

In summary, the general tendency today is to interfere with normal gestation as little as possible, either by therapeutic abortion, especially after the first trimester, or by abnormal methods of delivery. Constant supervision aims at ensuring adequate rest, permits the early detection and treatment of the factors which lead to heart failure and allows the heart failure itself to be promptly controlled when the first signs appear.

**The Treatment of Rheumatic Heart Failure**

In recent years it has become increasingly clear that the renal circulation plays a key role in the production of heart failure, for it seems probable that it is the reduction in renal blood flow which
sets the stage for the retention of salt and water which causes the principal signs and symptoms of congestive heart failure, no matter whether the raised venous pressure due to left heart failure localizes the oedema in the lungs, or the corresponding rise of pressure behind the failing right ventricle directs the oedema to the legs, sacrum and abdomen. There is evidence to suggest that in heart failure the renal blood flow may be diminished out of proportion to the fall in heart output.

If we base our ideas of the mode of action of the several remedies for heart failure (rest, water and salt restriction, digitalis, mercurial diuretics and ion exchange resins) upon this sort of concept, their action becomes easier to understand. Rest reduces the demand of the heart and muscles for blood and so enables a greater proportion of the output to be partitioned to the kidneys; water and salt restriction and the ion exchange resins relieve the kidneys of some of their burden; digitalis acts directly upon the myocardium, enhancing the heart output (in addition to its action in controlling the ventricular rate in auricular fibrillation) and, finally, mercurial diuretics allow the kidney to excrete much greater quantities of salt with the same blood flow.

Speed of treatment. Demands for hospital beds and the economic aspects of prolonged hospitalization have led to a tendency to more rapid techniques for the control of heart failure. This tendency has naturally been most striking in the United States and is exemplified by the 'five-prong' programme of Gold and his colleagues: (1) rest in bed or chair, (2) extreme sodium restriction, (3) daily mercurial diuretics, (4) single dose rapid digitalization and (5) daily weighing until a steady weight is reached. This drastic regime contrasts with the more leisurely traditional British method of complete bed rest, moderate sodium restriction, bi-weekly mercurial diuretics and weekly weighing. Probably something between the two methods is the best and our recent practice has been to modify bed rest by the use of a commode (rather than a bedpan) and gentle leg and breathing exercises, to restrict salt to about 3 g. per day and fluids to 40 oz., to digitalize over a period of 72 hours, to give mercurial diuretics on alternate days and to weigh twice a week. Complete bed rest carries so great a risk of thrombo-embolic accidents that it should be avoided especially in the older patient. Digitalization is not often very urgent, but 1.5 mg. of intravenous digoxin may be life-saving in very ill patients with auricular fibrillation and an apex rate of around 180. Sodium restriction by the avoidance of all added salt at table and in cooking may be sufficient in the milder cases, but this implies that at least 4 gm. of salt will be taken daily. Elimination of salt in bread and butter reduces the intake to about 2 gm. Special low salt diets may reduce the intake to 1.5 g., and the Karell regime, which limits food and fluid intake to 800 cc. of milk daily, gives an intake of 1 g. of salt and 800 calories; this diet should not be used for more than a few days. Salt substitutes have often caused serious toxic symptoms and are better avoided.

Prevention of recurrence of heart failure. No very great therapeutic skill is necessary to control heart failure in the earlier attacks, but the prevention of recurrence makes much greater demands upon the ability of the physician and especially upon his skill in securing the cooperation of the patient. Perhaps the best rule is to adopt a cautious attitude in relaxing the regime of treatment after the acute phase, and this is particularly important if there is no obvious precipitating cause for the failure, such as the onset of auricular fibrillation, a respiratory infection or anaemia. In these cases the precipitating factor is either removable or controllable, and the outlook correspondingly improved, so that after a few weeks no measure other than restriction of activity may be necessary. In most other cases moderate salt and fluid restriction, digitalis and mercurial diuretics at intervals between weekly and monthly are desirable. The vital thing is the constant watch upon the patient's weight; this should be recorded at least weekly using the same scales and any progressive increase in weight is an indication for more active treatment. There is no more desirable expenditure for the patient who has had one attack of failure than the purchase of a reliable bathroom weighing machine.

Cation exchange resins. In recent years it has become clear that heart failure can sometimes be controlled by severe dietetic salt restriction when all other measures fail. In such cases it is often necessary to continue to restrict salt to 1 g. daily or even less if a relapse is to be prevented. Such a diet is savourless and leads to cooking difficulties at home, so that patients are apt to become intolerant of it. Nor is a very low sodium diet free from danger. The cation exchange resins were introduced for the treatment of heart failure in an attempt to provide an alternative in such refractory cases and their use is at present best confined to such cases. Although they have created many new dangers and difficulties, they do seem to have a place in the treatment of some cases of refractory heart failure.

In our experience 15 g. t.d.s. is a suitable dose of one of the balanced ammonium-potassium carboxylic cation exchange resins, but up to twice this dose has been necessary in some cases. Many patients find difficulty in swallowing such amounts,
however. In the initial stages of treatment it is essential to estimate the blood electrolytes, particularly chloride and potassium, at least weekly. There is a tendency to hyperchloraemia, so ammonium chloride should not be used as an adjuvant to mercurial diuretics while resins are being given. Special care is necessary when there is any evidence of renal damage. Treatment should always be started in hospital but can be maintained after discharge.

In some of our cases we have noticed that although mercurial diuretics produced little response before resin treatment, a good diuresis followed subsequent injections. Some patients who improve very little with resin treatment alone may improve when this is combined with a low sodium diet. The best combination of sodium intake, mercurial diuretics and resin treatment still seems to be a matter of trial and error in refractory cases of heart failure and it must be admitted that although the cation exchange resins are a valuable new weapon in the control of sodium metabolism in heart failure our use of them is still rather tentative and exploratory.

In covering so broad a field as the medical management of rheumatic heart disease it is not possible to discuss details comprehensively, but I have tried to place some emphasis upon three aspects of the approach to management; first, upon the paramount importance of regular moderate exercise in maintaining general fitness, especially in the earlier stages of the disease; next, upon the need for constant vigilance in the anticipation and early recognition of complications; and finally upon the necessity to search for and treat causes of deterioration not directly connected with the heart disease. It will be obvious that in such an approach constant alert supervision by the family doctor is far more likely to ensure success than occasional survey by a consultant.

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**DIAGNOSIS AND TREATMENT OF RHEUMATIC FEVER WITH SPECIAL REFERENCE TO EARLY CARDITIS**

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**Diagnosis of Rheumatic Fever**

The diagnosis of rheumatic fever is seldom wrongly made when a migratory polyarthritis and fever follow a sore throat. Occasionally it may be difficult to distinguish between rheumatic fever and other conditions, notably Still's disease, osteomyelitis, Henoch-Schonlein purpura, leukaemia and polyomyelitis. In Still's disease there may be involvement of several joints at the onset and the joint changes may be of such short duration as to simulate rheumatic fever. Furthermore, pericarditis may occur; friction may easily be mistaken for heart murmurs and effusion for cardiac dilatation. Often in early cases of Still's disease a characteristic rash consisting of discrete pink macules is present which enables the correct diagnosis to be made. Furthermore there is frequently a persistent high swinging temperature and generalized glandular enlargement. Rarely the joint involvement in rheumatic fever may be most marked in the hands, and these changes may persist for days or even weeks, suggesting a diagnosis of Still's disease. In long-standing rheumatic fever also, there may be nodule formation over the knuckles simulating the fusiform fingers of rheumatoid arthritis; rarely ulnar deviation may result as a residual deformity (Jacquod's syndrome).

The diagnosis between rheumatic fever and osteomyelitis may be particularly difficult. The presenting symptom in osteomyelitis may be pain in the joints above and below the site of the lesion; there may be pain in the shoulder and elbow from osteomyelitis of the humerus. On the other hand, in rheumatic fever there may be severe involvement of one joint only, often a large one such as the hip, and the signs may persist in that joint alone for several days; the differential diagnosis is then between rheumatic fever and supplicative arthritis or osteomyelitis. X-rays are of no value in diagnosis at this stage as bone changes do not occur until later. Neither is the total or differential white blood count, for there may be little or no leukocytosis in the first 48 hours of osteomyelitis and there is frequently a high white count in rheu-