Rheumatic fever
A clinico-pathological conference held at the Royal Alexandra Hospital for Sick Children, Brighton, on Tuesday, 8 February 1966

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R. KEMBALL-PRICE: Ladies and Gentlemen, this evening's subject for discussion is the problem of rheumatic fever and we are particularly fortunate in having Dr Michael Joseph here as guest speaker. Dr Joseph has for some years been a member of the consultant staff of Guy's Hospital, where he works as a paediatrician with a special interest in cardiology. More recently he has been appointed as Consultant Paediatrician to the Brompton Hospital and so you will appreciate that his experience and knowledge of heart disease in children is quite extensive. We are particularly pleased to welcome him here tonight because he comes, not simply as a visitor from London, but as a friend of many in Brighton whom he has met at the regular heart clinics that are held at the Children's Hospital. I am quite sure that we shall have an entertaining and instructive session this evening.

And now, to start the proceedings, I should like to ask Dr Nash to present the details of his patient who forms the subject of this clinico-pathological conference.

F. W. NASH: This young boy, Vasfi M., died in our hospital on 25 May 1965, at the age of 9½ years, during his fourth attack of rheumatic fever. The first attack had occurred some 5 years previously.

The social background of the family is of some importance and the medical details would be incomplete without telling you a little about it. Vasfi was a member of a Turkish Cypriot family which came to Britain in 1952. The parents and five other children (with ages ranging from 4 to 20 years) live in a small three-roomed basement flat in London. One of the children, a girl 13 years old, has so far had two attacks of rheumatic fever. There was also another child who died from miliary tuberculosis in 1959. Although the family is

over-crowded and living conditions are not very good, there is no real shortage of money, for both parents and the two eldest children are out at work. One of the important aetiological factors in our patient's illness appears to have been an inability to spend the family income properly and to make adequate use of available medical and social facilities. This was largely due to intellectual limitations of both parents and recurrent spells of depression on the part of the mother.

In 1959, when he was aged 4 years, Vasfi was admitted to the Westminster Children's Hospital with a chest infection complicated by congestive heart failure and this illness was subsequently diagnosed, in retrospect, as rheumatic fever on the basis of the appearance of cardiac enlargement and established mitral incompetence. Two years later (1961) the boy was investigated in Guy's Hospital for an obscure illness which might have been subacute bacterial endocarditis, though a firm diagnosis was never established. Soon afterwards he had an atypical attack of rheumatic fever with pain and swelling of a single joint (the right knee), and some pyrexia. There was no history of a preceding throat infection. The heart enlarged further and signs of mitral stenosis appeared in addition to those of incompetence. The illness was treated with prednisone as well as aspirin and penicillin. Interestingly, the highest ASO titre was only 280 units. A comment appears in the notes that the parents had been very lax over giving their child prophylactic oral penicillin.

In 1962 there was yet another illness with involvement of the right knee associated with pyrexia, a raised ESR, but a normal ASO titre (166 units). Rheumatic fever was again diagnosed and on this occasion steroids were not given because of cardiac enlargement. After discharge from hospital an attempt was made to give prophylactic penicillin (Triplopen) by injections, but Vasfi frequently failed to attend for this treatment. Eventually, in September 1962, he was admitted to a

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boarding school for physically handicapped children (Staplefield School). He remained an active child with only slight limitation of exercise tolerance and was generally very fit, though examinations showed that the heart was large and the murmurs persisted. Oral penicillin was given regularly whilst he was at school and he had a supply to take home for the holidays, but we do not know that he had it regularly whilst at home.

My first contact with Vasfi was on 21 May when I was asked to see him at the school. He had been unwell for 3 days with a sore throat, raised temperature and vague pains in his joints. When I examined him he appeared to be a very anxious boy, but not extremely ill—temperature 102°F, pulse rate 120/min, respiratory rate 30/min. There was no evidence of congestive heart failure, though the heart was considerably enlarged and there were clear signs of mitral stenosis with incompetence and also aortic incompetence. Both knee joints were slightly swollen, but not tender or reddened; however, there was some redness and tenderness over the inner side of the left ankle. Admission to hospital was discussed with the school doctor, but we decided against it at this stage because of the boy’s anxiety about himself and the separation it would involve. I recommended increasing the dose of aspirin to 60 grains/day and giving intramuscular instead of oral penicillin, because a throat swab taken at the beginning of his illness produced a growth of haemolytic streptococcus (though not of Lancefield Group A).

Later that night Vasfi suddenly became very ill with high pyrexia (104°F) and he was transferred to the Children’s Hospital early the next morning. He was then clearly in early congestive heart failure; there was no clinical evidence of pericarditis. After treatment with digoxin and prednisone, whilst being nursed in an oxygen tent, he improved a little. Throughout the following day (24 May), the child remained quite ill. In the evening of the 24 May he complained of some abdominal pain and had a haemoptysis of about 2 or 3 oz. Signs of consolidation in the left lower lobe were noted and, although a pulmonary embolus may have been the cause of the new symptoms, it was decided to give him chloramphenicol since there was a possibility that he was developing pneumonia in addition to the rheumatic carditis. The boy seemed much more comfortable for a time and he even had a chat with the night sister when she was doing her rounds but, quite suddenly, at about 01.30 hours on the 25 May, he slumped forward in his bed and died.

R. Kemball-Price: Thank you, Dr Nash. Now would Dr Rubin please tell us something about the X-rays of this boy. Afterwards I shall ask Dr Trott to describe the post-mortem findings and Dr Elliott will discuss the histology.

J. Rubin: There are two films (supine and lateral) which were taken on 22 May 1966; I believe this was 3 days before the child died. They show that the heart is severely enlarged with quite definite pulmonary congestion as revealed by generalized pulmonary vascular plethora (Fig. 1). The appearances are really those of early congestive heart failure.

Fig. 1.

A small pericardial effusion cannot be excluded. The left costophrenic recess is less well illuminated than the right and this may be due to slight pleural reaction, but there is no obvious pleural effusion at the time of this portable X-ray examination.

P. Trott: At post-mortem the principal findings were in the heart. This was grossly enlarged and weighed 330 g, which is at least double the normal weight for a heart in a boy of this age. The increase in size was predominantly due to a grossly enlarged left ventricle which was dilated and had a very thick wall (1·2 cm), somewhat thicker than a normal adult’s left ventricle. The myocardium was generally pale but there were no rheumatic

THE CONCLUSION IS THAT THE CHILD DIED FROM HEART FAILURE DUE TO ACUTE-ON-CHRONIC RHEUMATOID CARDITIS.

R. I. K. ELLIOTT: THE QUESTION THAT WE HAVE TO TRY TO ANSWER HISTOLOGICALLY IS WHETHER THIS CHILD'S TERMINAL ILLNESS WAS STILL BASICALLY RHEUMATIC; NOT AS SIMPLE, IN FACT, AS IT SOUNDS. WE ALL KNOW THAT THE CLASSICAL LESION IN RHEUMATIC DISEASE IS THE ASCHOFF NODULE; BUT THE TROUBLE ABOUT CLASSICAL THINGS IS THAT NOWADAYS ONE SEES THEM ONLY IN RUINS: THE RAVAGES IN THIS INSTANCE BEING THOSE OF THERAPY, RATHER THAN TIME. BUT QUITE APART FROM MODIFICATIONS DUE TO TREATMENT, THE ASCHOFF NODULE IS NOT A STRUCTURE READILY PINNED DOWN: IT DEVELOPS AND CHANGES, SO THAT EVEN IN THE FLORID UNTREATED DISEASE ONE SEES A COLLECTION OF STAGES RATHER THAN A SINGLE UNVARYING PATTERN. FOR A PICTURE OF THE HISTOLOGICAL INGREDIENTS OF THIS LESION, IT IS EASIER TO TAKE A SMALL FOCUS FROM A RHEUMATOID NODULE, WHICH IS SIMILAR, BUT MORE STEREOTYPED; AND MORE READILY AVAILABLE. IN SUCH A FOCUS, TAKEN FROM AN ADULT PATIENT (FIG. 2), ONE FINDS A CENTRAL AREA OF FIBRINOID MATERIAL SURROUNDED BY A RADIAL PALISADE OF MONONUCLEAR CELLS, WHICH Merges without a distinct border into the surrounding fibrous tissue.

IN THIS CHILD'S MYOCARDIUM, LOW-POWER EXAMINATION SHOWS EXTENSIVE FIBROSIS, PATCHILY DISTRIBUTED, HEAVIEST BENEATH THE ENDOCARDIUM AND AT THE SITES OF ATTACHMENT OF THE VALVES. IN THE FIBROUS TISSUE ARE CELLULAR INFILTRATES, ROUGHLY FUSIFORM, WITH INDISTINCT BOUNDARIES. UNDER THE HIGH POWER, THEY SHOW A CENTRAL AREA OF FIBRINOID MATERIAL SIMILAR TO THAT OF THE RHEUMATOID NODULE, BUT SMALLER. ROUND IT, YOU CAN TRACE A STRAGGLING PALISADE (FIG. 3). THE CELLS ARE FEWER AND LESS REGULARLY DISPOSED THAN IN THE RHEUMATOID NODULE, BUT THEY ARE OF THE SAME TYPE, SOMEWHERE BETWEEN A HISTIOCYTE AND A FIBROBLAST. IN SOME FOCI, A FEW LYMPHOCYTES ARE ALSO PRESENT IN THIS ZONE. BY COMPARISON WITH A RHEUMATOID NODULE, THE CELLULAR REACTION IS FEEBLE—THIS I INTERPRET AS THE EFFECT OF

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**FIG. 2.** A SMALL RHEUMATOID FOCUS IN THE JOINT CAPSULE IN SEVERE RHEUMATOID ARTHRITIS, SHOWING A CENTRAL FIBRINOID LAKE WITH A PALISADED BORDER OF HISTIOCYTES AND FIBROBLASTS. (×128).
Rheumatic fever

Fig. 3. An Aschoff node from the patient’s myocardium; with some fibrinoid staining present centrally, but reduced cellular infiltration as a result of treatment. (×128).

Fig. 4. Renal medulla showing the edge of the infarcted area: viable tubules on right, dilated vessels centrally, necrotic tissue on left. (×32).
steroid therapy—nevertheless, it is clear that we are dealing with reactions of a similar type. It is not difficult to find a number of lesions of this kind scattered through the excessive fibrous tissue in this boy's myocardium and I think the conclusion must be that in spite of treatment there was still active rheumatic disease in progress in his final illness, and that this was a major factor in his death.

Apart from the myocardial lesions, there is not a great deal to show in other organs. In one of the sections of kidney there is a focus of pyramidal necrosis (Fig. 4); although several kidney sections were examined, no other necrotic areas were found. In the lungs, as Dr Trott described, there was a severe degree of oedema and congestion, and the histology confirms this; detailed examination also shows occasional necrotic foci surrounded by heavy inflammatory infiltration. It is tempting to regard these as a form of Aschoff body but the usual view is that Aschoff lesions are found only in the myocardium. Finally, there are quite frequent multinucleate giant cells in the alveoli, often associated with fibrinoid exudate (Fig. 5). This combination of findings: oedema, congestion, fibrinoid exudate and giant cells, constitute the main features of rheumatic pneumonitis, and confirms further that the rheumatic process was the major cause of his death.

R. KEMBALL-PRICE: Thank you, Dr Elliott. Now that we have had the clinical and pathological presentation of this interesting case, perhaps Dr Joseph would open the discussion.

M. C. JOSEPH: Dr Kemball-Price, Ladies and Gentlemen. First of all I would like to thank Dr Mann and Dr Nash for inviting me down here to join you in this interesting clinico-pathological discussion and, secondly, I would like to thank Dr Kemball-Price for the kind remarks he made about me.

Could I perhaps at this stage just start with something fundamental and go over some of the points in rheumatic fever from a clinical aspect which were first described and well documented by Duckett Jones (1944), who, you may remember, made a long-term follow up study of 1000 patients with rheumatic fever. He was the first to describe what he considered to be the major and minor criteria of the disease. Now he did this, not because he thought this was necessarily the whole truth, but because he felt that when people were describing rheumatic fever it was as well to have some sort of agreement on the criteria needed for a reasonably firm diagnosis. These criteria could then be used as a future basis for comparison with different series. Duckett Jones (1944) divided both the clinical and laboratory findings into major and

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Fig. 5. Lung in rheumatic pneumonia, showing fibrinoid material and giant cells in two alveoli. (× 320).
minor groups (Table 1). He suggested that the presence of one major plus two minor criteria made the diagnosis of rheumatic fever highly likely. Now, there have been some suggested alterations to these criteria (Table 1) and one of these (and I would like to hear your views about it) was that a recurrence should be considered minor (Royal College of Physicians, 1957), though surely a recurrence should persuade us very hard that we might be dealing with a second attack of rheumatic fever. Another suggestion was that erythema marginatum should be major.

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<th>Table 1</th>
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<tr>
<td>Criteria for diagnosis of rheumatic fever (based on Duckett Jones, 1944)</td>
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<tr>
<td>Major</td>
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<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Carditis</td>
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<tr>
<td>Recurrences*</td>
</tr>
<tr>
<td>Nodules</td>
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<td>Chorea</td>
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Duckett Jones recommends one major and two minor criteria.

* Royal College of Physicians (1957) regards recurrences as a minor criterion and considers that the presence of two major or one major and two minor criteria indicates a high possibility of rheumatic fever.

Arthralgia describes the symptom of pain in a joint without objective evidence of joint involvement. It is a difficult symptom to evaluate because it is so common in young children. In 1957 a Committee of the Royal College of Physicians suggested that arthralgia be classified as a minor criterion and arthritis as a major criterion. So, on the whole, if one uses these criteria as a guide, I think one can indicate the diagnosis with more certainty when two major criteria are present (Royal College of Physicians, 1957). But one is still left in doubt without necropsy evidence of the reliability of these particular criteria. You can get nearer the diagnosis if a nodule is present which can be examined histologically, and I would like to hear Dr Elliott's views about this.

Now there is one particular combination which is difficult and that is when you have a combination of arthritis (major), fever (minor) and a raised sedimentation rate (minor). On the basis of Duckett Jones' criteria you would be correct in diagnosing rheumatic fever—but there are other conditions which can simulate this, such as rheumatoid arthritis or disseminated lupus erythematosus, so that when you have this particular combination the criteria are less reliable, but it seems reasonably good for everything else.

Next, let us discuss this particular child. We know that initially, I think when he was aged 4 years, he had arthritis. That is correct isn't it?

F. W. Nash: I think his first illness was said to be a chest infection followed by the carditis which, in retrospect, was diagnosed as rheumatic fever.

M. C. Joseph: He had this at the age of 4 years, didn't he?

F. W. Nash: Yes.

M. C. Joseph: A chest infection?

F. W. Nash: Yes. Now we haven't access to the original notes, but there is no mention of arthritis in the summary of his first illness. But he did have arthritis, limited to one joint, in a second attack and also in his third attack. He also suffered a long illness which was investigated as subacute bacterial endocarditis, but it seems that his terminal illness was the only one in which more than one joint was affected.

M. C. Joseph: As regards the question of arthritis, we know that it may be absent in rheumatic fever and it is said to be less common in childhood (Wood, 1956), but joint pain occurred in 90% of 457 initial attacks of rheumatic fever in patients under the age of 17 years (Massell, 1958).

On the basis of the pathological findings you seem to have demonstrated the presence of the rheumatic process very clearly, and we cannot argue about this, but one of the points of a clinico-pathological conference is to go back over the clinical side and see where we might have gone wrong. I think we have here a good illustration that throughout the history this has not been typical. The boy had undoubted carditis, but I believe he did not have a raised ASO titre each time he showed activity. The ASO titre is almost always over 400 units when you have other reasonable evidence of rheumatic fever, but there is no doubt that with two or even three major features you do sometimes find an ASO titre of 125 or less. Massell (1958) has stated that the titre was at least 400 units in more than 90% of proven cases and that less than 125 units was strong evidence against rheumatic fever, especially if the illness was of less than 4 months' duration; he regarded 160–320 units as borderline. This boy may have had a
sensitizing infection when he had a chest infection, yet he never showed this response in his blood.

Going back and arguing against myself, could this boy have had a non-streptococcal infection of his lungs at the age of 4 years unrelated to rheumatic fever, and then when he was seen at the age of 5 years the anatomical cardiac condition was recognized, but the mitral incompetence might have been congenital in origin? Well, I think without any more data it would have been a very reasonable diagnosis and I believe he was going to be investigated, wasn’t he, at another hospital for his heart condition on the grounds that it might not be rheumatic? I am not certain about this. However, it seems that subsequently he had arthritis; he had evidence of cardiac involvement and he had four attacks and this is where, I think, the criterion of recurrence is largely useful although, of course, rheumatoid arthritis and lupus also characteristically recur. Abdominal pain is a useful minor criterion and, I think, it reminds us that rheumatic fever sometimes masquerades as appendicitis; it is said that some patients have had normal appendices removed and a few days later additional features have appeared which make the diagnosis of rheumatic fever evident. I myself, have no experience of patients with precordial pain, but presumably this is a reflection of pericarditis. Epistaxis, when it does occur, is said to be useful in diagnosis. I was interested to hear that this child had pulmonary manifestations proven histologically. On a clinical basis this is classified as a minor criterion, but I think it is difficult to establish whether the radiological changes can be recognized during life as distinctive of a rheumatic process. Rheumatic pneumonia is a rare manifestation only occurring in 1–2% of active cases (Wood, 1956). Chorea speaks for itself, but about one-third of patients with chorea subsequently develop rheumatic heart disease (Ash, 1948). The arthritis and arthralgia we have already referred to, but I would like to point out that it is easy to talk about arthritis and arthralgia, although, when it comes to the actual child, he tells his mother that he has pain and she interprets its site, but when you actually ask the child he points somewhere else. So that I think it is very difficult to be certain on the history. Objectively, if you see the child at the time of the acute attack (more often you see the child a day or two after when the ‘arthritis’ is subsiding), the joint is so painful that if a lower limb joint is involved, the child has to be off his feet and in bed. However, you do get intermediate grades of severity which are a problem in diagnosis.

Carditis is next on our list. Both from a disability and a killing point of view, as in this child, this is the most important single aspect. Perhaps we could just talk about that for a few minutes. What do we mean by carditis? Perhaps a better term is ‘cardiac involvement’ (Table 2). Tachycardia is often mentioned, but is not evidence of carditis; it is part of the general disease process. So what are the real features that one looks for as evidence of cardiac involvement? Firstly, murmurs, which may be systolic or diastolic. The systolic murmur, which may be evidence of mitral incompetence (organic or functional), is pansystolic. It occurs at the apex, is conducted into the axilla, is blowing in character and at least grade two out of six in intensity. Then there are two types of diastolic murmur, one of which is rumbling, situated at the apex and resembles the rumbling murmur of mitral stenosis. This is sometimes called a Carey Coombe’s murmur. Another category of diastolic murmur is that of aortic regurgitation, commonly a quiet (grade 2–3 out of 6) blowing murmur occurring immediately after the second sound along the left sternal border. Now either of these two diastolic murmurs is good evidence of carditis. Because children so often have systolic murmurs which are of no significance it can be difficult to interpret a murmur. If it is a new one, or it changes during the course of the illness, then this may be worth-while evidence of cardiac involvement, but you are still left with the difficulty that anaemia may give rise to a systolic murmur. Now, anaemia is common in children and it occurs also in rheumatic fever; it is particularly likely to be present in those children of a social class which is more likely to be subject to rheumatic fever. Cardiac enlargement (not included by Massell) is another piece of evidence and this may be detected on clinical grounds or, better still, radiologically, but it may be difficult to differentiate from pericardial effusion. Pericarditis is further evidence of cardiac involvement and this may be in the form of a friction rub, or clinical and radiological evidence of an effusion, or electrocardiographic evidence of pericarditis. There is one more electrocardiographic change

### Table 2

Cardiac involvement in 457 initial attacks of rheumatic fever (exclusive of pure chorea), Massell (1958)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Per cent</th>
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<tr>
<td>Mitral regurgitation</td>
<td>38</td>
</tr>
<tr>
<td>Mitral and aortic regurgitation</td>
<td>12</td>
</tr>
<tr>
<td>Aortic regurgitation alone</td>
<td>4</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
</tr>
<tr>
<td>Prolonged PR interval</td>
<td>25</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>8</td>
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which is useful; that is a lengthening of the P-R interval. There are tables available which indicate the percentiles at varying ages (McCunm, 1961): borderline lengthening (less than the 90th percentile) is only helpful if you know that it is a new finding.

In practice in the home one may be faced with a child who is a little off-colour, who has not 'snapped out' of his sore throat in the usual way and it is difficult to put your finger on anything more specific. I think it is this group of patients which needs to be more fully investigated, or have a period of observation in hospital in order to make a more certain diagnosis.

One more point I would just like to bring up concerning this particular patient is to ask why we failed here. How did we allow him to succumb? It seems that Dr Nash had the care of this child right at the end of a period after he had been exposed to four attacks of rheumatic fever, each one damaging his heart further. He was left with a heart with severe mitral incompetence which finally ended in cardiac failure with, in addition, pulmonary manifestations of the rheumatic process. One other point Dr Nash has already made is this difficulty of being certain that the child took his prophylactic penicillin. We are not certain about that, are we?

F. W. Nash: We are certain that he did not get it regularly until he went away to school and then he did get it regularly.

M. C. Joseph: Did he get an attack while he was on regular prophylactic penicillin?

F. W. Nash: No, except his last attack. During this last illness he was still on oral penicillin. The only proviso I have to make is that we do not know the details of what he had during school holidays. It is quite likely, I would have thought, that the parents had not kept it going during the holidays, but he was on prophylactic penicillin and he developed an illness with a sore throat whilst he was still on it.

M. C. Joseph: I think this is a very important point. It seems that he was not taking penicillin all the time or, perhaps, adequate blood levels were not achieved. It must be very rare for the organism to be insensitive to penicillin and perhaps Dr Elliott will tell us about this.

R. I. K. Elliott: Then perhaps he was not taking sufficient.

F. W. Nash: This is possible. I mean, no one believes, I am sure, that oral penicillin prevents every invasion with the haemolytic streptococcus, it simply reduces the likelihood, doesn't it? If you examine control studies you find that the incidence of infection and of relapses of rheumatic fever is much lower in the treated group than in the untreated group.

M. C. Joseph: This is a very good point, isn't it? You just do better, but do not achieve complete prophylaxis. I suppose this might be one example. However, I would like to hear other people's views about this.

R. Kemball-Price: May I thank all the speakers so far, especially Dr Joseph for his most interesting comments on rheumatic fever and discussion of this particular patient.

And now Dr Trevor Mann has a contribution to make; he is going to say something about the differential diagnosis of rheumatic fever.

Trevor P. Mann: To overlook rheumatic fever in a child may have life-long repercussions for that individual; to misdiagnose the condition may also have serious and long-lasting effects on the child and perhaps on his family. The assessment of a child with possible rheumatic fever is, therefore, a most responsible task for the physician and there are no specific laboratory tests to assist one. Fortunately its recognition in childhood is, in the majority of instances, relatively straight-forward especially if one bears in mind the major and minor criteria which we have just heard about from Dr Joseph.

If one was writing about the differential diagnosis of rheumatic fever in Finals, or let us say the Membership examination, one would certainly consider acute leukaemia, rheumatoid arthritis (Still's Disease), anaphylactoid purpura (Henoch-Schönlein syndrome), and acute osteomyelitis with or without joint involvement, all of which can mimic rheumatic fever quite closely, especially early in the illness. Some reference would also have to be made to rarer disorders such as disseminated lupus erythematosus, subacute bacterial endocarditis, brucellosis and, in coloured children, to sickle cell anaemia, which in the African is a great imitator rather as syphilis used to be when it was prevalent. A few years ago one would have given poliomyelitis some prominence in the differential diagnosis and even today this condition must be considered in countries where the infection remains endemic.
There are atypical ways in which rheumatic fever may present which, at times, may make things difficult for the physician or even the surgeon! Thus, as Dr Joseph has reminded us, abdominal pain may be an early and impressive symptom, so much so that the child may find his way into a surgical ward as a possible 'acute abdomen'.

I am going to confine my remarks on differential diagnosis to the first group of disorders because in all of these pain in and around joints may be an early and impressive feature. I shall conclude by mentioning one other disorder of a non-specific nature which may confuse the diagnostician.

Acute leukaemia may present with joint pains and, as I shall illustrate shortly, these, at times, may be migratory and simulate very closely the arthralgia of rheumatic fever. There may be associated fever to add to the clinician’s difficulties with diagnosis. When leukaemia starts in this way there may be no initial anaemia or thrombocytopenia and so pallor and bruising, which are such constant presenting features in the ordinary run of cases, may be absent. Here, now, is a brief account of the early illness in a child with acute lymphatic leukaemia with osseous involvement where for obvious reasons rheumatic fever, glandular fever and Still's disease were all considered in turn as the clinical picture unfurled.

Case report

A.A. Female. Aged 9 years. Illness began with sore throat, enlarged neck glands and abdominal pain. She responded to a course of tetracycline and returned to school after 4 days.

Three days later recurrence of fever (101°F). Complained of pain in hips, knees, shoulders, elbows and wrists. Pain flitted from one joint to another and lasted several hours in each joint; never more than two were affected at once. General Practitioner at first suspected rheumatic fever and prescribed aspirin and penicillin. No response and following day neck pain was experienced. Marked hepatosplenomegaly noted at this stage. Blood count: Haemoglobin 92%. White cells 16,000/mm³—typical mononuclear cells 6%. Paul Bunnell screening test positive; full test negative. Anti-streptolysin O titre 123 units.

Comment. In this child hepatosplenomegaly was a striking early finding and pointed to a diagnosis other than rheumatic fever. However, such gross changes in the lymphatic system are unusual in children with acute leukaemia presenting with skeletal involvement. Note the misleadingly high haemoglobin value, a not uncommon initial finding in cases of this kind.

Turning now to Still's disease, this disorder may come to our notice in two contrasting ways. A child may simply complain of pain and swelling in one joint, often the knee. There may be no associated ill health or fever. These youngsters not infrequently find their way to an Orthopaedic Clinic, sometimes with a tentative diagnosis of tuberculous arthritis, a rare disorder nowadays in this country. In contradistinction, Still's disease may present as an acute febrile illness with multiple joint involvement and the clinical picture, initially, can resemble rheumatic fever, especially if there should be changing heart murmurs. It is worth bearing in mind that rheumatic fever is exceedingly unusual under 5 years of age whereas 'rheumatoid', especially the acute form, quite commonly affects the pre-school child and may occur in early infancy. In Still's disease, especially the acute febrile form, the small joints of the fingers and toes, both proximal and distal, may become swollen and painful, an infrequent happening in rheumatic fever. One must remember that unusual joints may be affected in rheumatoid arthritis, such as those of the cervical spine leading to pain and stiffness in the neck. Again, one or other tempo-mandibular joints may be involved producing discomfort and limitation of movement on opening the mouth. In Still's disease there may also be changes in the lymphatic system (especially in young patients) with localized or generalized lymphadenopathy. The spleen, too, may be enlarged at the same time. The pericardium is sometimes affected and a friction sound may then be heard perhaps accompanied by a complaint of retro-ster nal pain which can at times be severe. Pericarditis can occur, too, in rheumatic fever. Although endocarditis does not occur in 'rheumatoid' cases, systolic murmurs may yet be heard, even changing ones. These variable bruits may be related to anaemia and tachycardia. On the laboratory side the total white count is generally low in 'rheumatoid' whereas in rheumatic fever an initial polymorpho-leucocytosis is usual although by no means constant. The anti-streptolysin O titre may be of some help in differentiating these two disorders, an elevated and often rising value being found in rheumatic fever but not in Still's disease. Incidentally, it is unusual in 'rheumatoid' to obtain a history of a preceding sore throat but this is a fairly constant finding in rheumatic fever, the latent period between the onset of infection and the appearance of rheumatic symptoms being 1–6 weeks. Finally, the response to salicylates in adequate dosage may prove helpful. In rheumatic fever the effect on the joint picture and fever is immediate (24–48 hr) and dramatic whereas in Still's disease there may be some relief of pain but the response is not striking and remittent fever often continues.

Anaphylactoid purpura may manifest itself in several ways and when joint symptoms are a prominent early feature rheumatic fever may be simulated. In this condition there is often a history of a preceding infection, even a sore throat. The joints most frequently affected are the knees and
ankles, sometimes the wrists. Swelling, tenderness and loss of joint mobility may occur. However, local heat is unusual and the pains are not migratory in character. In cases presenting with joint involvement diagnosis may be straightforward when there are, in addition, other suggestive features such as colicky abdominal pain, perhaps associated with the passage of blood in the stools, or the characteristic haemorrhagic skin lesions distributed about the elbows, buttocks, knees, ankles and feet. One should remember that the eruption of anaphylactoid purpura may be urticarial or erythematous at first although the individual lesions soon become purpuric and occasionally necrotic. Sometimes the tell-tale rash is late in appearing and the differential diagnosis may at first be wide in a child with the Henoch–Schönlein syndrome and include not only rheumatic fever but also rheumatoid arthritis, intussusception and even acute glomerulo-nephritis, depending on the initial pattern of symptoms and clinical manifestations. Perhaps the most difficult condition at times to differentiate from rheumatic fever is acute osteomyelitis, especially in the early stages of the illness. I can best illustrate this point by giving two case reports.

**Case reports**

C.J.A. Male. Aged 11 years. Admitted with 3-day history of chills, anorexia, vomiting and swelling and heat of both knees. No recent sore throat although very susceptible to tonsillitis. Had received several doses of aspirin before admission.

**Examination.** Temperature 101°F. Pulse 130. Tonsils enlarged with white exudate on both sides. Cardio-vascular system normal. Presumed subcutaneous nodule left elbow. Vague tenderness both shoulder joints; no swelling or redness. Hips tender on palpation. Both knees tender, swollen and hot; no erythema. Shortly before admission several epistaxes. Haemoglobin 75%. White cells 4000/mm³—polymorphs 85%. Corrected ESR 22 mm/hr.

An initial diagnosis of rheumatic fever was made and the child started on aspirin grains 20, 4-hourly and prophylactic penicillin V, 125 mg b.d. orally. The temperature fell normal, by crisis, within 48 hr, but the boy remained ill. A red, tender swollen area then appeared over the medial aspect of the upper end of the left tibia. The diagnosis was then revised to acute osteomyelitis and a sub-periosteal abscess was drained from which staphylococcus pyogenes was isolated.

**Comment.** The apparent response to salicylates was due to temporary suppression of fever by oral penicillin. In treating rheumatic fever prophylactic penicillin should on no account be started until the response to salicylates has been adequately assessed. The initial white cell count in this boy was misleadingly low for acute osteomyelitis and rheumatic fever alike. A temperature as high as 105°F is unusual in rheumatic fever.

M.H. Male. Aged 6 years. Six days before admission febrile head cold with associated cough. Three days later, having returned to school, became febrile again and complained of pain in the left knee. Following day, temperature 101°F. Left knee hot and painful. Aspirin and penicillin prescribed by General Practitioner. Forty-eight hours later developed painful right ankle; left knee more painful. At this stage referred to hospital. Family history of rheumatic fever.

**Examination (on admission).** Temperature 101°F. Pulse 120. Left knee warm; no active movements and all passive movements limited by pain and muscle spasm. No redness or swelling at this joint. Small clean cut lower part of knee. Tender erythematous area over lower part of right fibula. Greyish blue exudate over lower part of left fibula. Grayish red, thick, pus filled fluctuant abscess left ankle. Haemoglobin 83%. White cells 14,200/mm³—polymorphs 88%. Corrected ESR 27 mm/hr. Antistreptolysin O titre 388 units.

The differential diagnosis was between rheumatic fever and acute osteomyelitis. The boy was treated initially with large doses of aspirin. After 48 hr the temperature had settled but the left knee remained hot and painful. In order to exclude an osteomyelitis of the upper end of the left tibia the area was explored with negative findings. However, swabs taken from the wound subsequently grew staphylococcus pyogenes (the admission blood culture was negative) and a course of erythromycin was started. His anti-streptolysin O titre fell to 50 units 8 days after admission. Several weeks later X-ray changes consistent with a healing osteomyelitis in the upper third of the left tibia and the lower end of the shaft of the right fibula.

**Comment.** The first antistreptolysin O titre was marginally raised. The fall to 50 units in just over a week was very much against a rheumatic aetiology.

The last thing I want to mention, because it tends to get left out of the textbooks, is that it can be quite difficult to differentiate rheumatic fever from vague febrile myalgias which are probably caused by non-specific virus infections. I have seen two children at home recently with fever and a history of joint pains who had responded to full doses of aspirin by the time I examined them. In one case there was a family history of rheumatic fever and this child had quite an impressive systolic murmur which I now regard as innocent. The only thing to do in the absence of continuing rheumatic manifestations, especially signs of active carditis, is to stop the salicylates, and with the child in bed to watch his behaviour and temperature chart. If fever and joint pains do not recur within a few days of stopping treatment then the young patient can be mobilized. At this stage it would be wise to check the sedimentation rate and determine the anti-streptolysin O titre before continuing with convalescence.

Perhaps the doctors who were looking after the two patients I have just mentioned would like to say something. Dr Hartsilver?

J. HARTSILVER: Well, I was called to see a girl of 11 years, about 2 weeks ago, with a complaint of sickness and abdominal pain and, on enquiry, I found the child had had some liver sausage and I made a provisional diagnosis of food poisoning. I felt the child's abdomen, because sometimes one may be caught out with an acute abdomen in that way, and felt nothing abnormal so I put the child...
on a sulphadimidine mixture because there had been a few cases in my practice of food poisoning. But just before I went out of the house I was told that the child had had a sore throat and had gone swimming with the school and, subsequently, had pains flitting from one joint to another. I have always regarded pain in joints changing over like that as very strongly suspicious of rheumatic fever, so I revised my ideas at once and said the child had better keep to bed and also put her on penicillin and aspirin which is not the correct thing to do, but I thought so at the time. Now, subsequently the temperature came down: I forgot to mention the temperature was 101–102°F. The joint pains disappeared completely; there was no further nausea and the child seemed perfectly well, but because of the joint pains flitting from one joint to another I still felt unhappy. I felt all over for nodules and listened to the heart for changing heart sounds which is another important sign of rheumatic fever. Also, this child twitched a little at the mouth, but I happened to remember that we had had that twitch before, for she was a nervous child, and the mother corroborated that she was not making any purposeless movements suggestive of chorea. Well then, the question arose as to whether the child, although she seemed well, should be regarded as having rheumatic fever or not and I felt influenced in favour of rheumatic fever when I heard that another boy in the class at school the child attended had tonsillitis.

I informed the School Medical Officer according to the Ministry of Health brochure (the brochure that has just appeared on Rheumatic Fever), in which it is advised that where there is any shadow of a doubt, the Principal School Medical Officer should be informed with a view to swabbing throats; though I think it was not done in this case. In future I shall take a culture every time to see if there is a haemolytic streptococcus. Because of the doubt about the diagnosis I asked Dr Mann if he would be good enough to come and see my patient, and he very kindly suggested that the child should be regarded with suspicion and be kept under observation. At the present time—2 weeks later—there are no signs of rheumatic fever, no heart signs and no nodules; but the question is whether that child should be kept in bed longer or allowed to go about in the normal way. Well now, I think the thing to do is to keep her under observation and gradually get her up. Dr Mann suggested that the penicillin and salicylates should be left off and that he would be interested to know whether any signs of rheumatic fever have recurred. Well, there have been no joint pains and what I propose is that this patient be seen periodically; the mother will certainly let me know if there is any malaise of any sort which might lead one to suspect a recurrence.

T. P. Mann: Perhaps I could just say that this child had been on penicillin and Disprin for 5 days when I saw her. I am interested to hear that 4 days later, when off this treatment, there has been no recurrence of arthralgia. The pains were in both wrists, left elbow, shoulders and knees—quite a disseminated affection of joints. I think the other thing we should consider, just to add to what Dr Hartsilver has said, is to do a full white count, ESR and an ASO titre within the next 48 hr. If the ASO titre is, say, 800 units or something of that order, then it would be very much in favour of this being rheumatic fever. The other case was one I saw with Dr Alexander of Newhaven, an 8-year-old child. I don't know whether he would like to say something about that one? Well, this child had been poorly for 4 days when I first saw her; she had become moey, listless and developed pains in her knees, shins and feet. She was put to bed, examined by Dr Barton (Dr Alexander's partner), and was found to have a temperature of 103°F. There were no other abnormal signs except that she complained of pains in her elbows and wrists. There was a possible scarlatiniform rash about the ankles, so he put her on aspirin, gr. 10 t.d.s., and there was great improvement within 24 hr. I saw her 4 days later, after she had been on salicylates, and there were no abnormal signs. I should mention that there had been a vague history of sore throat 2 weeks previously. With this child, too, there was the remains of a rash over the left ankle which I thought at first was purpuric and I wondered about anaphylactoid purpura, but we looked at this very carefully and I don't think it really was purpuric. By the time I saw the girl it really was not possible to make a firm diagnosis and, as the child had been on salicylates for 4 days, I suggested stopping the treatment and seeing what happened. That was 8 days ago and perhaps Dr Alexander could tell us what has happened in the meantime.

R. Alexander: We are waiting for an ASO titre.

T. P. Mann: Is the ESR raised?

R. Alexander: It has not come through yet.

T. P. Mann: Is the child better?

R. Alexander: Quite.

T. P. Mann: Could I, perhaps, ask Dr Joseph what he makes of this type of case? Do you see
Rheumatic fever

these children; because I am quite sure that general practitioners see them and we, too, see the odd one with this sort of syndrome—fever, joint pains, limb pains and response to aspirin.

M. C. JOSEPH: Yes, I indicated earlier that I think this is a very difficult situation and I don't consider it too diffuse to say that if there is clinical suspicion of rheumatic fever one should investigate further as you have here. There is bound to be a group of patients who, on clinical grounds, you have doubts about but have not got enough weighty evidence to say 'this is rheumatic fever', and I think that it is this group that needs, as I mentioned, further laboratory and perhaps electro-cardiographic and radiological investigation. You will obviously say 'we can't do that on every patient who has a bit of pain in or near a joint', and I would just say: 'Well, if you clinically suspect rheumatic fever you should'. But if one doesn't clinically suspect the disease and if one is satisfied on the basis of the clinical findings, then there is no need to investigate further.

The really difficult situation is when you are in the country and you may be 50 miles away from laboratory help; but it is, I think, this very group that needs this extra help.

Could I just make one or two comments about some of the discussion earlier on? Dr Mann mentioned two points—one was about the response of rheumatoid arthritis versus rheumatic fever to salicylates. I get the impression that it is the fever that responds in both, but not the arthritis of rheumatoid, though it is still the fever that responds. I am making this point because I think it is sometimes misunderstood and said rather loosely that if you give salicylates and the patient responds, or the symptoms improve, then it is more likely to be rheumatic fever than rheumatoid arthritis. It should be made clear that in both conditions the fever responds, but in rheumatic fever the fever and the joint involvement respond, whereas in rheumatoid arthritis or in lupus erythematosus the joints do not improve dramatically within the first 24 hr; I mean you certainly alleviate the pain to a certain extent, but it is not the really striking response as in rheumatic fever.

The other point is the question of the family history; I do agree about this and I should have put it in. It has, I believe, been recommended recently that this is a genuine minor criterion because it is very useful; a fact well brought out in this particular child, wasn't it, whose sister, now aged 13, has had what seems to be typical rheumatic fever. This is really a soil as well as a seed disease; you have to have the streptococci around, but you also have to have a type of patient who is susceptible.

Another matter I just wonder about in Dr Mann's very interesting case of osteomyelitis, which is an important differential diagnosis, is how long it took for the temperature to drop. Was it a sudden fall?—because usually osteomyelitis takes 2–3 days for the temperature to drop and I think sometimes this is a useful point in the differential diagnosis, though one must admit it is usually a differential diagnosis in retrospect.

T. P. MANN: Well, to answer the last question first—the temperature came down by crisis from 104 to 96°F in a matter of just over 24 hr—a very dramatic response. It stayed down for 48 hr and then spiked up to about 101°F.

This point about Still's disease—I would say there are some children with Still's disease, particularly younger ones, with a very fulminating picture with a septic sort of temperature chart and, if you put them on full doses of salicylates, I would say that the joints won't respond very much—they may have less pain, but I think the physical signs will be just as apparent 48 hr later and I think that in this group the temperature may come down, but the joints very often are quite uninfluenced by salicylates and even by steroids. If you give them steroids after a week or so if they are doing badly quite a few of them do not respond dramatically even to the right sort of treatment.

R. KEMBALL-PRICE: Time is getting on and most of you have not had any opportunity of speaking yet so it is open for free discussion now if anyone else would like to speak.

L. B. PETERS: Perhaps I should mention that the tonsils of this child were twice as large as normal. Now I know that tonsillectomy medically is rather inclined to be a dirty word these days, but I often wonder whether in the case of rheumatic disease if you remove the tonsils you may prevent secondary cardiac complications. Can I ask if there was anything pathological in these tonsils at post-mortem and whether Dr Joseph feels that this has any significance?

M. C. JOSEPH: Can I be outspoken about size and say that I do not know what 'normal' is in terms of size of the tonsils. By this I mean that if you look at 500 normal children, say aged 5–7 years, I am sure you will find that the tonsils are anything from tiny little peas to huge giants, aren't they? Would you agree with that? And, therefore, I don't want to use the term 'enlarged' as being pathological just because I don't think I can tell. There is also some evidence that you and I anyhow are hopeless at saying what size the tonsils
are; an E.N.T. surgeon and his colleague got together and said: 'Let us say what size these tonsils are prior to operation', and when the anaesthetist had anaesthetized, they all graded the tonsils. After enucleation the tonsils were weighed and there was a complete lack of correlation with what had been forecast. In other words, I would like to suggest that size perhaps is less important than whether the tonsils look unhealthy, are fibrosed or have exudate on them and whether there is adenitis (by which I mean palpable tender glands bigger than you would expect). Personally I find it very difficult to evaluate diseased tonsils in the way that I have mentioned and if I was in any doubt I would ask my E.N.T. colleague what he thought about them. But there is a suggestion that if you remove the tonsils you have merely removed only one source of infection; that it is possible to get pharyngitis instead of tonsillitis. I believe that at this very moment the College of General Practitioners has a large research project on in which they are trying to assess which group of patients is benefited by tonsillectomy. One is very confused really as to the good or harm one does in advising parents to have a child’s tonsils removed. I don’t honestly know the answer to your specific point, Dr Peters. It might have done a world of good in this particular patient if we could be reasonably certain that the tonsils were diseased and a source of endogenous streptococcal infection, but one would have hoped that the penicillin might have eradicated this. I entirely agree with you. It is a very good point to have brought up and one which we have not talked about so far—as to whether indeed these tonsils, as a source of infection and no longer protecting the patient, might have been better out of the way.

R. KEMBALL-PRICE: Would anyone else like to say something? Dr Elliott?

R. I. K. ELLIOTT: Yes, just one point—a thing which came up when I was doing something quite different. I went through a series of post-mortems carried out at the Royal Sussex County Hospital over the last 50 years (up to 1956), and the thing which struck me was the change in the pattern of cardiac deaths. Over the 50-year period, deaths due to coronary heart disease showed a striking increase, whereas deaths due to rheumatic heart disease showed a numerically similar decrease; and, what is more, at the beginning of this period all the cases who were dying of rheumatic heart disease were young patients aged 20–30 years with severe, active carditis; but the patients who have died in recent years who came under this heading were all in the late stages of chronic valvular disease—in other words it does seem that over the last 50 years the incidence in severity of active rheumatic carditis has decreased very considerably. I wonder whether Dr Joseph would like to comment on this point which ties in with what he was saying about the social background.

M. C. JOSEPH: One of the things that strikes one is that it is said that the incidence of rheumatic fever is declining, but talking to Dr Mann and Dr Nash over the past 3–4 years (and I am sure our colleagues will substantiate this), there seem to have been quite a few patients—anyhow in this area—who have had rheumatic fever. We also have had an increase, not during the last 3 months but prior to that, either with rheumatic manifestations, chorea or rheumatic fever, although I believe there is some evidence that acute carditis during the active rheumatic process is probably less than it used to be.

R. KEMBALL-PRICE: I was very interested in the slide that Dr Elliott showed of the active myocarditis because I think with the obvious signs of old endocarditis people are sometimes apt to forget the permanent damage that may be done to the myocardium; and we see cases which, after successful mitral valvotomy, rapidly go into failure. There seems little doubt that this is due to the state of the myocardium which has been damaged by chronic disease from the rheumatic process.

Now I wonder if anybody else would like to comment?

QUESTIONER: This child had steroids in the second illness, I believe. How long did the child have them and do you think that if they had been continued the outlook would have been any better?

F. W. NASH: If my memory serves me right, I think he had steroids over a period of about 6–8 weeks. This was at the Evelina Hospital (Guy’s) and they noted that towards the end of this period of treatment he was getting mooned and his heart was enlarging fairly rapidly. Because of this they decided not to go on with steroids. In any event it is not now generally accepted policy to continue indefinitely with steroids because of the hazards of the treatment itself; one feels that if the rheumatic process has become inactive as far as one can tell by ordinary clinical and laboratory investigations, then there is really no object in continuing with steroid therapy in what is believed to be a hypersensitivity phenomenon; but there is, of course, some advantage to be gained by long-term penicillin prophylaxis to try to prevent infection with haemolytic streptococci. Would you agree with these general comments, Dr Joseph?
M. C. JOSEPH: Yes, certainly. I don’t quite know what the cardiac enlargement was due to—whether it was heart failure or continuation of rheumatic activity or both; one just cannot tell.

The rationale of using steroids is really because fundamentally they suppress the inflammatory process and in particular prevent the sequelae. In actual fact, I think it is very well documented that if you have two groups of patients and you give steroids to one and not to the other the signs of carditis diminish much more rapidly in the group treated with steroids so that they do seem to have an important anti-inflammatory effect. The use of steroids is also considered of special importance in the prevention of fibrosis and its end-results, and this is why there is all this argument still as to whether steroids should be given to every patient with rheumatic fever or only to those who have, as far as one can tell, evidence of carditis. There are some people who say every patient who has rheumatic fever also has carditis but that you and I cannot always detect it, but I don’t know how we prove this point without post-mortem evidence.

R. KEMBALL-PRICE: I think it might be relevant here to mention the differentiation of pericardial effusion and heart failure in the course of rheumatic fever because they have certain points of similarity. In both you have cardiac enlargement on X-ray and you may also have engorged neck veins and an enlarged liver, but the prognosis of heart failure in the course of rheumatic fever is far worse than that of pericardial effusion. About 10 years ago Gerald Thomas (1954) as a result of his experience at Taplow, laid down certain points of differentiation, and there were ten that he mentioned. First was the time of onset, in that pericarditis and effusion tend to occur early in the attack whereas heart failure tends to come late. The temperature is practically always raised with pericarditis and is often normal in the state of heart failure. The sedimentation rate is always up with pericarditis and may be normal at the time when heart failure develops; the same is true of leucocytosis. Oedema and ascites are both common in heart failure but are not seen with pericardial effusion. In addition, a pleural effusion is common with a pericardial effusion and it is rare in heart failure. And then again in pericarditis a rapid change in the heart size on X-ray is in favour of fluid coming and going rather than the cardiac size changing. Furthermore, the hilar congestion of pulmonary oedema is common in heart failure but is not commonly seen with pericardial effusion. Finally, we find that heart failure tends to respond to digitalis whereas a pericardial effusion is unaffected by this treatment.

Well now would anybody else like to speak? Perhaps as it is getting late we ought to end our proceedings, but before doing so I should like to thank all the speakers, particularly Dr Joseph who has made such a useful contribution to our knowledge about rheumatic fever. Thank you, Dr Joseph.

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