DISCUSSION

Professor Kellgren: The first question I am asked is whether clinical rheumatoid arthritis may be found with negative serological tests. The answer to that is that you certainly do find this, even in patients who have undoubted rheumatoid arthritis with nodules. There are occasions in the course of the disease when tests become negative. It is not a finding which is present all the time, and this is particularly true in patients who have had a period of disease activity and then go into a very prolonged remission with anatomical changes, as well as in patients at a very early stage of the disease. Many who appear to have rheumatoid arthritis and have a negative reaction may really be suffering from one of the other forms of inflammatory erosive polyarthritis like a psoriatic or spondylitic arthritis; we are not always able to recognize at the time a patient with Reiter's disease unless he has urethritis. Then it depends on which test you use and the sensitivity of the test. Latex fixation tests give more positive results in inflammatory polyarthritis of all kinds, and thus they are rather less useful in diagnosis, giving positive results for example in tuberculosis or sarcoidosis whereas the tests using sensitized red cells show a lower proportion of positive reactions but are more specific.

Another question is whether rheumatoid arthritis is associated with gynaecological and urinary infections. I think this really relates to the Reiter group of polyarthropathies, rather than ordinary rheumatoid arthritis.

The next question, " What is the incidence of rheumatoid arthritis in children? Does it differ in the various regions of the country, and what are the diagnostic signs if different from those in adult patients?" There are no data on incidence, but it is pretty uncommon in children compared with adults. Diagnostically, there are differences. Rheumatoid arthritis in children, or Still's disease, has at times embraced all chronic inflammatory polyarthritis in children, and differential diagnosis is less well developed in children than in adults. However, children with rheumatoid arthritis more often have large limb joints involved than the small joints of the hands and feet. Also they more often have x-ray changes in the sacro-iliac joints. There is a much greater tendency to ankylosis than in adult rheumatoid arthritis, and there is a definite incidence of iritis. All these features are really features of ankylosing spondylitis and not of rheumatoid arthritis. What is really fascinating is that, in a recent survey by Professor Bywaters of the parents and blood relatives of children with so-called Still's disease, to everybody's great surprise

what was found was not an excess of rheumatoid factor or rheumatoid arthritis, but an excess of ankylosing spondylitis. Therefore it does look as if a substantial proportion of cases of so-called Still's disease are really suffering from juvenile spondylitis and not juvenile rheumatoid arthritis. This of course has very important therapeutic implications, because in ankylosing spondylitis it is absolutely essential to keep the joints moving and the result of plaster splintage is disastrous. Hence, it is important to make the differential diagnosis; many people through bitter experience have learned that most children should be treated by mobilization and not by splintage.

Then finally, " Does the use of ACTH lead to subsequent pituitary failure to secrete natural ACTH? " I do not think there is a great deal of data on this. There is not quite the same tendency to collapse, but there is no doubt that when a patient has been given ACTH in effective doses the response to external stress may not be normal. The difficulty about ACTH is that it is biologically standardized and this is not very accurate, while patients may also develop resistance to it.

Dr Duthie: Might I clarify one point about your family study? I recollect that they found more rheumatoid disease in the female relatives and more ankylosing spondylitis in the males and there was a double genetic inheritance.

Professor Kellgren: What they found in the females was erosive polyarthritis with negative sheep-cell reactions, which is not quite the same thing. This of course raises the interesting point that there is an excess in all populations of females who have erosive arthritis without rheumatoid factor. Is this rheumatoid arthritis or is it actually a female peripheral variant of some of the conditions giving rise to central arthritis in the male?

Dr Thompson: I have been asked about pre-pubertal ankylosing spondylitis, which is a very real thing. Both in our series and in Hart's at the Westminster Hospital, the first symptoms in ten per cent of patients with spondylitis began before puberty. The other point I was asked about concerned genital infection in rheumatoid arthritis; in our series the incidence was the same as in the general population.

Dr Mason: I have been asked two questions about acute gout. The first is " Can gout be painless? " A patient of mine with gout diagnosed by the hospital has a very large tophus on the dorsum of a terminal interphalangeal joint of the fourth finger. It is unsightly and a nuisance but painless. I think that a striking thing about gout is the acuteness of the acute attack and the painlessness of chronic gout. This makes one wonder what the mechanism is which produces pain in the acute attack. It is probably due to the deposi-

tion of uric acid, but once urate has been deposited the lesion seems to be practically painless. There is a faint criticism in the second question: " The classical description of the pain of gout likens it to a vice being tightened and retightened. I do not believe this is true; all the descriptions which have been given to me are of much milder pain ". I think it is very uncommon to have painless or relatively painless acute gout, and I just do not know what the questioner's diagnostic criteria are for gout. Maybe the patient has tabes or something else.

" In the long-term management of gout with benemid or anturan, how often should serum uric acid be estimated; once stabilized, does uric acid level stay stable on a given dosage? " I do not know that one can really give an absolutely firm answer to that. There tends to be a pretty rapid and early fall and sometimes a bit of a rebound. You do not always achieve an immediate dramatic effect and maintain it, but my own practice would be to control the dosage by estimations of serum uric acid monthly or every two or three months, and then every six months, and then perhaps once a year.

" In view of the effectiveness of uricosuric agents, is there any indication for dietary restrictions, solid or liquid, in gouty patients? " The fact is that if you have the patient on full doses of uricosuric agents and he does overstep the mark a little, at a banquet for example, he probably simply spills it out in the urine almost immediately and the episode has quite a transient effect on serum uric acid levels. Maybe with a patient in whom there is difficulty in keeping the serum level below 6 mg. per cent, dietary restriction is needed. Aim to get the serum uric acid level below 6 mg. per cent, and if you are not succeeding by uricosuric drugs, restrict the food; I usually restrict offal, simply to make it easier. I allow patients to drink gin or whisky within the ordinary social limits but discourage them from drinking too much beer or heavy wine; if they are doing well and are fully controlled after a year or so chemically and clinically, I usually encourage them to believe that they can return to a more normal life. I think this is common sense. If a glass of champagne gives them gout, obviously they are silly to take it, but I do recommend whisky or gin.

" Does diet have any useful part to play in the modern treatment of gout? " One point is that some people tend to have a sensitivity to certain foods or drinks, and obviously if every time they eat caviare they get acute gout, the answer is to stop eating caviare.

" Are urate calculi and incapacitating renal colic common in treatment? " I would not say that they are common, but they present a very real problem. This is why you should produce

uricosuria very gently and why you want to ensure an adequate fluid intake. If necessary, give the patient alkaline agents such as sodium citrate, and teach him how to use litmus paper to maintain the urine slightly alkaline and prevent the deposition of uric acid or urate. The alternative is to reduce the dose of uricosuric agent until you have drained them of their excess urate, but in certain cases you will be in difficulty. I can think of one particular patient on one tablet of anturan every other day, who had a roaring attack of renal colic for which he did not thank me. We do not know whether long-term uricosuric agent treatment prevents complications of gout. Indeed we tried to plan a nation-wide study to determine just this, but the statisticians showed us quite clearly that this was not possible. Nor do we know whether long-term uricosuric treatment will increase the renal complications of gout.

Dr Duthie: I would underline the dangers of unduly enthusiastic use of uricosuric agents. We had one rather unusually young sufferer from gout who developed complete blockage of both ureters and anuria and was very lucky to live. There is some evidence on the mechanism of the acute attack. Injection of uric acid in its ordinary forms or as urates into the joints never precipitated an acute attack, but you can produce an acute inflammation with microcrystals injected into the skin which you can inhibit by colchicine; these very sharp, tiny crystals are phagocytosed by leucocytes and there is thus the possibility that the injury to the leucocytes releases some of the intracellular enzymes, which may be the basis of the acute attack, and that colchicine in some way inhibits the phagocytosis of the crystals.

Dr Mason: If I had a serum uric acid level of over 7.5 mg. per cent, I would be on a uricosuric agent. I think that is the answer.

Dr Duthie: I am asked about the place of enteric-coated salicylates in rheumatoid arthritis. I think they have a very real place for people who suffer from the troublesome dyspepsia that aspirin not uncommonly causes. " Dyspepsia " does not mean bleeding, and bleeding does not mean haematemesis; a patient can have aspirin dyspepsia and not bleed, and another can bleed a little with no dyspepsia, but there is no question that if significant bleeding causing iron deficiency is happening, giving enteric-coated aspirin or sodium salicylate tablets markedly reduces the incidence of bleeding. With modern coatings, perfectly satisfactory serum salicylate levels can be maintained either with enteric-coated aspirin or sodium salicylate. All clinicians think that aspirin is a much better drug than sodium salicylate, but if there is an undue sensitivity to aspirin sodium salicylate can certainly be used in an enteric-coated tablet, and although there will be a delay in attaining the initial level, once it is

attained it can be maintained.

Phenylbutazone does not cause the mucosal oozing of blood that aspirin does; for if you tag the patient's own red cells with radioactive chromium and reinject them, then collect the faeces and measure its radioactivity, 70 per cent of people on aspirin will show some blood loss (an average 4.9 ml. per day), whereas this does not happen with phenylbutazone or oxyphenbutazone. However, massive haematemesis from phenylbutazone does occur. I think we all agree on this. Haemorrhage can be of two kinds: mucosal oozing or a massive haemorrhage from an erosive ulcer, which is clinically dangerous.

Another questioner asks whether it is essential for rheumatoid arthritis patients to obtain their bed rest in hospital or whether treatment at home is a possible alternative. This is really an extremely fundamental question. In the early case where the patient is not as yet disabled enough even to think about coming to hospital, if one could persuade the patient to come in, maybe for a week or two weeks, to have a prophylactic light splint made and be taught how to wear it and what simple remedial exercises to do, I think this would give a very valuable opportunity for training right at the beginning of the disease, even although it means occupying a bed with a rather benign case. It is like the minimal tuberculous lesion, I think. If rheumatoid arthritis were as lethal as tuberculosis, we should want to treat it as early as possible by the most effective means available; we are tending now to give a much higher priority to the early and active case for admission to hospital than we are to the patient with established deformity and a lot of joint damage. I am firmly convinced, without being able to prove it to anybody, that at a certain stage a rheumatoid lesion is potentially reversible, and I am equally convinced that after it has gone on a certain length there is a vicious circle which you cannot break; I do not think that if we ever got a drug that would cure rheumatoid arthritis it would cure it other than at this rather early stage. Once the chronic inflammatory vicious circle is established, palliation is all that you can hope for, so I would say that a lot more beds should be available in each region for early cases of rheumatoid arthritis. Whether or not this would alter the long-term prognosis I do not know, but it appears to do so. There is a second reason for this training. If you make splints for outpatients, 50 per cent of them will not wear them because they are uncomfortable at night, whereas if they were a week or ten days in hospital and were disciplined, they would get over this stage and would go on wearing them for months. I am convinced of this. Consequently, I would say that from the point of view of getting control of the disease and educating

the patient there should be a lot more beds, and they would not be blocked for months and months as they often are now by chronic cripples.

We have used two preparations of intravenous iron, iviron and ferrivenin. After a test dose of 50 mg. we give 200 mg. daily until the patient has had 3 G. The initial total was 5 G., and we may go back to a slightly higher level, say 4 G., because improvement in the red cell count and general haematological indices occurred in all patients given 5 G. A newer preparation of iron, dextrin-iron (not dextr*an*-iron which can be given intravenously but is primarily used by the intramuscular route, and which came under some suspicion) is claimed to be very free from toxicity. All I can say is that we have had little or no trouble using either ferrivenin or iviron intravenously. I am interested to hear that the manufacturers of intramuscular iron are said to state that a side-effect is a poly-arthritis, possibly due to the sugar radical. This is news to me. If a person has already got an arthritis, it is difficult to say that anything more is happening. I have no great experience of people given iron who have not already got arthritis, so I really cannot say whether the preparation might have such an effect, but it certainly has not been our experience.

Question: How can one treat the intractable secondary anaemia associated with acute rheumatoid arthtritis, if oral, intramuscular, and intravenous iron have all failed to raise the haemoglobin value?

Dr Duthie: This does occasionally happen, usually in the late, chronically debilitated cases. It is certainly true that a lot of patients will not respond to, say, 1 G. of intravenous iron. You have got to give 2 or 3 grams. If anaemia is intractable and the haemoglobin at a clinically undesirable level transfusion is indicated, although it is a palliative method and has all the inherent dangers of giving blood. This is rare in my experience, and if I had found somebody with a very severe anaemia of this sort and all the indices of rheumatoid anaemia, I should be very suspicious and would go through the case with a toothcomb to find out whether there was not some other cause. For example, going through our case records, we began to suspect that megaloblastic anaemia was not too uncommon an accompaniment of rheumatoid arthritis, and over the last ten years we have collected 35 cases of megaloblastic anaemia in rheumatoid arthritis, which is roughly five to six times the incidence in the population as a whole. One of these cases of megaloblastic anaemia would respond only to vitamin B_{12}. The interesting thing about this anaemia is that in half of the 17 cases where we were able to measure absorption of radioactive vitamin B_{12} it was

normal, in spite of the fact that there was a megaloblastic bone marrow.

Question: Where do we stand with gold therapy?

Dr Duthie: I have quoted briefly the results of the Empire Rheumatism Council trial. There was a significant betterment in the cases given gold which was still present a year after the end of the course, although the last assessment shows that it is diminishing. The dose used in the Empire Rheumatism Council trial was 50 mg. weekly until a total of 1 G. had been given. The question of optimum dosage, interval between courses, and repetition of the course cannot be answered, certainly not on the basis of a controlled clinical trial, because we plan first of all to submit to trial the method by which gold was most commonly used, which was to give a total of 1 G. at the rate of 50 mg. a week, which takes over six months. A lot of people would suggest that a maintenance dose of gold given at first every fortnight and then maybe every month, and continued almost indefinitely, will maintain the effect, but I have no personal experience of this. I do not like gold. I am reporting that it is respectable, but any of us who have worked with it for long enough have seen ghastly cases of exfoliative dermatitis, aplastic anaemia, and thrombocytopenia. I know that you have to accept certain risks with all powerful drugs, but we do not use gold as a routine.

Professor Kellgren: I should like if I may to amplify these questions, because some of them are very important. I agree with Dr Duthie that ideally any case of rheumatoid arthritis should be treated where possible by bed rest in hospital. I am entirely in agreement with the reasons he has put forward, but there are two real difficulties, firstly, that the Health Service is not set up to do this at present, and secondly, that there are situations in the family where the separation of the mother from the children and so on does lead to difficulties. Where there are a good home and excellent facilities for nursing I see no reason why, particularly in the not too severe case, a period of bed rest should not be carried out at home, provided that the practitioner in charge can organize the proper positioning of the patient in bed, the supervision of daily exercises, and if necessary splintage for prevention of deformity as required. This all seems to me to be well within the competence of most practices, given a good enough home. This is the method that we use extensively in the Manchester region, simply because the clinical problem is way beyond the resources of the hospital service as at present organized. I think that on general principles the more diseases are treated in the home rather than in the hospital, the better for all concerned.

We have not touched at all on the question of development of

more serious visceral and vascular and other lesions in rheumatoid arthritis, and the need for steroid therapy to save life. I was going to use intractable anaemia as a bait to raise this question, because a very small proportion of patients do suddenly develop an auto-immune haemolytic anaemia which you can treat very effectively with steroids and with nothing else. They are patients who have apparently had ordinary rheumatoid arthritis affecting only the joints for years and years; they get worse and you find that they have developed all sorts of visceral lesions. They now have lots of L.E. cells in their blood and all sorts of peculiarities, or have developed periarthritis nodosa or some late complication. This happens much more commonly than by chance and these people are treated satsfactorily by steroids.

Dr Duthie: I quite agree. If these patients begin to show extensive visceral lesions, there is no alternative. I should only point out on the other side of the picture that necrotizing vasculitis has apparently become much commoner since steroids have been used, certainly in the experience of the Mayo Clinic. However, in the individual case with severe anaemia and visceral involvement steroids can be life-saving. As regards bed rest, my own quoted figures make it obvious that these people must be treated at home. The only slight amendment I would make to Professor Kellgren's statement is that a mere three or four weeks in hospital does not mean that the patient is not going to be treated by his family doctor most of the time. All I was saying was that if the patient was in hospital for this period you could start educational programmes for the doctor and hope that he would co-operate with it.

Question: During the 1962 rubella epidemic, a child of six years developed a Henoch-Schoenlein purpura about six weeks after an attack of rubella. Is this a recognized complication or was it coincidental?

Dr Thompson: The quick answer to the first part of the question is " no ". I have come across no reference to this in the literature but I should think that the relationship is probably significant. Henoch-Schoenlein purpura is a non-specific allergic response and all sorts of things have been blamed as allergens, from streptococcal infection which is the usual one to such apparently innocuous agents as chocolate. If a streptococcus can cause a sensitivity state resulting in a diffuse vasculitis with cutaneous manifestations, because that is what a Henoch-Schoenlein purpura is, then it is quite possible that a rubella virus, or even some agent used in treatment, might have provoked this allergic response. The time interval is about right. There is usually an interval between the application of the antigen

and a delayed tissue type of immune response.

Question: A child of four has a throat infection with a Lancefield group-A haemolytic streptococcus. How long should penicillin therapy be continued to avoid possible development of acute rheumatism?

Dr Thompson: Generally speaking until all the haemolytic streptococci have been eradicated from the throat. Fortunately bacteriologists say that this particular type of streptococcus is very sensitive to penicillin and rarely if ever develops immunity, so that it is very effectively dealt with by pencillin. Provided adequate dosage is given (most practitioners give a loading dose by intramuscular injection in addition to continuing with an oral preparation, usually penicillin V) one week's treatment is probably adequate. Within about 48 hours of starting therapy for the throat infection, the throat is usually clear. If there is any doubt, depending upon local signs in the throat or persistent symptoms, throat swabs must be taken, and treatment continued until you are sure.

Question: Are steroids necessary in the treatment of acute rheumatism of childhood to prevent cardiac lesions?

Dr Thompson: Unfortunately there is no evidence that steroids can prevent cardiac lesions. I should mention the incidence of cardiac lesions in the cortisone versus aspirin trial conducted for about five years and at considerable expense in New York, Toronto, and London. It was an attempt by physicians in Canada, United States, and Great Britain, at a co-ordinated clinical trial, and it showed at the end of several years of assessment that there was really no significant difference between the cortisone-treated group and the aspirin-treated group. However, I should stress that this was on a fixed dosage schedule and also with the use of cortisone, which has unpleasant side-effects, particularly as regards water and salt retention. Prednisolone does not have these side-effects, or only to a negligible extent. Aspirin in large dosage in rheumatic fever has been shown to cause cardiac embarrassment by electrolyte changes and by causing hypervolaemia, so that cardiac dilatation and pulmonary congestion may develop during massive aspirin therapy. The point about steroid therapy is that it will be comparatively brief. We are not discussing steroid therapy for rheumatoid arthritis, where the risks of neuropathy, arteriopathy, myopathy, osteoporosis, and gastric ulcer come in. The contraindications to steroids in acute rheumatism are probably few, and treatment is going to be circumscribed and limited. I would feel morally obliged, in dealing with a child in a severe acute attack of rheumatic fever or with established carditis, to give steroid therapy in addition to aspirin. There is no reason why you should not give both. At the same time I would

strike the note of caution that Dr Pickworth sounded this afternoon, that you may have to stay your hand a little in these circumstances to be absolutely sure of the diagnosis, because, of course, rheumatic fever can mimic osteomyelitis, septicaemia and various other conditions in which steroid therapy could be hazardous, but once you are sure of your ground prednisolone and aspirin represent the safest, most effective and most morally justifiable treatment of very severe acute rheumatism in children, especially if there is carditis.

Question: Should trained physiotherapists be available for treatment of patients in the home?

Dr Pickworth: My answer is " yes and no ". If the hospital is near and if travel to hospital is really quite easy, I am inclined to think that patients should go to hospital because of the power of the group urge. In my part of the country where some patients live a long way from hospitals, to have a physiotherapist for the treatment of patients at home would be a very good thing.

SUMMING UP

Chairman of Faculty: It is now my pleasant duty to propose a vote of thanks to all those who have helped to make this meeting the great success it has undoubtedly been. Firstly, Professor Kellgren, may I say how much we have appreciated your presiding over the meeting today. We count ourselves fortunate to have had such an eminent person as yourself as our chairman. Dr Dudley Hart of the Westminster Hospital, Dr Mason from the London Hospital, and Dr Duthie from the University of Edinburgh have all travelled considerable distances to be with us, I am sure at great inconvenience to themselves. As some recompense, gentlemen, please be assured that your contributions have been highly valued. Dr Malcolm Thompson is of course our own consultant in physical medicine; he has not only addressed us, but has also taken a personal interest in many of the arrangements for today. Dr Newton has, I think, put into perspective the more controversial aspects of the problems of arthritis, namely, the role of manipulative treatment. Undeterred by the presence of a number of well-known physicians, Mr Peter