DR. B. M. ANSELL (Taplow) Dr. Huskisson, you dismissed the method very readily. I want to comment particularly on this because of some work that we have been doing at Taplow over some years. About 5 years ago I presented some work on the DAT and the tube latex tests in synovial fluid in Still's disease, in which we found relatively few positive tube latex results. Subsequently, David Champion has been working with a slide latex test and has found that this correlates much better with the synovial fluid DAT and the blood latex than the tube latex test. We have not yet worked out why, Dr. Holborow thinks that it may be something to do with immune complex development in the synovial fluid. I would therefore like to ask your method. Secondly, there is the question of pre-treatment of the synovial fluid. This is relevant because the technician working with us found, particularly in the viscous fluids, that all sorts of queer things happened if he did not pre-treat them with hyaluronidase. Our findings, of course, are at complete variance with yours because we have had only one positive latex in a synovial fluid using the slide method in a patient whom we did not consider to have rheumatoid arthritis.

DR. HUSKISSON I should be pleased to supply full details of our slide latex test. We found that the latex test gave false positive results less commonly than the Waaler-Rose test. I agree that it is necessary to use hyaluronidase for very viscous fluids but we avoided it because it has been shown to increase the incidence of positive tests.

DR. A. ST. J. DIXON (Bath) Results such as these are of considerable interest for the criteria for diagnosis of rheumatoid arthritis and their international standardization. Dr. Rotes-Quérol in Barcelona has suggested that joint fluid diagnostic for rheumatoid arthritis may show the combination of a positive Waaler-Rose test plus ragocytes.

DR. W. W. BUCHANAN (Glasgow) We have looked for ragocytes in synovial fluids in a large number of different joint diseases, and found them to lack diagnostic specificity. Inflammatory joint fluid contains many dead or dying polymorphonuclear leucocytes, and these will appear as ragocytes when examined by conventional staining methods. The polymorphonuclear leucocytes in chronic bronchitic sputum also appear as ragocytes.

Synovial Rupture, Experiments on Cadaveric Knees. By R. ASTLEY COWPER, M. I. V. JAYSON, and A. ST. J. DIXON (Royal National Hospital, Bath, and University of Bristol). This paper and the discussion thereon were published in the March issue of the *Annals* (1971, 30, 162).

Microradiographic Aspects of Articular Cartilage Ageing. By A. DHEM (Department of Anatomy, University of Louvain, Belgium).

This study was performed on the lower end of the human tibia at the ankle joint; 84 pieces were taken at autopsy from patients aged between 16 and 96 years, who had died from acute illness or after trauma. Undecalcified sagittal sections, embedded in methyl methacrylate, were submitted to microradiographic analysis. This

technique revealed clefts, or microfissures, in the calcified layer of cartilage only in subjects more than 50 years old. These clefts are limited by the tidemark (the interface between the hyaline and calcified cartilage), and extend to a variable depth into the subchondral bone plate; some are filled with hypermineralized material. The same features were found in decalcified paraffin embedded sections.

These observations suggest that ageing of joints is a specific phenomenon different from arthrosis.

Discussion

DR. D. L. GARDNER (Kennedy Institute) It would be important to know whether these fissures which you have demonstrated so clearly are real phenomena; are they present during life, or are they a reproducible result of a constant artefactual biophysical change in the matrix of the cartilage or bone? There is some evidence in other species (e.g. turkey) that, even in young creatures, a series of splits in cartilage can be observed in preparations like this. One thinks they are present because of a change in the biophysical structure during section preparation, the change taking place at a constant zone.

DR. DHEM No, we never find these changes before the age of 50 years, and in only half the specimens from subjects aged 50 to 60 years. We have not taken account of fissures which appear black under microradiography, but only of those in which the fissure is calcified. I have found the same changes in the hip joint but I have studied only five specimens.

Hearing in Rheumatoid Arthritis: Results of Audiometry in 76 Patients. By C. J. GOODWILL, I. J. LORD, and R. P. KNILL-JONES (King's College Hospital).

Copeman (1963) reported three patients with rheumatoid arthritis in whom increased activity of the arthritis was associated with deafness; in two the deafness was of conductive type. The incudo-stapedial and incudo-malleolar joints are synovial joints and so presumably could be involved in the rheumatoid process.

An unselected series of 76 patients with classical or definite rheumatoid arthritis have been examined by pure air-conduction and bone-conduction audiometry, salicylates being discontinued 3 days before. Patients with other possible causes for deafness, such as chronic otitis media, Menière's disease, and acoustic trauma, were excluded.

The activity of the arthritis was assessed using the Systemic and Articular Indices of Lansbury (1956). The duration of the arthritis, Waaler-Rose titre, and presence of nodules were noted, and the functional activity was graded 1 to 5.

No patient was found with conductive deafness sufficiently severe to merit exploratory tympanotomy, although minor degrees of deafness were found; no patient complained of deafness, and none had a negative Rinne test. Two patients had a single 'dead ear' preceding the rheumatoid arthritis by many years; these two patients were excluded, leaving 148 ears for analysis.

The mean hearing loss was not related to the duration of the arthritis or to the Systemic or Articular Indices.

However, there was a greater hearing loss in the sixteen patients with rheumatoid nodules, these being significant in the left ears only. Those with nodules had a higher Systemic Index and more severe disability but were otherwise comparable.

One man aged 60 years, who was seen before the study commenced, had classical rheumatoid arthritis and unilateral conductive deafness for which no explanation was found apart from his arthritis, even at exploratory tympanotomy.

No evidence of rheumatoid arthritis was found in three sets of ossicles obtained *post mortem* from three further patients.

We have found no relation between hearing loss and the activity or duration of rheumatoid arthritis although the cases reported and those of Copeman indicate that conductive deafness can occur with rheumatoid arthritis. The hearing loss in the patients with rheumatoid nodules was sensorineural in type. Any effect of salicylates is reversible within 72 hours of stopping them (Myers, 1965).

References

- Copeman, W. S. C. (1963) *Brit. med. J.*, 2, 1526
 Lansbury, J. (1956) See 'Arthritis', ed. J. L. Hollander, 6th ed., 1960, pp. 266-7. Lea and Febiger, Philadelphia
 Myers, E. N., and Bernstein, J. M. (1965) *Arch. Otolaryng.* (Chicago), 82, 483

Discussion

PROF. V. WRIGHT (*Leeds*) The Lansbury Systemic Index has five parts to it, not four. Was that taken into account? I was not clear what the 'friction resistance' was. Was it the flow of air over the middle ear or the resistance between the ossicles?

DR. GOODWILL I agree there are five parts to this index, the fifth being the daily number of aspirin tablets, but so many of our patients were on regular dosage and not taking aspirin on demand that we included only the first four parts of the index. We compared hearing loss in patients not taking salicylate (38 ears) with those in whom we were obliged to stop salicylate to perform audiometry; those who were taking salicylate recently had less hearing loss than those who had not. I am not suggesting any significance because there were differences in duration, but it does not seem to be an aspirin effect.

The specific acoustic impedance refers to the ease with which the ossicles can be moved, and it is in mechanical ohms/sq. cm., here plotted against frequency. This is observed data and there is remarkable correlation with theoretic calculation. About 2000 Hz. is the lowest point of the curve and the frequency at which increasing this resistance would produce most hearing loss. This is calculated from an involved formula, which I am happy to go over if necessary, which applies to any mechanical system. The total impedance is related to the frictional resistance between the ossicles, the effective mass of the moving parts, and the elasticity of the ligaments. These results are obtained assuming these three are constant, and I accept that the elasticity of the ligaments will not be so; we may ignore ligaments elasticity for the moment because movement in these joints is very small.

DR. D. A. PITKEATHLY (*Manchester Region*) How many patients with nodules also had peripheral neuropathy? Secondly, there were presumably more patients on steroids with nodules than without nodules. Is there any information on this?

DR. GOODWILL We did not analyse patients with peripheral neuropathy separately, but very few were included in this group. The results would not have been significant, but certainly the few were not notable for being more deaf. We did not find a relationship between steroids and deafness, although this was related to the duration of arthritis and age so that it could have been obscured.

DR. S. P. LIYANAGE (*Reading*) We have studied 33 patients with rheumatoid arthritis and there were three with conductive deafness, all due to infection. We concluded that there was no evidence that rheumatoid arthritis of the synovial joints of the middle ear contributed to deafness. We found, although we did not stop salicylates, that nearly half had a significant deafness, and about 40 per cent. complained of some hearing loss, which is in contrast to your results.

You have excluded patients with otosclerosis from the trial. How was this diagnosis made? Some of these cases with conductive loss could, theoretically, be due to rheumatoid involvement of the ossicles.

DR. GOODWILL I cannot explain why so few of our patients did not complain of deafness. They were asked 'Have you any difficulty in hearing', not 'Are you deaf'? Some patients did admit to mild deafness on direct questioning. We excluded any infected ears. The figures for otosclerosis in East London are 3 per 1,000; it is unlikely that this could influence our series. Secondly, otosclerosis occurs in a younger age group, 15 to 45 years, and the majority of our patients were aged 45 to 65, so that, if present, it would have been apparent—as in one patient who was inadvertently included. I agree we could not exclude it except in the one ear which was subjected to tympanotomy.

PROF. E. G. L. BYWATERS (*London*) I should like to return to Dr. Pitkeathly's question. Do you think that the hearing loss that you have shown could be associated with a sensory ischaemic neuropathy affecting the auditory nerve, because this is the most likely event if you have shown a significant association with nodules and arteritis?

DR. GOODWILL Yes, this certainly occurred to us, whether there could be a neuropathy possibly due to an arteritis affecting the nerve. We did not have enough patients with clinical evidence of peripheral neuropathy to suggest a correlation but this could be the explanation.

DR. P. A. BACON (*London*) We have recently seen a woman with non-nodular long-standing rheumatoid arthritis who showed a degree of conductive deafness on the audiogram. This was significantly but reversibly improved by a single dose of corticosteroid, suggesting that it could have been due to inflammatory disease. Have you seen this type of case?

DR. GOODWILL We have not seen this condition. In our patient with conductive deafness it was felt advisable to perform an exploratory tympanotomy in view of the severity of the hearing loss and so we were not able to do

serial audiometry or to find out whether steroids would have improved that deafness.

Analysis of the Joint Capsule Collagen Content. Studies in Control, Rheumatoid, and Ehlers-Danlos Knees. By M. I. V. JAYSON, G. STEER, A. ST. J. DIXON, and P. BEIGHTON (*Royal National Hospital, Bath*). This paper and the discussion thereon will appear in a future issue of the *Annals*.

Chlorambucil in the Management of Juvenile Chronic Polyarthritis complicated by Amyloidosis. By B. M. ANSELL, A. EGHTEDARI, and E. G. L. BYWATERS (*Canadian Red Cross Memorial Hospital, Taplow*).

The overall prognosis in Still's disease is reasonably good since the disease usually becomes inactive and, with adequate supervision, function is well maintained. However, even in comparatively mild cases, amyloidosis may develop and lead to death. To date, no therapy has been shown to influence the progress of the amyloidosis, but in patients in whom the disease has become quiescent, the progression of the amyloidosis appears to stop. Because of this, during the past 3½ years, we have used chlorambucil in an attempt to control disease activity in twelve children with Still's disease who had developed this complication. The initial dosage was 0.2 mg./kg. bodyweight/day and this was modified according to the clinical response or to the effect on the white blood count and platelets.

Initially the aim was to give 6 months of therapy. In two cases this was not possible because of thrombocytopenia in one and severe skin infection in one. One of these patients who already showed a rise in blood urea at the commencement of therapy has died. The others have received at least 6 months of therapy. All have shown a reduction in the number of active joints and an improvement in function tests. On eight occasions it was necessary to stop treatment on account of a fall in the white blood count or platelets, but the blood picture recovered rapidly, and when necessary it has been possible to resume treatment at a lower dosage without haematological problems. In two cases it has been possible to discontinue corticosteroid and all have had reduced dosage. In two, chlorambucil has been stopped with maintenance of a satisfactory clinical state to date, but in two others, after remissions of 8 and 10 months, relapse has occurred requiring re-treatment. One of these is now off treatment. In three, the amyloidosis, as shown by a fall in total urinary protein excretion and return of the serum protein pattern to normal, return of the cholesterol or maintenance of the normal cholesterol, and maintenance of the normal blood urea, has apparently improved. As might be expected before treatment, the immunoglobulins in the majority of cases showed particularly high IgG, although in three it was lower than our usual levels in active Still's disease. The IgG showed a marked fall during treatment; the level tended to rise when chlorambucil was stopped but not to previous levels in those patients who had gone into remission.

One further death has occurred, but this was in the case of a patient in whom treatment could be maintained for only 6 months and who was already severely ill when therapy was started. A further patient in whom therapy could be maintained for only 3 months is showing a

deterioration of renal function.

It is concluded that treatment with chlorambucil, if it is to be of any value, should be started before there is evidence of serious renal dysfunction, and that every effort should be made to control the disease activity with the lowest possible dosage. In this way haematological side-effects can be minimized.

Discussion

DR. D. L. GARDNER (*Kennedy Institute*) What is the effect of chlorambucil upon the glomerulus? Is there a direct action upon the deposits of amyloid or an indirect action mediated through the lymphoreticular system?

DR. ANSELL We consider that the process is not a direct action on the glomeruli but probably the disease itself improving and further deposition not occurring. Whether the amyloid is resorbing I do not know; we have one rectal biopsy which appears to show no amyloid after treatment.

DR. J. H. GLYN (*London*) Is it established whether steroids have any effect in the production of amyloid or on the course of established amyloidosis? There was discussion about this in the early days of steroids. I believe Dr. West postulated that they actually caused amyloidosis.

DR. ANSELL We know that in the majority of our cases the disease has been severe and that many had been on steroids; those which I discussed today had all had steroids. In our previous work we found that the addition of steroids did not seem to help those patients who had amyloid, but if their disease went into remission they improved. In the pre-steroid era we saw about the same number as we are seeing now.

Reduced Glomerular Function in Rheumatoid Arthritis. By H. C. BERRY (*Guy's Hospital*).

In the course of a survey of the renal function of 97 unselected patients with classical or definite rheumatoid arthritis, the glomerular filtration rate was estimated by means of the endogenous creatinine clearance test. The average age of the group was 53.1 years and the average duration of arthritis 9.7 years. 76 per cent. had an erosive arthritis, 67 per cent. were seropositive, and 33 per cent. had subcutaneous rheumatoid nodules.

In 49 patients the creatinine clearance was less than 80 ml./min. As expected, lower values were found in females and in older patients, but no correlation was seen with duration of disease. It was observed that patients whose disease was characterized by the presence of erosions and/or nodules had lower clearance values than the remainder, the difference being statistically significant and not explicable by difference of age.

No correlation was found between glomerular function and treatment with salicylate-containing analgesic compounds, gold, or steroids.

It is concluded that the glomerular functional impairment is an expression of rheumatoid disease *per se*.

Discussion

PROF. E. G. L. BYWATERS (*Hammersmith*) Would Dr. Berry say whether he has looked at his patients for