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

evidence of vasculitis, as shown, for instance, in the fingers, because if there was a correlation here, arterial obliteration might well explain a decrease in renal function.

DR. BURRY This is an important omission. We did not see any nail-fold lesions in the whole series of 97 cases, nor evidence of arteritis in the renal biopsies.

DR. K. WHALEY (*Glasgow*) Did you screen your patients for keratoconjunctivitis sicca? Sjögren's syndrome is occasionally complicated by glomerulonephritis, and it would be interesting to know whether the diminished creatinine clearance is related to keratoconjunctivitis sicca.

DR. BURRY There were no cases of Sjögren's syndrome.

Cellular Immune Mechanisms in Rheumatoid Arthritis and Sjögren's Syndrome. By K. WHALEY, A. C. A. GLEN, S. D. DEODHAR, W. C. DICK, G. NUKI, and W. W. BUCHANAN (*Glasgow*).

The immune responses to 2, 4-dinitrochlorobenzene (DNCB) and old tuberculin (OT) were studied in four groups of patients in addition to controls: sicca syndrome, Sjögren's syndrome complicated by rheumatoid arthritis, and seropositive and seronegative rheumatoid arthritis. Patients with seropositive rheumatoid arthritis and patients with rheumatoid arthritis complicated by Sjögren's syndrome demonstrated a diminished ability to become sensitized to DNCB, whereas normal responses were found in the other two groups. Testing with OT, on the other hand, revealed normal responses in patients in all groups except the sicca syndrome group, which showed diminished sensitivity. Analysis of the RNA/DNA content of the peripheral blood lymphocytes revealed elevated values in those groups of patients with diminished DNCB responsiveness, whereas normal ratios were found in the other clinical groups. The mean diameter of the peripheral lymphocytes was closely related to the RNA/DNA ratio, which suggests that patients having elevated RNA/DNA ratios have a higher proportion of circulating lymphocytes of the large type, presumably lymphocytes committed in response to some antigenic stimulus. It is concluded that cutaneous anergy to DNCB may be due to a functional depletion of thymic dependent lymphocytes.

Discussion

PROF. K. W. WALTON (*Birmingham*) It has been shown in one or two other conditions with widespread involvement of the reticuloendothelial system that there may be some relation between the severity of the disease process and the lack of response to cellular immunity. I think it was Waldorf, Sheagren, Trautman, and Block (1966) who showed a difference between lepromatous and tuberculoid leprosy in the response to DNCB. In Hodgkin's disease, which may fluctuate, it has been found that the degree of response depends very much on disease activity. Have you had the opportunity in your cases, some of whom presumably will have waxed and waned, to see whether there was any difference in their DNCB response in relation to the disease?

DR. WHALEY No, we have not. We thought it would be adequate to study the disease parameters in the entire

group to determine correlations in those that were DNCB-positive and DNCB-negative because there was a spectrum of disease activity at the time of sensitization. The mechanism of anergy to DNCB in lepromatous leprosy and Hodgkin's disease is probably different. Patients with lepromatous leprosy show depletion of the thymic-dependent areas of the lymph node caused by the disease and this is probably why they do not respond to DNCB. It is not known whether treatment with Dapsone will reveal sensitization to DNCB, but I think it has been shown that the thymic-dependent areas become repopulated with small lymphocytes once the disease has been treated.

DR. P. J. L. HOLT (*Hammersmith*) First of all, you have not necessarily shown the dependence on thymic lymphocytes. After all there are several steps between antigen challenge and skin response. The first step would be macrophage digestion of the antigen and it has been shown that chemotaxis and phagocytosis is reduced in the rheumatoid subject, so the skin concentration of DNCB may have to be higher or maintained longer to see whether sensitized lymphocytes have been produced; in other words there is transformation in the circulating blood. Perhaps the last, and in some ways the most interesting, question is whether there are lymphocytes capable of expressing the skin sensitivity as measured by Mantoux type reactions. These may all be different defects, and I think they must be shown independently. You said that there was a diminished incidence of A2 isohaemagglutinin. We have been studying another condition with diminished skin expression to migration inhibition factor, all patients are group O with one exception who is A₂. Finally, returning to lepromatous leprosy, there is a genetic basis for the lack of skin expression in the leprin response.

DR. WHALEY Do you think the genetic basis depends on depletion of the thymic dependent areas in lepromatous leprosy?

DR. P. J. L. HOLT (*Hammersmith*) That I am not capable of answering. You were judging a chain of events by one end-factor without saying at which level this chain went wrong.

DR. WHALEY We used the DNCB and Mantoux tests because we believe the latter tests the ability of the memory cell to mount a delayed hypersensitivity reaction in response to OT and the efferent part of the arc. I agree that study of macrophage function in these patients should be tested.

DR. P. J. L. HOLT (*Hammersmith*) The thymic cell does not necessarily express skin sensitivity. There may be another cell that is conditioned by the thymic cell.

DR. WHALEY Agreed.

DR. P. A. BACON (*St. Bartholomew's Hospital*) We have been looking at peripheral lymphocytes in rheumatoid arthritis. In about 60 per cent. of rheumatoid subjects we have found large circulating lymphocytes which are similar to those seen in Hodgkin's disease, are metabolically active, and look like lymphoblasts. The presence of