- (9) Authors will be notified (i) when an abstract is received, (ii) when it is either accepted or rejected, (iii) when it is placed on a programme for a particular meeting.
- (10) It is the author's responsibility to keep the Senior Hon. Secretary informed of the date of publication of any paper submitted to the Society.

Clinical meeting

The following papers were presented at the Annual General Meeting on November 24 and 25, 1972.

Articular Mobility in an African Population. By P. BEIGHTON, L. SOLOMON, and C. SOSKOLNE (*Department of Orthopaedic Surgery, University of the Witwatersrand, South Africa*)
To be published in the *Annals* in September, 1973.

Role of Thymic and Bursal Lymphocyte Subclasses in Chronic Allergic Synovitis in the Chicken. By D. C. DUMONDE, C. M. OATES, R. N. MAINI, and L. N. PAYNE (*Kennedy Institute of Rheumatology, London, and Houghton Poultry Research Station, Houghton, Hunts*)

Studies of experimental allergic monoarthritis indicate that both cellular and humoral immune mechanisms are involved in the pathogenesis of these laboratory models of the rheumatoid joint. The present experiments investigated the ability of thymic and bursal lymphocyte systems to support antigen-induced chronic synovitis in sensitized chickens. Adult chickens were sensitized to bovine γ -globulin (BGG) by intramuscular injection of BGG emulsified in a mycobacterial adjuvant; 3 weeks later, a suspension of BGG coated on to silica particles was injected into the ankle joints. A chronic proliferative synovitis developed with widespread synovial infiltration by lymphocytes, macrophages, and plasma cells and the gradual formation of two types of ectopic lymphoid foci:

(a) large lymphoid follicles with mature germinal centres;

(b) large aggregates of macrophages and lymphocytes.

Neonatal thymectomy markedly suppressed synovial mononuclear cell infiltration and suppressed both types of lymphoid foci. Agammaglobulinaemic neonatally bursectomized birds supported a chronic allergic synovitis with intense lymphocyte-macrophage infiltration but absence of germinal centre follicles and plasma cells. Cell-mediated (thymus-dependent) mechanisms alone were therefore capable of supporting a chronic allergic synovitis; but both thymic (T-cell) and bursal (B-cell) systems were necessary for full development of the rheumatoid-like histology. Studies *in vitro* likewise showed that the peripheral lymphocytes of bursectomized chickens were able to generate mediators of delayed hypersensitivity (lymphokines), but that both T-cells and B-cells were needed for maximum lymphokine activity. It is suggested that an early event in the development of the ectopic synovial lymphoid foci involves the production of T-cell

lymphokines which then recruit other lymphoid cells (e.g. B-cells and macrophages) into activity in the local (synovial) environment. On this basis local persistence of antigen might provide the continuing stimulus to generation of further T-cell and B-cell activation products which would facilitate the histogenesis of the synovial lymphoid foci.

Discussion

DR. W. CARSON DICK (*Glasgow*) Could you expand on the question of recruitment? Do you envisage the interaction of either a Lawrence type of transfer factor or an immunogenic RNA molecule in the recruitment phase in the model that you have described?

DR. DUMONDE We would not go as far as that. We think it is lymphokines which do the recruiting and once the cells get there lymphokines do the activating and the co-ordinating. There is no evidence for the existence of immunogenic RNA or of Lawrence type transfer factor in the bird but of course your suggestion is one which could well be investigated.

PROF. E. G. L. BYWATERS (*London*) I am not quite sure why the birds were irradiated before they were sensitized.

DR. DUMONDE It is difficult to knock out the T-cell or B-cell system by simple surgical intervention and the avian immunologists have got round this by following the surgery at birth by whole-body irradiation to suppress the activity of T-cells or B-cells in various peripheral areas. 5 or 6 weeks usually elapses before a newly-hatched chick given 900 rads whole-body radiation attains full recovery of the T-cell and B-cell systems in the normal non-surgically treated animals.

PROF. E. G. L. BYWATERS (*London*) So it is a question of dosage. If you give too much presumably in the bursectomized animal the thymic type of cells will not survive?

DR. DUMONDE If you give too much you will kill the bird. If you give too little you may end with such a low yield of totally bursectomized and adequately thymectomized animals that the difference between the groups is less significant.

Joint Capsule Collagen in Osteoarthritis. By C. HERBERT, A. J. BAILEY, and M. I. V. JAYSON (*Department of Medicine, University of Bristol, Meat Research Institute, Langford and Royal National Hospital for Rheumatic Disease, Bath*)
To be published in full in the *Annals*.

533 Patients with Ankylosing Spondylitis, seen and followed in the Period 1948 to 1971. By J. J. DE BLÉCOURT (*Groningen, Holland*)

Since 1948 the 'fight against rheumatism' in the Groningen-area ($\pm 600,000$ inhabitants) has been organized as a 'closed circuit', both the intramural (hospital) and extramural (general practitioner, public health nurse, social services) services being under the direction of one team of rheumatologists.

Between 1948 and 1971, 533 patients with definite ankylosing spondylitis (AS) were present among approximately 25,000 patients attending (*i.e.* 2.5 per cent. compared with approximately 25 per cent. with rheumatoid arthritis). When these patients with AS were followed up, this partly prospective/retrospective study gave the following results:

Sex incidence:

Males 439 (82 per cent.); Females 94 (18 per cent.);
Ratio 4:1

Average age in 1970:

50 yrs (range 17 to 103)

Expected prevalence of AS in persons aged 15 years and above in population:

0.08 per cent. = ± 400 patients in Groningen area (population 600,000).

23 year prevalence = at least 533 patients (probably ± 600 patients).

Incidence among relatives:

First, second, and third-degree relatives of 100 controls, RA and AS patients (completion rate 87 per cent.).

Secondary cases	RA	AS
In RA relatives	3 $\times$ expected	No increase
In AS relatives	No increase	22 $\times$ expected
In control relatives	0.8 per cent.	0.08 per cent.

Age at diagnosis:

Patients born before 1910: 60 per cent. diagnosed > 35 years.

Patients born after 1930: 80 per cent. diagnosed < 25 years.

In the periods 1948–51: 22 per cent. diagnosed < 20 years.

1951–61: 39 per cent. diagnosed < 20 years.

1961–71: 45 per cent. diagnosed < 20 years.

Initial complaint:

Low back pain 70 per cent.

Morning stiffness 9 per cent.

Myalgic and arthralgic pains 21 per cent.

Peripheral arthropathy—20 per cent.

Iritis and/or iridocyclitis—14 per cent.

Investigations:

Erythrocyte sedimentation rate < 20 mm./1st hr—40 per cent.

Normal sacroiliac x-rays—5 per cent.

Positive latex/Waaler-Rose tests—2 per cent. (4 per cent. in normal population)

Treatment:

Radiotherapy—1948–60—60 per cent. patients

1960–71—11 per cent. patients

In the first period there were significantly more cases of leukaemia than in the second.

Progress (per cent.)

Result	Improved	Deteriorated
1948–60	20 per cent.	20 per cent.
1960–71	50 per cent.	10 per cent.

At first attendance:

60 per cent. of the men were performing heavy labour.

At the end 10 per cent. remained in the same job, 40 per cent. had changed to a lighter job, and 10 per cent. had become invalids.

68 per cent. of the females were housewives and 48 per cent. continued as such.

Main conclusions

We 'pushed ankylosing spondylitis back' with a system of early diagnosis and continued 'total treatment and care'.

This early diagnosis and continued treatment (analgesics, physiotherapy, and social help and guidance) had a significant effect on the course of the disease. Medical and social improvement in the first 5 years was 10 per cent. and in the last 10 years 50 per cent.

Not only the rheumatologists but also other specialists and general practitioners in our area have learned much about this disease (including undergraduate and post-graduate teaching). In the first 5 years 70 per cent. attended with uncertain diagnosis, whereas in the last 5 years 70 per cent. first attended with the correct diagnosis.

Discussion

DR. J. M. H. MOLL (*Oxford*) Was an increased frequency of psoriasis, colitis, or other spondylitis-linked disorder found in relatives of probands with ankylosing spondylitis?

PROF. DE BLÉCOURT These studies were carried out from 1953 until 1960 when our knowledge of this association was not as advanced as today. It is a very interesting question and in future we hope to go deeper, but our material does not give a definite answer at present.

PROF. E. G. L. BYWATERS (*London*) This interesting survey runs over such a long period of 23 years that there are two points that I want to ask. First, I noted that 5 per cent. of 26 patients had initially normal sacroiliac joints. What other criteria were there for inclusion and were they distributed in the earlier or later part of the 23-year survey? Secondly, you say that in the last period from 1960 to 1971 there was a greater percentage of improvement and I wondered whether you thought that this might be because they were diagnosed earlier so that less severe cases were included in the later series? This is a well known bias of selection which we have been familiar with for many years in the field of rheumatoid arthritis and many other chronic diseases.

PROF. DE BLÉCOURT Well the first question about the sacroiliac joints on x-ray. We followed patients over the years. The diagnosis without positive x-rays was made on other clinical signs, but in follow-up we saw the changes at the sacroiliac joints appearing and confirming the diagnosis. By earlier diagnosis and improved treatment you may expect better results and that is what we have seen.

DR. A. ST J. DIXON (*Bath*) The great revolution in treatment during this period has been the policy of using vigorous remedial exercises. Until 10 or 15 years ago we were still seeing a film from de Sèze's Unit suggesting that these patients might be treated with Swain's corsets and plaster jackets. These have now been almost universally

abandoned but this change has taken place over the period that you mention. Could some of the improvement of results have been the abandoning of immobilization therapy?

PROF. DEBLÉCOURT Immobilization was not used. We saw in the beginning too many patients treated as cases of tuberculosis or immobilized for other reasons and completely crippled, and initially there was a marked shortage of physiotherapists, but nowadays we have quite a number of very skilled physiotherapists and physiotherapy was much better in the later than in the earlier years.

DR. A. G. S. HILL (*Stoke Mandeville*) Do we all mean the same thing when we talk about peripheral joints and would your figures be different if you separated the intermediate joints of the extremities from the true peripheral joints, *i.e.* those of the hands and feet.

PROF. DE BLÉCOURT The peripheral joints involved were the knees, elbows, ankles, hands, and feet, not the shoulders and hips. The intermediate joints (knees mostly) were more frequently affected than the feet and hands.

DR. J. A. D. ANDERSON (*London*) You carried out a combined retrospective and prospective study over a number of years but gave no indication of the turnover of the population at risk. As you said, identified cases of a serious disease can be followed up because they are likely to continue to attend. Less serious cases may be lost and if the turnover of population of the area is high, could this not affect some of the conclusions about prevalences?

PROF. DE BLÉCOURT I cannot answer this question now. The prevalence of ankylosing spondylitis is estimated at 0.12 in the Netherlands and the turnover rate will certainly influence comparisons, but not, I think, in a very significant way.

DR. J. A. COSH (*Bath*) Did you find any patients with Reiter's syndrome who progressed to spondylitis? I notice that a proportion of your patients in the past decade are still being treated with radiotherapy. Have you any comments on the value and safety of radiotherapy for peripheral joints?

PROF. DEBLÉCOURT Patients with Reiter's disease and spondylitis are not included in this review. But we see quite a few who start with Reiter's disease which develops into something which is very like ankylosing spondylitis. Most of the radiotherapy was given by radiotherapists not from the university hospital. We have no experience in treating peripheral joints with radiotherapy. We now use it only occasionally for a very painful cervical column. To my knowledge we have never treated peripheral joints with radiotherapy in ankylosing spondylitis.

Controlled Trial of Penicillamine in Severe Rheumatoid Arthritis. By J. R. GOLDING, F. M. ANDREWS, VIRGINIA CAMP, A. T. DAY, A. M. FREEMAN, D. N. GOLDING, A. G. S. HILL, W. H. LYLE and A. G. MOWAT (*Oxford*)

A trial of D(—) penicillamine (Distamine) in severe uncontrolled rheumatoid disease has been carried out at five different centres, 105 patients with definite or classical rheumatoid arthritis of at least 2 years' duration and meeting additional criteria of disease severity were admitted. Allocation of patients to penicillamine (52) or

control (53) groups was randomized after stratification by age, sex, and current use of steroids and the trial was double-blind.

Measurements included erythrocyte sedimentation rate, Hb, differential agglutination test, pain, morning stiffness, articular index, grip strength, functional index, well-being, weight, and x-radiology of hands and feet. Results have been analysed to show mean improvement, percentage improvement, and the number and proportion of persons who were much, moderately, or at all improved in the various measurements after 3, 6, and 12 months of treatment.

There were no significant differences in the mean scores for each of these measurements between the two treatment groups at the start of the trial, but there were differences in almost all, with advantage to penicillamine, at the conclusion of the study, the differences being of statistically significant degree for erythrocyte sedimentation rate, Hb, morning stiffness, pain, articular index, function index, and grip strength.

Adverse reactions were more prevalent amongst the penicillamine group during the first 6 months of the trial but not during the second. Sixteen patients in the penicillamine group were withdrawn because of drug intolerance but none because of increasing rheumatoid activity. Nine of the controls withdrew because of increasing rheumatoid activity and one because of drug intolerance. Adverse reactions which led to withdrawal included rash, thrombocytopenia, albuminuria, and gastrointestinal upset. Recovery was invariable. Among the patients given penicillamine who had improved at 12 months, most of that improvement was already evident at 3 months.

The clinicians' opinion whether the trial treatment had been, with respect to the patient's rheumatoid disease, 'successful', 'of doubtful value', or 'of no value' was recorded whether the course was completed or not. Of the patients who completed the course, 71 per cent. of those on penicillamine and 8 per cent. of the controls were judged to have received 'successful' treatment. Similar figures are obtained even when the entire patient population is included.

It is evident that penicillamine is effective in severe and advanced rheumatoid disease. Controlled studies of its use in early disease are now indicated.

Discussion

DR. J. H. GLYN (*London*) What happened in terms of the disease process when you had to withdraw the patients because of toxic effects? Did they all deteriorate again or not?

DR. GOLDING This was very variable. I haven't got sufficient figures to comment on that.

PROF. C. A. KEELE (*London*) What was the dose of penicillamine used?

DR. GOLDING Penicillamine was given as Distamine capsules as follows: 0.2 weeks 1 b.d., from 2.4 weeks 1 q.i.d., 4.6 weeks 2 t.i.d. and so on rising to a maximum of 1.5 g of base. The controls were given dummy capsules.

PROF. C. A. KEELE (*London*) And any other treatment?

DR. GOLDING We did not stop the current treatment in either group. In other words, both the control and the penicillamine groups could have steroids.