Annals of the Rheumatic Diseases, 1978, **37**, 107–120

Heberden Oration, 1977

Chronic arthritis in childhood

BARBARA M. ANSELL

From the Juvenile Rheumatism Unit, Canadian Red Cross Memorial Hospital, Taplow, and Division of Rheumatology, Clinical Research Centre, Northwick Park Hospital, Harrow

Mr President, may I first thank you for the honour that you have done me in asking me to give this Oration. This I do with considerable trepidation, remembering the superb Orations I have heard and looking at the list of my distinguished predecessors which includes Eric Bywaters, who in 1966 surveyed Still's disease. In his summary he said, 'chronic juvenile polyarthritis is a wide term, Still's disease is an historical term, juvenile rheumatoid arthritis an exact but misleading term'. He considered that criteria chosen and verified by international agreement were necessary for further elucidation of chronic arthritis in childhood (Bywaters, 1967).

Eleven years have now passed. The growing interest in paediatric rheumatology has been reflected in the number of sessions devoted to it in meetings, the many papers published from Scandinavia, Europe, not forgetting Taplow and the Americas, particularly the United States. The suggested criteria have been constantly modified (Brewer *et al.*, 1977) and have not yet received general acceptance. At the workshop organised by the American Rheumatism Association Council on Paediatric Rheumatology last year at which both Eric Bywaters and I were guests, arguments on criteria and classification continued long after the sessions had closed. This year (1977), under the auspices of the European League against Rheumatism and the World Health Organisation, a symposium on the care of rheumatic children, to which leading US paediatric rheumatologists were invited, was held in Oslo. Despite problems of nomenclature and language, there was considerable uniformity of experience. At this meeting the Europeans managed to agree on a preliminary approach to nomenclature and classification (Table 1). In English the name is juvenile chronic arthritis. There was little disagreement about age of onset and the cut-off point of under 16 years is quite arbitrary. There was remarkable agreement on a minimum duration of 3 months before a definite diagnosis should be made. The uniformity with regard to modes of onset was also encouraging.

Table 1 *Agreed criteria for juvenile chronic arthritis—EULAR-WHO meeting, 1977*

Onset	— under 16 years
Duration	— minimum 3 months
Classification by onset	
	Systemic illness
	Polyarthritis
	Pauciarticular (4 or fewer joints)

Exclusions from juvenile chronic arthritis

As with any classification of this type, exclusions are many, but the following were generally accepted (Table 2). The first group consists of disorders with characteristic features. Considering infections, except for glandular fever which mimics systemic juvenile chronic arthritis, the typical arthropathies of viral infections are short-lived, but bacterial infections, particularly if treated initially with a short course of antibiotics, may be more difficult to recognise (Fig. 1). While in general partly treated infections

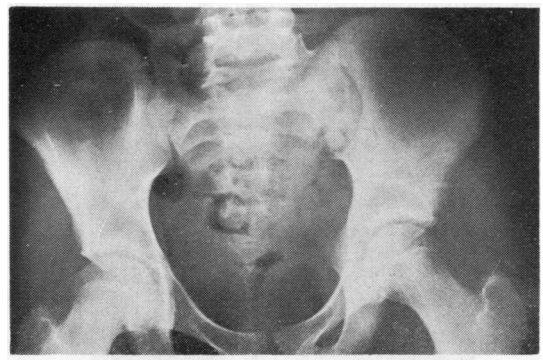


Fig. 1 *Because of the development of rash, this 12-year-old girl had had only 3 days of amoxycillin for a sore throat, fever, generalised arthralgia, with some pain in the left hip and knee 3 months previously. Systemic features of fever, high ESR, low haemoglobin, and persistent leucocytosis were present, while a mass developed in the left groin which at surgery was found to be an abcess containing Staphylococcus pyogenes, presumably tracking from the infected sacroiliac joint.*

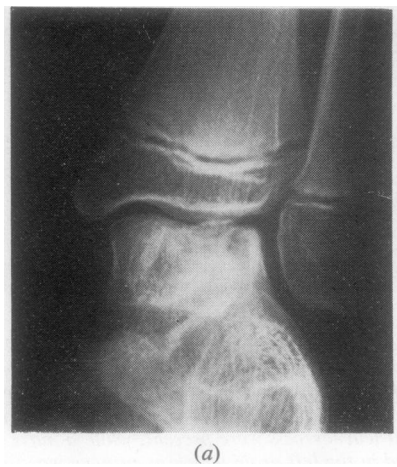
Table 2 *Exclusions from diagnosis of juvenile chronic arthritis*

(a) Arthropathies with characteristic specific features	(b) Distinct conditions of the musculoskeletal system	(c) Specific diseases which can cause problems in diagnosis
(i) Infectious	(i) Polymyositis and dermatomyositis	(i) Acute rheumatic fever
(ii) Nonrheumatological immunological disorders	(ii) Systemic sclerosis	(ii) SLE
(iii) Haematological disorders	(iii) Keratoconjunctivitis sicca	(iii) Postinfectious arthropathies
(iv) Neoplasm	(iv) Mixed connective tissue disease	
(v) Psychogenic	(v) Vasculitis (Henoch-Schönlein purpura, etc.)	
	(vi) Behcet's syndrome	
	vii) Nonrheumatological conditions (chondromalacia, synovitis of hip, etc.)	

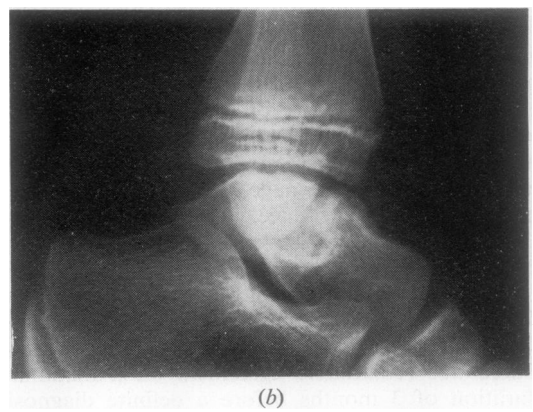
present as persistent monarticular arthritis, systemic illness with any late localising features can occur. Tuberculosis, though much less common, is still seen; usually monarticular, it can affect more than one joint as well as tendon sheaths. Hypogammaglobulinaemia, particularly the X-linked type, is associated not only with septic arthritis, but also with a recurrent mild synovitis and at times a more chronic form of arthritis, while a dermatomyositis-like syndrome is occasionally seen. This does not present a challenge in diagnosis but is of particular interest as a boy, referred with gradual stiffness of elbows, wrists, and ankles and with swelling of the knees more than 12 months after the first symptoms of stiffness, had Echo 19 virus isolated from the cerebrospinal fluid (D. Webster, personal communication, 1977).

Joint involvement tends to occur in children with known bleeding diatheses, but problems occur particularly in those with mild haemophilia, usually as a persistent monarticular arthritis, sometimes apparently initiated by trauma (Fig. 2*a*, *b*). In children who present with swelling around joints, as shown in Fig. 3*a* and *b*, leukaemia must be considered. This child also had widespread lymphadenopathy and splenomegaly. Bony pain and tenderness can also be confusing in patients with leukaemia and neoplasia. Neuroblastoma has given us the most problems, with its tendency to early boney infiltration. As in leukaemia, the significance of lymphadenopathy and low haemoglobin may be missed initially. Radiology is extremely helpful as changes occur early (Fig. 4).

The second group of exclusions are conditions which can usually be differentiated easily (Table 2*b*). However, some 30% of children with dermatomyositis have an arthropathy often presenting with it. Only the presence of associated features such as the typical rash, muscle weakness, and tenderness, as well as a raised creatine phosphokinase or the later development of calcinosis, allows a confident diagnosis. Scleroderma too can cause confusion, particularly when presentation is with joint pain and stiffness associated with multiple nodule formation and the scleroderma is localised. The erythrocyte sedimentation rate (ESR) is usually normal, but

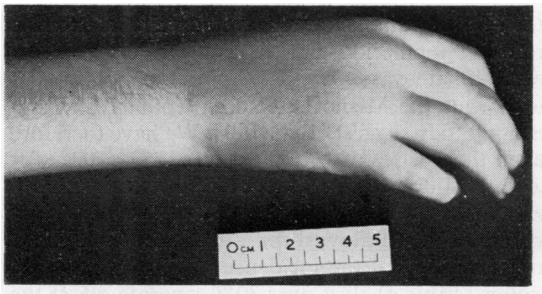


(*a*)

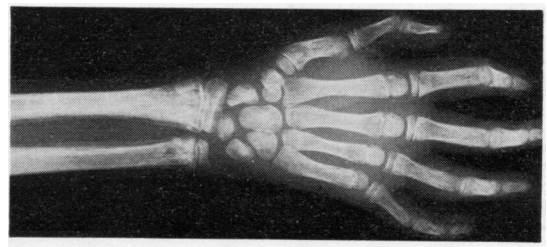


(*b*)

Fig. 2 (*a*, *b*) *Haemophilic joint disease initially with recurrent swelling of the ankle after minor trauma which subsequently presented as a persistent monarticular arthritis.*



(*a*)



(*b*)

Fig. 3 (*a, b*) *Swelling over wrist and carpus was present for 11 months. Initially the* x-*ray was normal, but by now, (3b), it had characteristic leukaemic changes.*

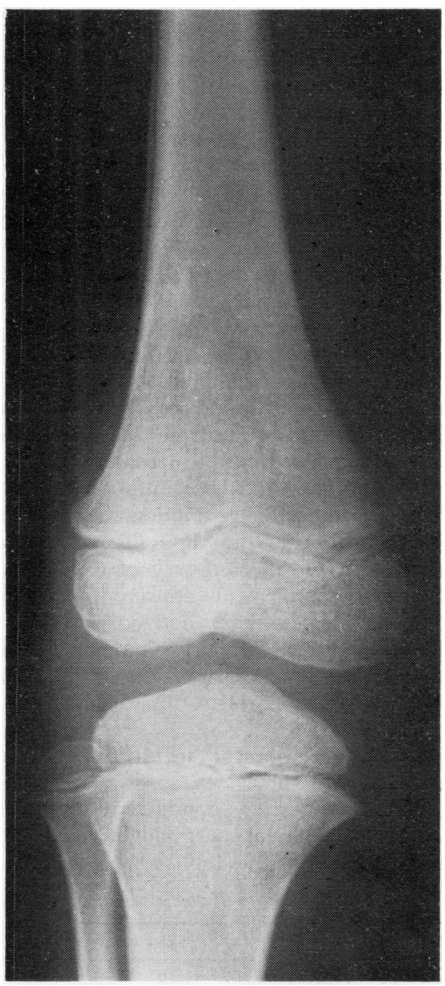


Fig. 4 *Two months previously this 6-year-old boy presented with pain in the left knee followed by the neck and wrist; ESR was raised to 98 mm/h and haemoglobin 9·8 g/dl; note the periostitis which developed down the femoral shaft.*

many patients have high titres of antinuclear antibodies (ANA) as is also seen in dermatomyositis (Ansell *et al.*, 1976). Keratoconjunctivitis sicca (Sjögren's syndrome) is uncommon in childhood, as is the mixed connective tissue syndrome. The latter needs to be considered when there is Raynaud's phenomenon, odd rashes, and muscle weakness as well as arthritis: speckled ANA and extractable antinuclear antigen support the diagnosis. In the group loosely labelled vasculitis, typical rashes or localised cutaneous lesions are helpful in differentiation.

Nonrheumatological conditions affecting the musculoskeletal system should also be excluded. These range from the orthopaedic problems of chondromalacia patellae, nonspecific synovitis of the hip, slipped femoral epiphyses, and Perthe's disease to congenital and genetically determined anomalies. Not only do simple things like the hypermobility syndrome require exclusion, but also the rarer ones such as the Ehler-Danlos syndrome, where the scars on the knees as well as the history give the clue. Of the mucopolysaccharidoses, Scheie's syndrome, with its normal mentality but gradual stiffening of joints, is the most difficult to distinguish.

The three disorders which are still the most difficult to differentiate from juvenile chronic arthritis are rheumatic fever, systemic lupus erythematosus, and postdysenteric arthritis (Table 2*c*). Despite the decline in rheumatic fever, it still occurs. The pattern of fever, which is sustained in rheumatic fever and intermittent in systemic juvenile chronic arthritis, is a helpful feature. The rash is also different. The presence of endocarditis suggests rheumatic fever, while widespread lymphadenopathy and hepatosplenomegaly suggest juvenile chronic arthritis (Table 3). Systemic lupus erythematosus is characterised by multisystem involvement. Initially, a very high ESR with relatively few affected joints and a low white cell count will suggest the diagnosis, while the presence of ANA antibody is helpful.

Table 3 *Comparison of features*

	Rheumatic fever	*Systemic JCA, 'Still's'*
Fever	Sustained	Intermittent
Rash	Erythema marginatum	Maculopapular
Pericarditis	+	+
Endocarditis	+	0
Lymphadenopathy	0	+
Hepatosplenomegaly	0	+

More specific findings are antibodies to DNA and a low C3, while biopsies of appropriate sites are helpful. Postdysenteric arthritis has been recognised for many years, but recently its association with HLA B27 has highlighted its importance (Robitaille *et al.*, 1976). While it tends to be a large joint arthropathy, often flitting, tendon sheath effusions have been seen, as has atypical Reiter's syndrome. Fever has been indistinguishable from that of systemic juvenile arthritis, but without a maculopapular rash. The course may be prolonged with residual deformities particularly in the feet (Fig. 5), while sacroiliitis has been seen to develop as early as 4 years from the initial symptoms.

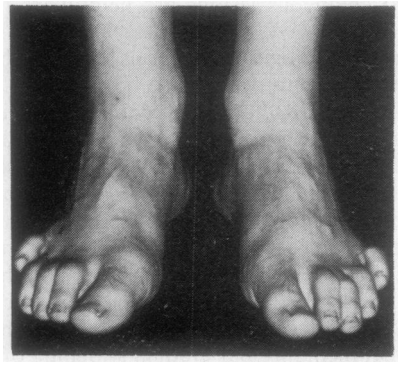


Fig. 5 *Typical Reiter's syndrome developed in this 9-year-old boy after a Salmonella infection; the arthritis was active but with decreasing severity for 4 years, leaving residual deformities in the feet.*

Juvenile chronic arthritis

After all these exclusions, the group which in this new nomenclature is called juvenile chronic arthritis, but in the USA still juvenile rheumatoid arthritis, is defined. This is a generic descriptive term. Within this group it is possible to identify juvenile ankylosing spondylitis, arthropathies associated with inflammatory bowel disease, psoriatic arthropathy, etc. However, the true nature of these conditions may be revealed only after a varying interval of follow-up extending for some years. Ideally one would like to study the natural history of juvenile chronic arthritis from the population, but this is a rare disease. Our own estimate was 6 per 10 000 of the school population, while the Medical Research Council Environmental Study suggests 1 per 1000. We have therefore taken those cases who fulfilled our 1959 criteria for definite Still's disease (Ansell and Bywaters, 1959) who were seen within one year of disease onset and who have been followed for a minimum of 15 years to get an idea of the incidence of the various subgroups (Table 4). Just over 30% separate off. If the probable cases (Ansell and Bywaters, 1962) are included, this figure is higher.

The majority of laboratory investigations reported both by us and from elsewhere have made no attempt at subclassification. I will therefore summarise the most important in the context of the whole group. Nonspecific mediators of inflammation, such as the ESR, acute phase reactants, and the immunoglobulins tend to be increased commensurate with disease activity. Selective IgA deficiency, which is associated with a variety of immune disorders, is reported in varying incidence from 1–4% (Pachman *et al.*, 1977; Cassidy *et al.*, 1977) and in our experience is seen in all patterns of disease, not just mild pauciarticular. Impaired cellular immunity has also been reported in juvenile chronic arthritis and preliminary studies suggest an alteration in T cell function in the IgA-deficient patients. Persistent IgM rheumatoid factor is found in about 12%, while antinuclear antibodies occur in 28%. To date we have not found a significant increase in extractable nuclear antibodies. Anti-IgG antibodies have been found by a number of techniques, their level often correlating with the total IgG (Torrigiani *et al.*, 1969; Turner *et al.*, 1976). Levels of C3 are usually normal, but complement consumption may be increased in patients with very active disease (Pachman and Baldwin, 1977). Similarly, immune complexes are present in a small proportion of patients. In unselected early cases, HLA B27 occurred in 25% (Hall *et al.*, 1975).

Just as all these laboratory features require appraisal in the light of subclasses, so do genetic studies. Our original family study, conducted long before we realised juvenile ankylosing spondylitis could present

Table 4 *15-year follow-up of early cases, October 1977*

	Seen	*Dead*	*Not traced*	*Total*
Juvenile ankylosing spondylitis	27	0	0	27
Juvenile rheumatoid arthritis	20	3	0	23
Juvenile chronic arthritis	93	10	3	106
Psoriasis	3	1	0	4
Other	1	0	0	1
Total	144	14	3	161

as peripheral arthritis, did show a slight increase in ankylosing spondylitis in male relatives (Ansell *et al.*, 1962), later correlating with sacroiliitis in the probands (Ansell *et al.*, 1968). What the 10% increase in monozygous phenotypes in all subgroups means is not known (Arnaud *et al.*, 1978). Nowhere does selection of material operate more than in twin patients (Table 5), only 3 of the monozygous group being referred solely on their disease, the others coming because of our known interest. Half of the 12 monozygous twins carry HLA B27, but to date only 2 with juvenile ankylosing spondylitis are concordant. The other four concordant pairs had varying patterns of disease and different HLA and B typing. Obviously there are some genetic factors which require further elucidation. Quite apart from genetics, the twin study allowed us to look at growth, as shown in Fig. 6. The one who has had polyarthritis, not treated with prednisolone, for almost 7 years is considerably smaller than her fit monozygotic twin. The difference in their hand size is clinically (Fig. 7*a*, *b*) and radiologically marked.

Table 5 *Twins with juvenile chronic arthritis, October 1977*

Monozygous	12	Dizygous	12
Concordant	6		0
6/12 monozygous carry HLA B27			
2/6 concordant carry HLA B27			

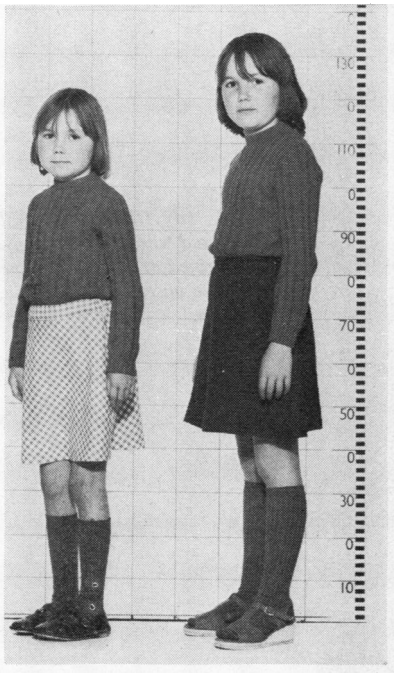


Fig. 6 *The smaller of these twins has had juvenile chronic polyarthritis, not treated with prednisolone, for almost 7 years.*

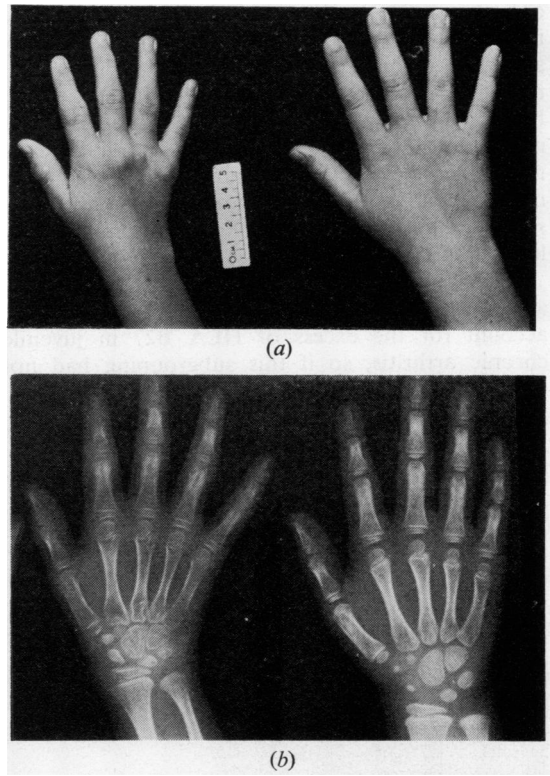


Fig. 7 (*a*) *The hand of the affected twin shows not only the soft tissue swelling, but also the marked alteration in overall growth.* (*b*) *While radiologically, as well as overall, smallness of the hand, there has been overgrowth of the carpal epiphyses on the affected side.*

Subgroups

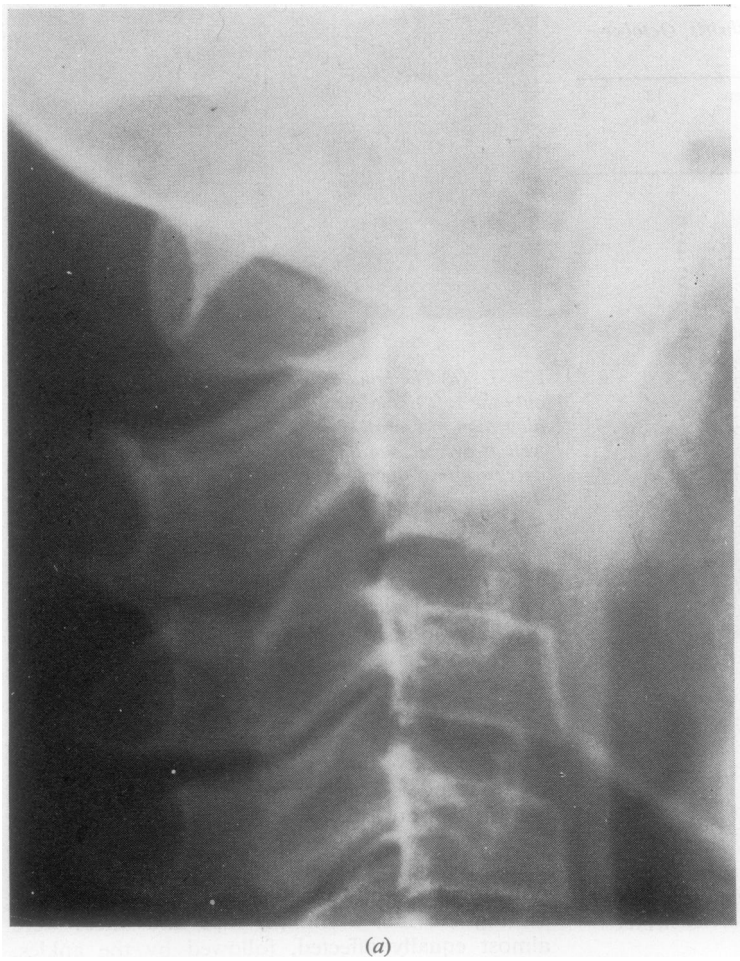
The various subgroups described at the 15-year follow-up of early cases will now be described in detail. In order to look closely at the features in each subgroup I have used the total number of patients available.

JUVENILE ANKYLOSING SPONDYLITIS

This occurs five times more frequently in boys than in girls and is the only form of juvenile chronic arthritis to show male predominance. Although the mean age of onset was 12 years, there was a wide scatter from 3 to 15 years. In only 16% was the onset polyarticular, while a single patient had back pain. During the first 3 months hips and knees were almost equally affected, followed by the ankles.

There was relative sparing of the upper limbs. Acute iridocyclitis was not encountered as a presenting feature but almost a quarter of the children had at least one attack during follow-up. At presentation only one patient had a doubtfully abnormal sacroiliac joint. In those 65 cases where approximately annual films had been taken, the mean duration from the onset of symptoms to sacroiliitis was 5½ years, but there was a very wide scatter. Limitation of movement in the back followed sacroiliitis at a mean age of 19·8 years and might not develop for many years. An unexpected finding was atlantoaxial subluxation (Fig. 8*a*, *b*) without serious thoracolumbar spine involvement in 2 of the 77 patients.

HLA B27 was present in 90% of the patients available for tissue typing. This subgroup could well account for the excess of HLA B27 in juvenile chronic arthritis, so if this subgrouping had not occurred the significance of HLA B27 in juvenile arthritis might have been lost (Edmonds *et al.*, 1974). There was a clear-cut family history of ankylosing spondylitis in a quarter of the patients and a suggestive one in a further third. Juvenile ankylosing spondylitis in association with gut disease gives the same problem of diagnosis as the lone disease. A relatively low haemoglobin for the severity of joint involvement, as well as the presence of persistent occult blood in the stools, is a suspicious feature, as are more definitive gut symptoms. Intestinal synovitis associated both with ulcerative colitis and regional enteritis can mimic many forms of childhood arthritis from Reiter's syndrome on one side to systemic juvenile chronic arthritis on the other. This is not associated with the carriage of HLA B27 and tends to improve with satisfactory management of the bowel disease.



(*a*)

Fig. 8 (*a*) *Atlantoaxial subluxation was noted when this 14-year-old boy complained of neck pain 4 years after the onset of the disease, with hip pain.*

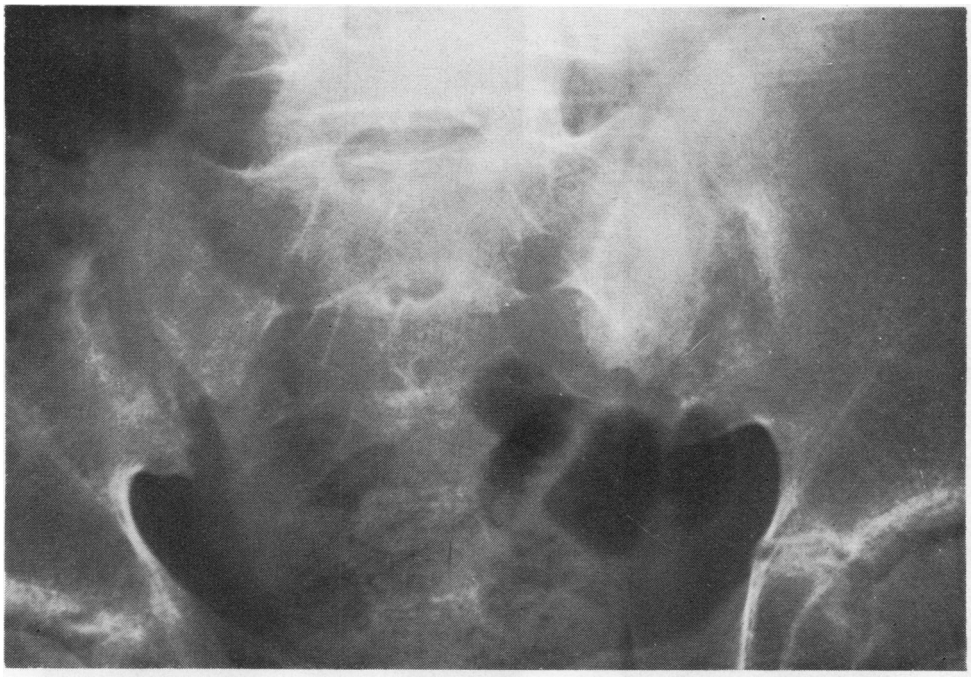


Fig. 8 Sacroiliitis is present; he carried HLA B27. (*b*)

SEROPOSITIVE JUVENILE RHEUMATOID ARTHRITIS

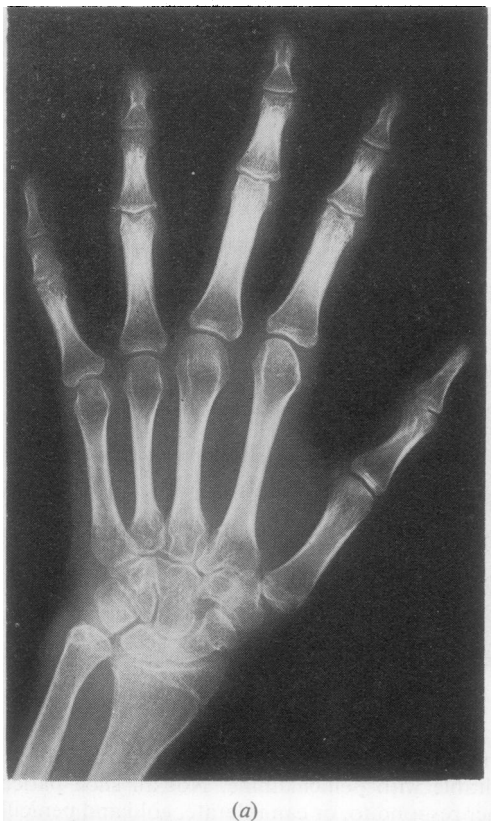
This looks and behaves like the adult disease. The persistent presence of IgM rheumatoid factor is usually noted within months of onset. There is a female predominance, and while it has been seen as early as 5 years, more than 70% were 10 years or older when symptoms first occurred. The onset is usually polyarthritic particularly affecting the small joints of the feet and hands, where the distribution of ulnar styloid, wrist, metacarpophalangeal, and proximal interphalangeal joints is typical. Radiological changes in hands and feet occur early so that the majority had definitive changes at one of these sites by the first year of follow-up. Persisting elbow nodules were seen in about a fifth which had the typical histology of adult rheumatoid arthritis. Vasculitis was rare in the first few years of the disease but as follow-up has proceeded, not only have the typical nail fold lesions occurred but an extensive vasculitic rash has been seen on several occasions.

The outstanding feature of this subgroup is the tendency to persistence of activity with serious joint destruction (Fig. 9 *a–d*). There is some evidence to suggest that long-term maintenance with gold is associated with improvement in *x*-rays (Fig. 10). Penicillamine may be similarly effective (Fig. 11). Long-term maintenance therapy is probably also desirable with penicillamine. Not all such patients either respond to, or can tolerate, gold and penicillamine, but the presence of persistently seropositive disease associated with early radiological change is enough to suggest the use of these therapies before untoward damage has occurred.

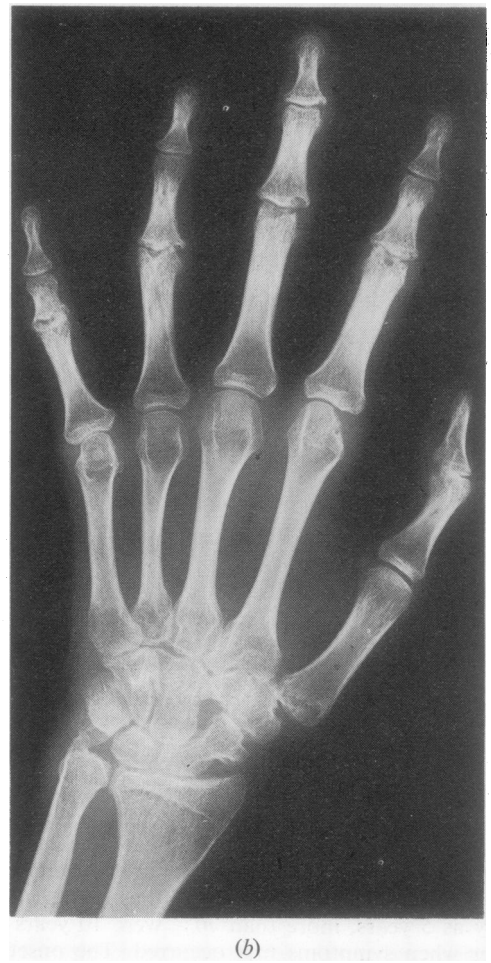
SERONEGATIVE CHRONIC ARTHRITIS

This remains as the main subgroup. We had defined the onset as systemic, monarticular oligoarthritis for two and three joints, and as polyarticular. In future, four or fewer joints affected in the first 3 months will count as pauciarticular onset. As yet definitions of systemic disease have not been reached. We had required fever of intermittent type for 2 weeks with one other feature which could be rash, generalised lymphadenopathy, splenomegaly, hepatomegaly, or pericarditis. Two-thirds of the patients with classical systemic disease were under the age of 5 and boys and girls were affected equally, but as the age of onset increased, girls predominated.

The typical maculopapular eruptions was seen at some time during the febrile course in the majority, while generalised lymphadenopathy was seen in 50%, and hepatosplenomegaly was also common. Pericarditis was relatively infrequent initially; it may well be that it has been underestimated, as



(*a*)



(*b*)

Fig. 9 *Serial* x-*rays of a teenage girl who developed seropositive rheumatoid arthritis in 1959 (a). There has been progressive erosive joint destruction in 1960 (b), 1964 (c), and 1972 (d), despite low-dose prednisolone, 1 year of gold therapy and chloroquine.*

suggested by recent work on echocardiography (Bernstein, 1977). Systemic disease is associated with a high ESR (Westergren), polymorphonuclear leucocytosis, high IgG, and the presence of immune complexes detected by many different techniques. Irrespective of whether polyarthritis has accompanied or followed systemic disease, or been the mode of onset, the younger the child at the onset of the polyarthritis the worse the long-term functional outcome.

Characteristic joint involvement consists of the carpus with the wrist, marked flexor tenosynovitis with involvement of the proximal and terminal interphalangeal joints (Fig. 12). In somewhat older children wrist drop and flexed fingers occur within a few months of onset. In the feet, ankle subtalar and midtarsal involvement is common, with relative sparing of metatarsophalangeal joints, but often involvement of toe joints. Apart from osteoporosis, radiological changes tend to be late (Ansell and Kent, 1977). Neck involvement is frequent and early, causing loss of extension. Radiological changes again occur late, are apophyseal in site, and may lead to residual changes (Fig. 13*a*, *b*). Hip involvement is common; while not usually a presenting feature, the earlier the age of onset and the longer the disease is active, the more likely are growth alterations followed by erosive changes. This is a major source of functional disability in later life so that the development and modification of total replacement hip arthroplasty has been one of the most outstanding features in helping these young people (Arden, 1978).

PAUCIARTICULAR DISEASE

With the joint distribution of ankle, knee, and elbow,

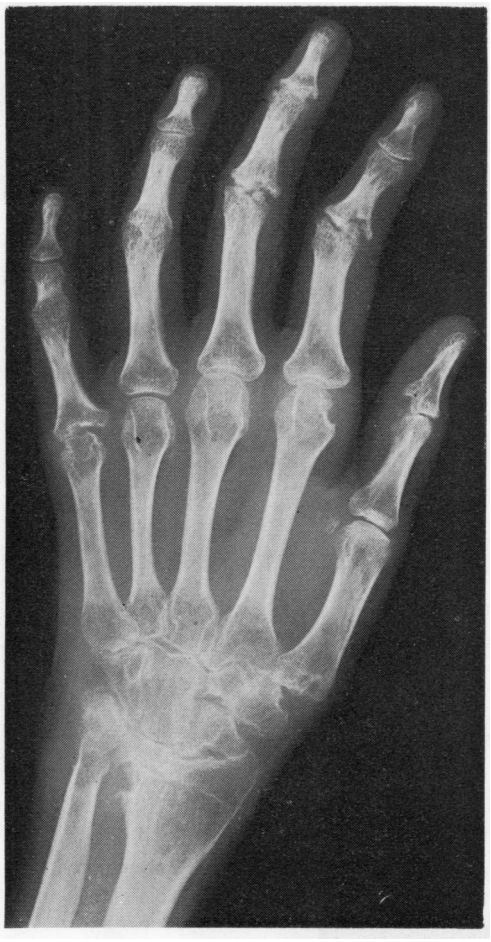


Fig. 9 (c)

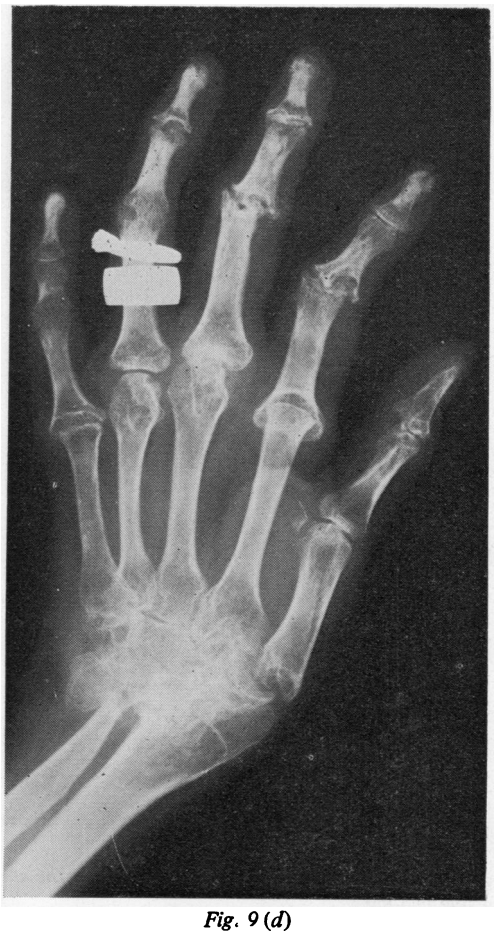


Fig. 9 (d)

pauciarticular disease is commonly seen and usually in young children, the older ones having already been sorted out into the ankylosing spondylitic subgroup. That this is a specific subgroup is further suggested by the high incidence of a new HLA D determinant: D TMLO, described by Stastny and Fink (1977). It is among these children that the serious complication of chronic iridocyclitis occurs. The age of onset is early (Table 6). There is a high incidence of ANAs without antibodies to DNA (Schaller *et al.*, 1974), which certainly accounts for most of the increased incidence of ANA in juvenile chronic arthritis. That ANA is an important indicator that the child is at risk is suggested by a recent follow-up study. As a result, in this group more frequent eye checks are suggested, preferably every 3 to 4 months. If noted early and managed adequately, the prognosis for this complication is reasonable (Fig. 14). Initially we used daily steroids, which completely stunted growth, then alternate-day steroids. Now we rely largely on local therapy to the eye. In the few cases where one eye is already severely damaged and the second eye has serious inflammation, we have considered cytotoxic therapy.

It is within this pauciarticular group that radiological growth changes (Fig. 15) are noticeable early, particularly in large joints such as the knee. Indeed, there appears to be a subgroup within the pauciarticular group who present with a swelling of a single knee which may go on to the second knee,

Table 6 *Chronic iridocyclitis, 1977*

No. of patients	124
Mean age at onset	3·9 years
Pauciarticular onset	85%
Antinuclear antibody present at diagnosis	80%

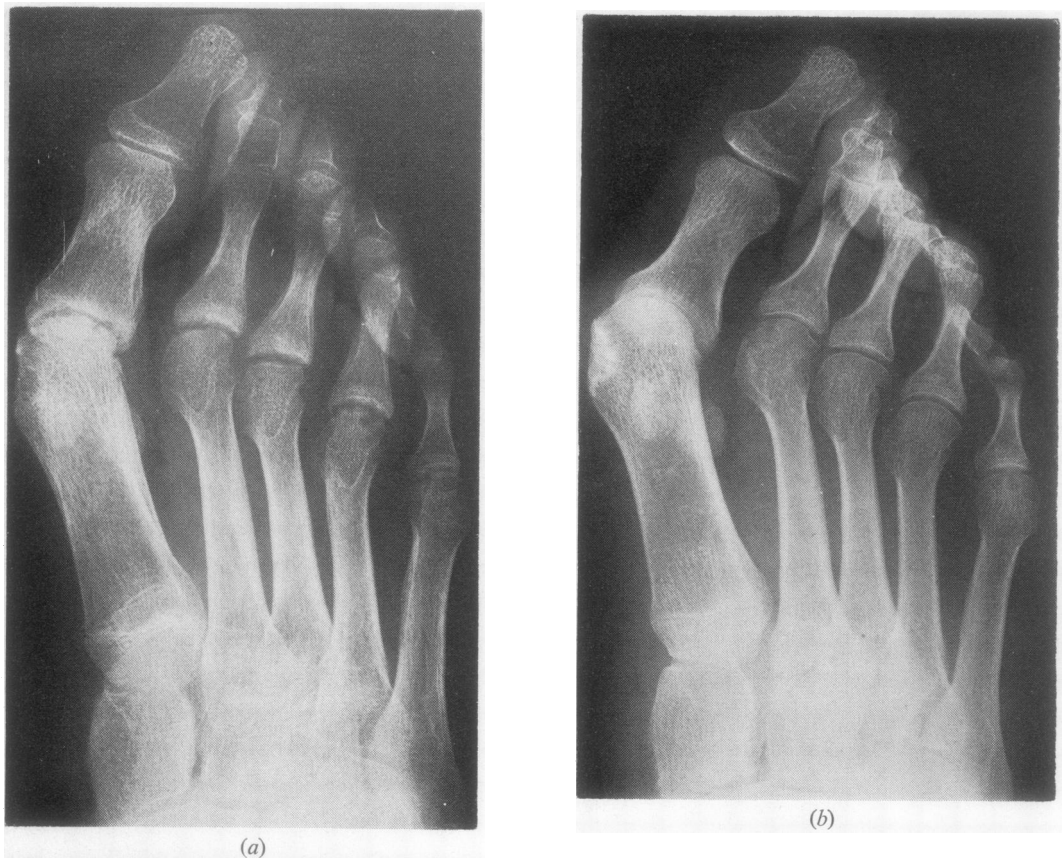


Fig. 10 X-*rays of the feet in a teenage girl at the start* (*a*) *and after 5 years of maintenance gold therapy* (*b*), *showing healing.*

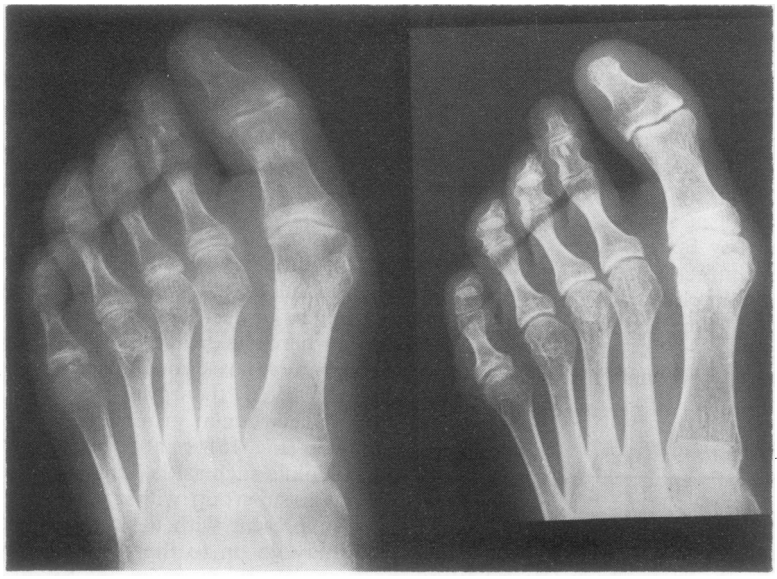
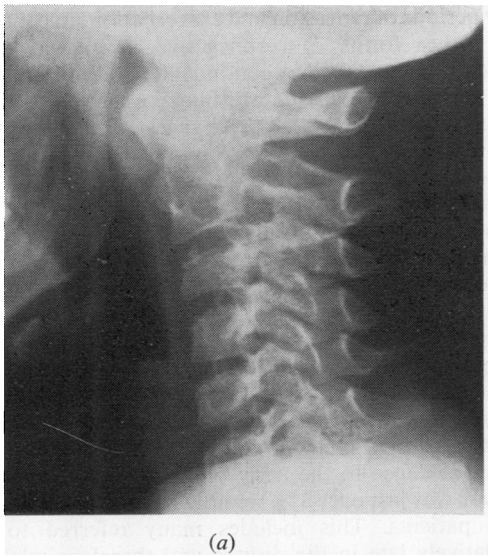
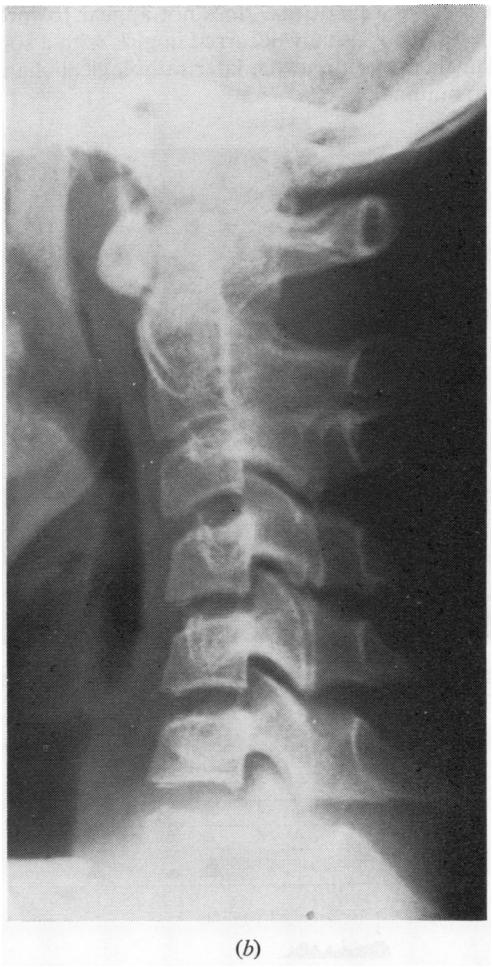


Fig. 11 X-*rays of the feet of a 15-year-old girl with seropositive juvenile rheumatoid arthritis treated with penicillamine; note healing on* x-*ray.*



(*a*)



(*b*)

Fig. 13 **X-***ray of cervical spine taken one year after onset of disease* (*a*) *showing straightening with some blurring of apophyseal joints and 7 years later* (*b*) *note growth has been resumed but there is bony fusion of apophyseal joints 2/3 and narrowing of the disc space between the 2nd and 3rd vertabrae.*

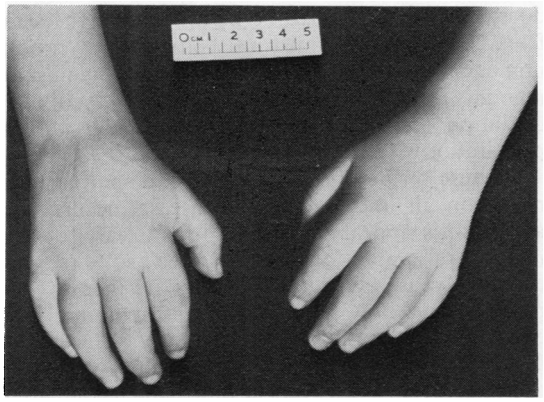


Fig. 12 *Typical appearance of the hand in seronegative chronic polyarthritis, with marked involvement of the carpus, dorsal sheath effusions, sparing of metacarpophalangeal joints, and thickening of fingers due to a combination of flexor tendon synovitis and proximal interphalangeal joint involvement.*

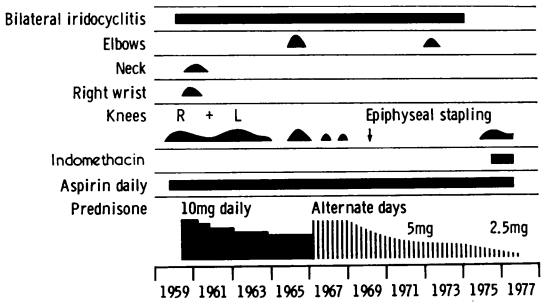


Fig. 14 *Showing the course of disease in a patient with pauciarticular arthritis complicated by chronic iridocyclitis who was started initially on daily corticosteroids and then switched to alternate-day dosage as well as receiving local steroids for her eyes. The eye disease has remitted but she is left with minor activity of the arthritis.*

but in whom the disease does not appear to spread (Fig. 16). This usually occurred in girls with a somewhat older onset and the later radiological changes were minimal.

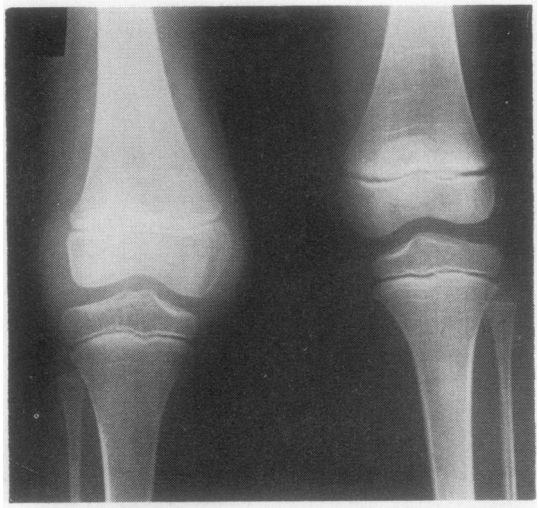


Fig. 15 *Unilateral knee involvement causing radiological overgrowth of epiphyses and metaphyses.*

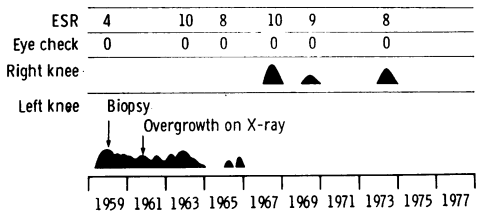


Fig. 16 *Arthritis affecting first one and then the other knee with an ultimate good prognosis in a female with monarticular onset aged 5 years (1958). DAT, latex, and ANA all negative.*

PSORIATIC ARTHRITIS

This is relatively uncommon in childhood and tends to occur about the age of 9 or 10; systemic features are rare. The arthritis can antedate the psoriasis and there is a close association with nail involvement, an unusual feature in juvenile psoriasis. Indeed, it is often the presence of nail pits, which also antedate skin change, that makes one question the family again. Asymmetry of joint involvement is usual, while rapid and serious destruction of one or two joints is not uncommon. The disease is characterised by periods of remission and exacerbation. In contrast to other forms of seronegative juvenile chronic arthritis, these tend to continue in adult life. In such cases the characteristic whittling is superimposed on the more typical growth changes of the juvenile. About a quarter have a family history of psoriasis, sometimes with arthritis. At times, despite a family history of psoriasis, the disease may be indistinguishable from the appropriate pattern of juvenile chronic arthritis. HLA studies are similar to those of adult psoriatic arthropathy (Lambert *et al.*, 1976).

AMYLOIDOSIS

This has been seen in all groups except those with persistent monarticular disease, and is particularly associated with a systemic onset; death is caused by renal failure (Schnitzer and Ansell, 1977). Although the incidence in the early patients followed for 15 years was just over 3%, we now have information on 59 patients. This includes many referred to us relatively late in the disease and therefore selected on severity. This, as well as the increasing incidence of amyloidosis the longer the follow-up, could explain the apparent differences in our findings with those of the USA. The mean duration from diagnosis of juvenile chronic arthritis to amyloidosis confirmed on biopsy was 9·9 years, with a range of from 1 to 23 years.

The most suggestive feature was proteinuria, irrespective of whether this had come on during drug therapy, associated with a high or rising ESR in the presence of active disease. Studies with SAA, the serum protein related to the AA protein of amyloid, is disappointing, behaving more like an acute phase reactant. Shortly before the diagnosis of amyloidosis IgG has tended to be high, while in the sera from 30 patients obtained just before biopsy proof, immune complexes were detected in significant amounts using the C1q and polyethylene glycol precipitation techniques (E. J. Holborow *et al.*, in preparation).

Because of the observation that if a spontaneous remission of the underlying disease occurs the amyloidosis appears to regress, or at least to stay in a sort of symbiotic state, it was decided to try and control disease activity with cytotoxic therapy. 40 patients have now been treated with chlorambucil either intermittently or continuously. The mean duration of survival of patients treated with continuous therapy for 2 years or more, when compared with intermittent therapy and conventional management, suggests improvement in survival. Fig. 17. shows a typical problem where, despite trying to maintain continuous therapy, chlorambucil had to be stopped because of leucopenia and thrombocytopenia which was followed by an upsurge in activity.

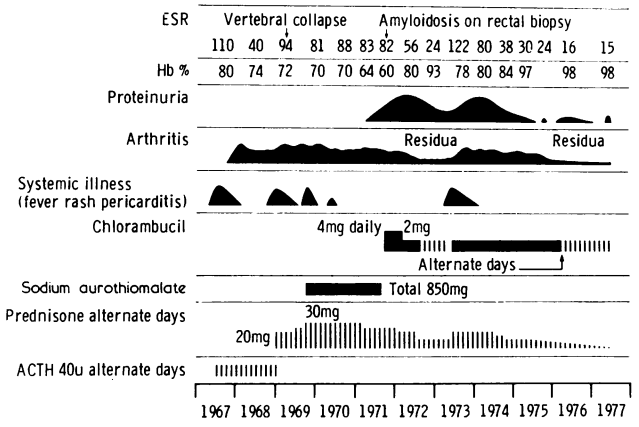


Fig. 17 *This patient, who had systemic onset of arthritis, later developed amyloidosis treated with chlorambucil. On discontinuing this treatment because of thrombocytopenia and leucopenia, there was a sharp upsurge of disease activity which settled on reintroduction of chlorambucil.*

Table 7 *Cause of death before 15-year follow-up*

	Infections	*Amyloidosis*	*Other*
Juvenile rheumatoid arthritis	1	0	2, fat embolus, cardiac failure
Juvenile chronic arthritis			
Juvenile chronic arthritis			
Systemic	3	3	2, postcardiac surgery, renal failure
Other	1	0	1 aplastic anaemia
Psoriasis	0	0	1 calcified colon

Presumably this is why intermittent therapy failed. Quite apart from blood dyscrasias and possible long-term side effects, this type of therapy is not without difficulties. Most of these patients are young, so we have had chicken pox, herpes zoster, and mumps, often making them seriously ill, while the one death so far recorded in the continuous therapy group was from myocarditis after influenza.

Prognosis

Quite apart from amyloidosis which accounted for 2%, the death rate was high in this early group of patients (Table 7). Juvenile chronic arthritis remains a serious disease particularly when systemic in onset, with infection the single commonest cause of death. Although some people have claimed that hepatitis has an ameliorating affect on juvenile chronic arthritis, hepatic problems have been a major cause of death in a number of series (Boone, 1977) including our own: these have varied from pancytopenia with infectious hepatitis to massive necrosis and infective hepatitis.

Provided these children survive, the chances of leading a normal life appear to be high, with seropositive juvenile rheumatoid arthritis the most likely to incapacitate, followed by a systemic onset associated with severe seronegative polyarthritis at an early age (Table 8). If such young people are to take their place in society, constant attention to detail in the active phase is required to keep joints in alignment, to maintain function, and to relieve inflammation, while growth of body and mind is encouraged.

Table 8 *Work/school at 15-years of 144 patients*

Diagnostic group	*Normal*	*Special*
Juvenile ankylosing spondylitis	27	0
Juvenile rheumatoid arthritis	14	6
Juvenile chronic arthritis		
Systemic onset	23	4
Chronic iridocyclitis	9	1
Other	54	2
Psoriatic	2	1

This has been an Oration and therefore I have had to generalise from the particular. I trust that I have shown you that chronic arthritis in childhood is heterogeneous. Much remains to be done to further elucidate these disorders and to improve the care of children so afflicted. Because we care, it is important to observe and document, as taught by that great physician, Heberden.

References

Ansell, B. M., and Bywaters, E. G. L. (1959). Prognosis in Still's disease. *Bulletin on Rheumatic Diseases*, **9**, 189–192.

Ansell, B. M., and Bywaters, E. G. L. (1962). Diagnosis of 'probable' Still's disease and its outcome. *Annals of the Rheumatic Diseases*, **21**, 253–262..

Ansell, B. M., and Kent, P. A. (1977). Radiological changes in juvenile chronic polyarthritis. *Skeletal Radiology*, **1**, 129–144.

Ansell, B. M., Bywaters, E. G. L., and Lawrence, J. S. (1962). A family study in Still's disease. *Annals of the Rheumatic Diseases*, **21**, 243–252.

Ansell, B. M., Bywaters, E. G. L., and Lawrence, J. S. (1968). Family studies in Still's disease (juvenile RA) *Population Studies of the Rheumatic Diseases*, pp. 229–234. Ed. by P. H. Bennett and P. H. N. Wood. International Congress Series No. 148. Excerpta Medica, Amsterdam.

Ansell, B. M., Nasseh, G. A., and Bywaters, E. G. L. (1976). Scleroderma in childhood. *Annals of the Rheumatic Diseases*, **35**, 189–197.

Arden, G. P. (1978). *The Surgical Management of Juvenile Chronic Polyarthritis* (in press). Academic Press, London.

Arnaud, P., Galbraith, R. M., Faulk, W. P., and Ansell, B. M. (1978). Increased frequency of the MZ phenotype of alpha-1-protease inhibitor in juvenile chronic polyarthritis. *Journal of Clinical Investigation*, **60**, 1442–1444.

Bernstein, B. (1977). Pericarditis in juvenile chronic arthritis. *Arthritis and Rheumatism*, **20**, Suppl. 2, 241.

Boone, J. E. (1977). Hepatic disease and mortality in juvenile rheumatoid arthritis. *Arthritis and Rheumatism*, **20**, Suppl. 2, 257–258.

Brewer, E. J., Bass, J., Baum, J., Cassidy, J. T., Fink, C., Jacobs, J., Hanson, V., Levinson, J. E., Schaller, J., and Stillman, J. (1977). Current proposed revision of JRA criteria. *Arthritis and Rheumatism*, **20**, Suppl. 2, 195–199.

Bywaters, E. G. L. (1967). Categorization in medicine—a survey of Still's disease. *Annals of the Rheumatic Diseases*, **26**, 185–193.

Cassidy, J. T., Petty, R. D., and Sullivan, D. B. (1977). Occurrence of selective IgA deficiency in children with juvenile chronic polyarthritis. *Arthritis and Rheumatism*, **20**, 231–233.

Edmonds, J., Morris, R., Metzger, A. L., Bluestone, R., Terasaki, P., Ansell, B. M., and Bywaters, E. G. L. (1974). Follow-up of juvenile chronic polyarthritis with particular reference to histocompatibility antigen W 27. *Annals of the Rheumatic Diseases*, **33**, 289–292.

Hall, A., Ansell, B. M., James, C. D. O., and Zylinski, P. (1975). HLA antigens in juvenile chronic polyarthritis (Still's disease). *Annals of the Rheumatic Diseases*, **34**, Suppl. 1, 36–38.

Lambert, J. R., Ansell, B. M., Stephenson, E., and Wright, V. (1976). Psoriatic arthritis in childhood. *Clinics in Rheumatic Diseases*, **2**, 339–352.

Pachman, L. M., and Baldwin, S. M. (1977). Assays of complement in polyarticular juvenile rheumatoid arthritis. *Arthritis and Rheumatism*, **20**, Suppl. 2, 467–470.

Pachman, L. M., Hafeman, C., and Jawor, D. (1977). IgA deficiency and juvenile rheumatoid arthritis. *Arthritis and Rheumatism*, **20**, Suppl. 2, 445–448.

Robitaille, A., Cockburn, G., James, D. C. O., and Ansell, B. M. (1976). HLA frequencies in less common arthropathies. *Annals of the Rheumatic Diseases*, **35**, 271–273.

Schaller, J., Johnson, G. H., Holborow, E. J., Ansell, B. M., and Smiley, W. K. (1974). The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis (Still's disease). *Arthritis and Rheumatism*, **17**, 409–416.

Schnitzer, T. J., and Ansell, B. M. (1977). Amyloidosis in juvenile chronic polyarthritis. *Arthritis and Rheumatism*, **20**, Suppl. 2, 245–252.

Stastny, D., and Fink, C. E. (1977). Different association of HLA D antigens with adult and juvenile rheumatoid arthritis. *Proceedings of the 14th International Congress of Rheumatology*, Abst. 181, 59.

Torrigiani, G., Ansell, B. M., Chown, E. E. A., and Roitt, I. M. (1969). Raised IgG antiglobulin factors in Still's disease. *Annals of the Rheumatic Diseases*, **28**, 424–427.

Turner, M. W., Okafor, G., and Ansell, B. M. (1976). Studies on the insolubilized immunosorbent procedure for the measurement of antiglobulins. *Still's Disease: Juvenile Chronic Polyarthritis*, pp. 145–159. Ed. by M. I. V. Jayson. Academic Press, London.