3

Juvenile Rheumatoid Arthritis

Diagnostic Criteria

Juvenile rheumatoid arthritis (JRA) has been the diagnostic label applied to any child whose arthritis is of unknown origin, begins under age 16, and persists for a minimum of 6 weeks.[1] Arthritis is defined as swelling or both pain and limitation of motion in at least one joint. "Unknown origin" means that the physician has considered and excluded all other diseases, both common and unusual, that may cause or be associated with arthritis (Table 3.1). These diagnostic criteria, adopted by a panel of experts (the JRA Criteria Subcommittee of the American Rheumatism Association) were extraordinarily successful in helping physicians distinguish arthritic disorders from other disorders in childhood. After 5 years, only 3% of children diagnosed as JRA by these criteria turned out to have some other disease. Interest in childhood arthritis was stimulated by publication of these criteria, and they helped to bring about the end of an era in which children with arthritis were frequently misdiagnosed and subjected to long hospitalizations, unnecessary surgery, harmful immobilization, and inadequate or inappropriate drug therapy.

Subtypes of JRA

During the past decade, it has become apparent that these criteria actually identify a consortium of different disorders, a panache with different genetic susceptibility determinants, environmental offsets, pathology, prognoses, and clinical patterns (Table 3.2).[2–9] As a result, these criteria failed to provide a strong relationship between diagnosis and prognosis in a given patient. It had been noted by Still in 1896[10] and was reemphasized by Green in 1940[11] and many subsequent authors[2–9] that there were great differences between children who had spiking fever to 106°F

J. C. Jacobs, *Pediatric Rheumatology for the Practitioner*

Table 3.1. Clues to Some Unusual Causes of Arthritis in Children *

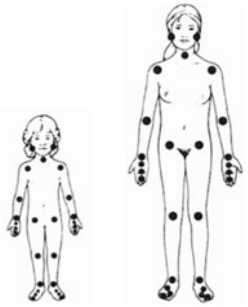
Clue	*Diagnosis*	*Diagnostic Procedure*
Strong family history of hip replacements in young individuals with degenerative hip disease	Spondyloepiphyseal dysplasia	Lateral spine x-ray
Pain in foot with atrophy of extremity	Osteoid osteoma	Bone scan, tomograms
Recurrent brief attacks of severe monarticular arthritis with slight ecchymosis	Synovial hemangioma	Phlebolith on x-ray, CT scan, arteriogram
Recurrent brief attacks with rash overlying affected joints	Familial Mediterranean fever	Observation of rash and attack
Punched-out lytic lesions in metacarpals and multiple bones	Child abuse with traumatic pancreatitis	Serum amylase/lipase Bone scan for hidden lesions
Initial onset of hip pain while doing a split	Acute chondrolysis or transient demineralization of the hip	Repeat hip x-rays
Thick hyperostotic erythematous proximal phalanges with periostitis and bone chards	Child abuse—beating across fingers with a ruler	X-ray
Exposure to plant thorns shortly before the onset of monarticular arthritis	Plant-thorn synovitis	Joint exploration
Bizarre (traumatic) lesions of fingers and toes with family history of "extraordinary brave deeds"	Congenital indifference to pain	History
Low-grade pain in the upper tibia in young boys with appearance of periosteal new bone	Stress fracture	X-ray, bone scan
Recurrent episodes of arthritis:		
with chickenpox-like rash	Mucha-Habermann disease	Lesion biopsy
with painful plaque rash and fever	Sweet's syndrome	Lesion biopsy

Table 3.1. Clues to Some Unusual Causes of Arthritis in Children* (*Continued*)

Clue	*Diagnosis*	*Diagnostic Procedure*
Recurrent episodes of arthritis:		
with severe and erysipeloid rash of lower extremities	Familial Mediterranean fever	History; trial of colchicine
with erythema nodosum or pyoderma	Inflammatory bowel disease	GI radiographs, colonoscopy
Pauciarticular arthritis with history of unusual skin lesion ("bug bite") the month before	Lyme arthritis	History
Arthritis with large postauricular lymph nodes	2° Syphilis	Serology; dark field of mucous membrane lesions
Arthritis with embolic skin lesions and tenosynovitis	Gonorrhea	Cervical/urethral/ synovial fluid cultures
Arthritis with intermittent refusal to bear weight, severe pain, anemia, transient episodes of severe bone pain	Leukemia or other malignancy	Bone marrow, IVP
Arthritis that starts with bent thumbs within a few months of birth	Familial hypertrophic synovitis	Family history
Arthritis with pyoderma gangrenosum and no systemic disease	"Streaking leukocyte factor"	Serum enhancement of WBC random mobility
Arthritis with rash appearing in newborn period	Congenital arthropathy with rash	History; skin or liver biopsy
Bizarre posturing of hand or foot	Reflex sympathetic (neurovascular) dystrophy	Physical examination
Monarticular arthritis with night pain at rest, exquisite response to aspirin	Osteoid osteoma	Bone scan, tomograms
Sudden episodes of flushing and fever in an infant	Solitary mastocytoma	Physical examination

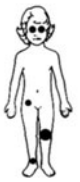
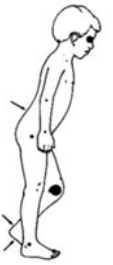
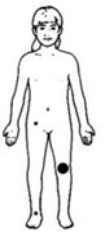
*See Chapter 2 for detailed discussion.

Table 3.2. The Spectrum of Childhood Arthritis

	Systemic		*Polyarticular*	
Type of onset	Spiking fever Rheumatoid rash Hepatosplenomegaly Lymphadenopathy Polyserositis Myalgia, arthralgia Leukocytosis, anemia		Symmetrical arthritis	
Pattern of joint symptoms	Same as pauciarticular JRA (40% of systemic onset patients)	Same as polyarticular JRA (60% of systemic onset patients)	 Arthritis involving upper and lower extremities; both small and large joints (wrists, hands, elbows, shoulders, hips, knees, ankles, feet, jaw, and neck); but not lumbodorsal spine	
Rheumatoid factor	Negative	Negative	Negative	Positive
Course of joint disease	Remitting—40%	Remitting with scarring—35% Severe, unremitting and destructive—25%	Remitting May "burn out"	Persistent chronic and destructive
Age at onset (median)	5 years	5 years	3 years	12 years
Sex ratio	M = F	M = F	F >> M	F >>> M
Antinuclear antibody	Absent	Absent	+ in 25%	+ in 75%
HLA-associated	?	?	None	DR4
Uveitis	Rare	Rare	Rare	Absent
Comments	Systemic manifestations usually ultimately remit even if arthritis continues		Extra-articular manifestations generally mild	Childhood onset of classical adult RA Subcutaneous rheumatoid nodules common

Modified from Wedgwood and Schaller, Hospital Practice, June 1977.

Table 3.2. The Spectrum of Childhood Arthritis *(Continued)*

Pauciarticular		
Asymmetrical arthritis		
 Onset in knee only in 50% of cases. Monarticular in 74%	 Few joints at onset (average 2); severe periarticular inflammation; periostitis; enthesopathy; SI joints, low back and first MTP joint; primarily lower extremity. Strong familial pattern	 Few joints involved; typically knee, hip, ankle; occasionally spotty involvement of other joints as well
Negative	Negative	Negative
Joint destruction rare but some chronic knee damage	Remitting—occasional rapid destruction, especially of hips; calcification of the inflamed entheses (heel spurs) follows lytic lesions in heel entheses	Remitting; mild enthesopathy; no joint destruction, no calcification of the enthesis
2 years	10 years	6 years
F >>>> M	M >> F	F > M
+ in 50%	Occasionally transiently positive at onset	Absent
DR5	B27	None (? many subsets)
+ in 40% Subacute and chronic	8% in childhood 25% in lifetime (Acute, subacute, and chronic)	Rare
Total blindness in 17% in the past was the major disability. Average number of joints at onset = 1.3	May progress to ankylosing spondylitis; may begin with Reiter's syndrome. Average number of joints at onset = 2.5	Not a well-defined group

daily, those children who had severe polyarticular disease but no systemic manifestations, and those whose arthritis was limited to one or a few joints. Accordingly, in 1977, the ARA-JRA diagnostic criteria were modified to divide patients with JRA into three onset subtypes: systemic (prolonged high fever), polyarticular (five or more affected joints; all cervical spine and all carpal or tarsal joints on one hand or foot count as only one each), and pauciarticular (four or fewer joints).[12] By general agreement, the onset subtype is determined 6 months after the beginning of disease. Preliminary studies have shown that 75–85% of children will remain in that subset 5 years later. Onset subtypes are convenient for study and for clinical trials, but they have less significance for the individual patient than the current pattern of disease and its course.

It has also become apparent that all forms of "childhood" arthritis may begin at any age.[13] The rarity of the rheumatoid-factor-positive ("seropositive") adult form of rheumatoid arthritis (RA) in childhood has merely served to cast the subsets of seronegative arthritis in sharper focus in the population of arthritic children. New understandings from the study of arthritis in childhood may be extended to seronegative arthritis in adults and vice versa. Subsets created by age, sex, or counting joints are only a temporary way of separating out various arthritic diseases. If diagnostic criteria are not subject to constant modification, they may serve to inhibit rather than to foster scientific progress.

Recent studies indicate that at least some of these clinical constellations are not accidentally derived but are predetermined by heritable susceptibility factors.[9,14–15] While much remains to be done, it appears inevitable that more intense study of arthritic subsets identified by genetic markers will lead to better understanding of both the pathogenesis and clinical manifestations of the various arthritic diseases. Neither the clinical subsets nor the genetic markers exist in isolation to each other. At this moment, to the author, pursuit of new information is most likely to be successful if groups are defined by genetic markers rather than by overlapping clinical characteristics. However, at the time of this writing, adequate information is not available to enable us to do so in this chapter. Thus, with the exception of the HLA-B27 group, we continue to divide patients into the officially recognized onset subtypes: systemic, polyarticular, and pauciarticular.

Laboratory Studies

The ARA-JRA diagnostic criteria do not include laboratory, histologic, or radiographic items.[12] The diagnosis of JRA is made by physical examination. Laboratory studies are performed to help in excluding other disorders that have specific laboratory abnormalities, to aid in identification of those subsets of JRA associated with specific serologic or immunologic markers, and to provide a measure of the extent of the inflammation and its systemic effects (see Table 1.6).

It is important to remember that rheumatoid factors are not specific for RA (Table 3.3). In childhood, most common causes of a positive test for rheumatoid factor are laboratory error (overly sensitive slide tests) or recent viral illness. The

Table 3.3. Disorders Associated with the Presence of Rheumatoid Factor

Rheumatic diseases: RA, SLE, scleroderma, MCTD, Sjögren's syndrome
Acute viral infections: mononucleosis, hepatitis, others, including recent immunizations
Parasitic infections: malaria, schistosomiasis, etc.
Chronic infections and inflammatory disorders: SBE, Tbc, syphillis, salmonellosis, sarcoid, chronic liver disease, etc.
Immune-complex diseases; Waldenström's hypergammaglobulinemia purpura, cryoglobulinemia

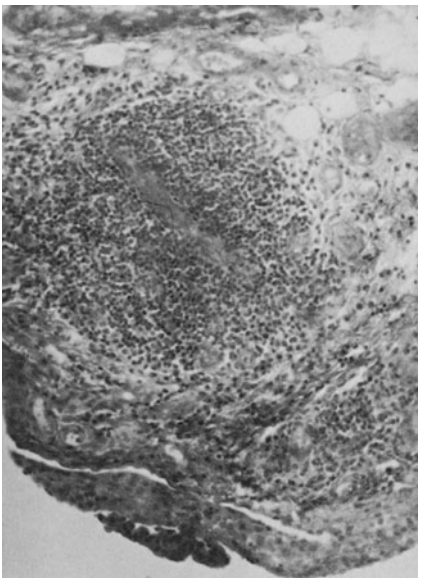
overwhelming majority of cases of childhood arthritis are not associated with the presence of rheumatoid factor, and the diagnosis of RA is always obvious in the subset of childhood arthritis that is characterized by the presence of consistently high titers of rheumatoid factor. The test for rheumatoid factor is, therefore, not performed to help in the diagnosis of JRA but to identify that subset of children whose disease is most likely to resemble early-onset severe adult RA. Tests for rheumatoid factor are also commonly positive in children with SLE and in both localized scleroderma and progressive systemic sclerosis.

Although demonstration of anti-T cell antibodies has been reported to be useful in the diagnosis and management of children with JRA, we and others have been unable to confirm this finding.[19] The laboratory studies we obtain in all children in whom we are considering a diagnosis of JRA are listed in Table 1.6. Other studies are performed when they seem appropriate to try to establish a specific cause for the arthritis.

Synovial fluid is examined to exclude bacterial infection in monarticular disease at its onset or in polyarticular disease in which septic infection seems a diagnostic consideration (see Chapter 2 under Acute and Chronic Infection of the Bones and Joints). Synovial biopsy is obtained only if the tuberculin test is positive. Needle biopsy of the knee in children has been a satisfactory technique in our clinic (Fig. 3.1).[16] However, while biopsy findings may be compatible with RA, the diagnosis cannot be established on the basis of a biopsy (Fig. 3.2).[17] Therefore, pathologic examination is of no value unless it shows a specific nonrheumatoid disease process. While open biopsy should be a harmless procedure, it has generally been followed by immobilization and/or disuse of the joint by the child, with resultant frequent permanent severe loss of function. The yield from open biopsies is so small and the risk so high that we have essentially abandoned doing them except in most unusual cases.[16,18]

Radiographic Studies

There are no radiographic findings that are characteristic of early JRA. Periarticular demineralization, bandlike areas of metaphyseal rarefaction identical to those of leukemia, and dense "growth-arrest" lines are all nonspecific findings that cannot be interpreted as diagnostic of JRA.[18,20] Periosteal new-bone formation,



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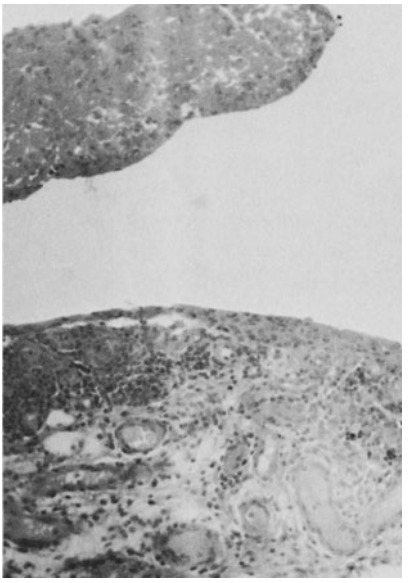

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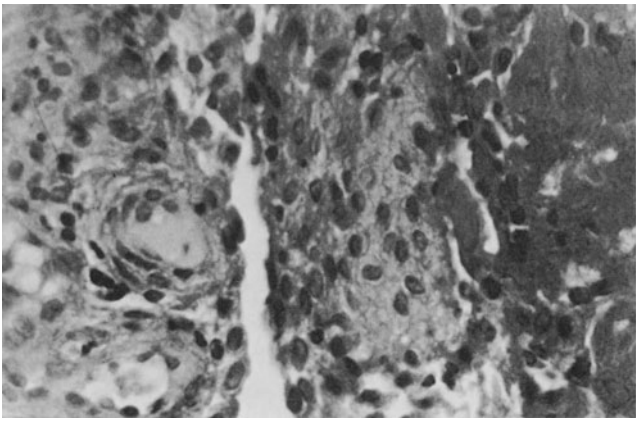
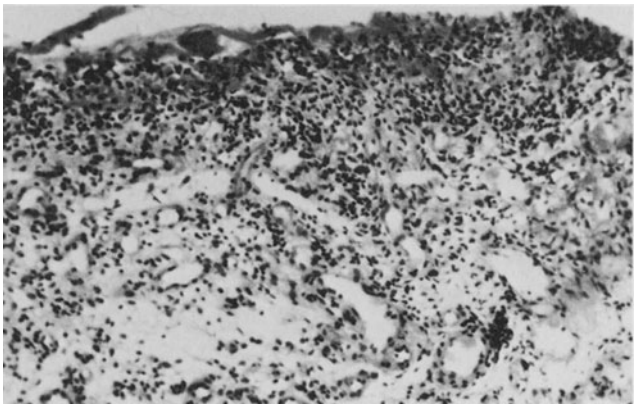


C

Figure 3.1. Three patterns of rheumatoid synovitis in one needle biopsy.(**A**) A lymphocytic (Allison-Ghormley) nodule in the center field is surrounded by a more diffuse infiltrate of "round" (plasma)) cells. (**B**) Necrotic villi *(top left);* hypervascular sublining tissues with a diffuse "round cell" (lymphocytic and plasma cell) infiltrate. (**C**) Fibrinoid necrosis *(right margin)* and hypertrophic synovial histiocytes lining villi. (**A** and **B**) ×200; (**C**) ×640. (From Jacobs et al., ref 16. Reprinted courtesy of the American Academy of Pediatrics.)



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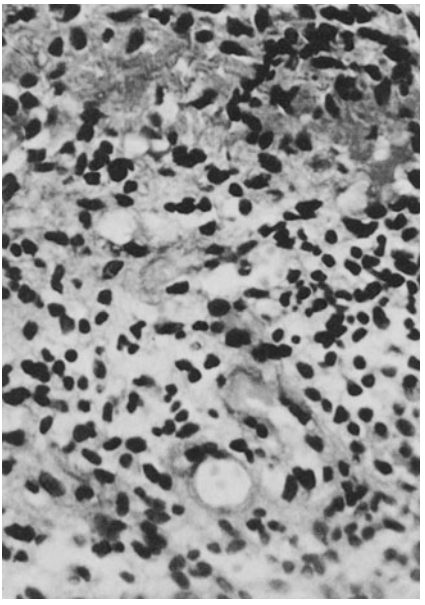


B

Figure 3.2. Rheumatoid synovitis mimicking septic synovitis. (**A**) The synovial surface is marked by granulation tissue comprising a dense capillary network and a cellular inflammatory exudate. (**B**) The exudate is largely lymphocytic but interpersed with occasional neutrophils. The surface is lined with necrotic fibrinoid material entrapping reactive cells. (**A**) ×200; (**B**) ×640. (From Jacobs et al., ref. 16. Reprinted courtesy of the American Academy of Pediatrics.)

especially in the fingers, described as an early finding in JRA, is rarely seen in our clinic. We suspect many previously reported cases really represented spondyloarthritis with sausage digits.

Radiographs, bone scans, and gallium scans are obtained solely to exclude other disorders that may be confused with JRA. The diagnosis of JRA is usually easily established long before the changes of chronic arthritis are radiographically apparent.[20] Rarely, a bone scan performed for possible osteomyelitis shows other subclinically involved joints and suggests the diagnosis of childhood arthritis.

Epidemiology of Arthritis in Childhood

Arthritis is not rare in pediatric practice. Although studies of childhood arthritis, using differing survey methods and diagnostic criteria, have shown varying prevalence,[21] a study from upper New York State showing a prevalence of 1.1 per 1000 in school-age children is probably the most accurate published estimate.[22] Minor transient musculoskeletal complaints of rheumatic origin are probably even more frequent.

Studies of the age of onset of childhood arthritis all show a peak incidence in the second year of life and a bimodal curve with a second rise later in the first decade.[18,21,23] Recent studies show that these curves are an amalgam of the varying age-incidence patterns of specific subsets; rheumatoid-factor-positive early-onset adult RA and HLA-B27–associated spondyloarthritis contribute to the late-onset peak; the other subsets all have an unusually high incidence between 1 and 4 years of age (Table 3.2).[4–8,21]

More females than males have arthritis at any age. Females are more frequently clinically affected in all subsets other than the systemic (equal) and HLA-B27–associated (males 2:1). Extrapolation of data from several studies suggests that the early-onset pauciarticular and polyarticular groups may have as high as 7:1 female preponderance (Table 3.2).[4,7,18]

The relative incidence of the various-onset subsets of JRA depends on the referral patterns to the reporting clinic. In our own clinic, at present, the overwhelming majority of new patients have pauciarticular disease (Table 3.4). In older reported series, polyarticular disease was the most common subset.[24]

Systemic JRA (Still's Disease)

Children with this form of JRA usually begin their illness with high spiking fever (>103°F daily), a typical rash, lymphadenopathy, hepatosplenomegaly, abdominal pain, myalgia, and arthralgia (Fig. 3.3). Sometimes pleurisy, pericarditis, and myocarditis are the predominant manifestations. Arthritis is often relatively inap-

Table 3.4. Mode of Onset of Juvenile Rheumatoid Arthritis

Author	*Years*	*Number of Cases*	*Systemic (%)*	*Polyarticular (%)*	*Pauciarticular (%)*
Calabro et al.[38]	1960–1977	200	20	49	31
Stillman and Barry[5]	1923–1977	204	19	41	40
Schaller[4]	1967–1977	112	20	30	50
Fink[6]	1970–1977	151	23	18	59
Hanson et al.[7]	1955–1977	563	43	23	34
Levinson et al.[8]	1958–1977	156	20	33	47
Jacobs	1978–1981	260	9	16	75

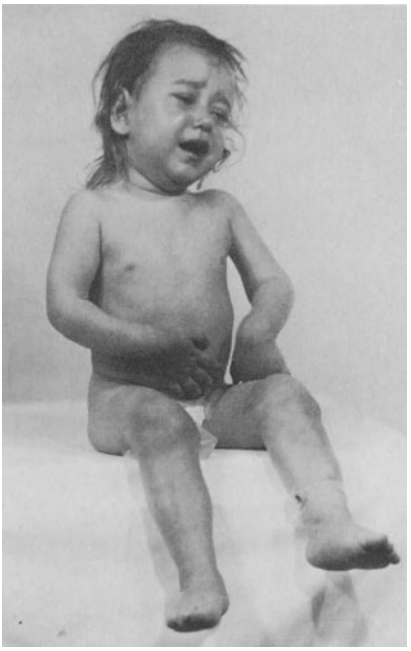


Figure 3.3. Systemic JRA that had its onset at age 5 months.

parent at the onset of the illness.[25] Uveitis is uncommon in this form of JRA but does occur occasionally. The first clear description of this form of JRA was by Still in 1896.[10] Systemic-onset disease accounts for 9% of new childhood arthritis patients registered in our clinic (Table 3.4).

Differential Diagnosis

JRA is an important consideration in the differential diagnosis of unexplained fever. However, popularization of the notion of JRA as a cause of most unexplained fevers in childhood has unfortunately resulted in considerable diagnostic error. Physicians sometimes forget that a definite diagnosis of JRA requires *arthritis,* persistent for at least 6 weeks, *plus exclusion* of all other disorders that could conceivably cause the fever and arthritis.[12] Experienced pediatric rheumatologists are well aware that many children for whom this diagnosis is considered on the basis of fever alone will have some other disorder (Table 3.5).[26–28] The differential diagnosis of arthritis in childhood is discussed in Chapter 2 and in the chapters on the other specific connective tissue syndromes. However, the three groups of disorders most frequently mistaken for systemic JRA are infection, inflammatory bowel disease, and malignancy; these entities account for 50–73% of children with prolonged "fever of unknown origin." The infections tend to be osteomyelitis or hidden abscess, most often in the abdomen or pelvis. The most common malignancies are leukemia, lymphomas, and neuroblastoma. Weight loss,

Table 3.5. Prolonged Causes of Fever of Unknown Origin in Childhood

			Pizzo et al.[26]		
Ultimate Diagnosis (%)	*McClung*[28]	*Lohr and Hendley*[27]	*Under Age 6*	*Over Age 6*	*Adults**
Infection	29	33	65	40	36
JRA	6	13	6	15	
Inflammatory bowel disease	3	6		9	
Malignancy	8	13	8	4	19
SLE	3			6	5
Familial Mediterranean fever	4				5
Factitious fever (parent- or child-induced)	9	4			3
Other causes	17	12	15	6	25
Never diagnosed	21	19	6	20	7

*Adult data from Petersdorf and Beeson, Medicine 40:1–30, 1961.

fever, and arthralgia are common presenting manifestations of these malignant disorders.[29] Bone pain out of proportion to visible arthritis or accompanied by refusal to walk suggests malignancy rather than JRA. Even after exclusion of malignancy and infection, only 10–20% of children with unexplained fever turn out to have JRA (Table 3.5).

There is no way to avoid an extensive workup for children who are thought to have systemic JRA but who do not fulfill the diagnostic criteria. As we have emphasized, even in those with arthritis, other causes must be excluded. For those *without obvious arthritis,* a presumptive diagnosis of JRA may be made only after the most thorough study excludes the common mimics. Such a workup routinely includes chest and skeletal radiographic surveys, IVP, technetium bone scan, gallium scan, bone marrow examination, and, when appropriate, a small-bowel series, colonoscopy, and barium enema. If lymphadenopathy is present, a lymph node biopsy may also be necessary.[30] The entire workup can be completed in a few days. If all of these studies are normal, a child with hectic fever, in the absence of arthritis, may be considered to probably have JRA and may be *managed as if he does.* The diagnosis, however, remains *tentative,* and it is appropriate to remain alert to other diagnostic possibilities.

Epidemiology

The most common age at onset is between the first and fourth birthday.[18,21,31,32] However, both adults and children at any age may be affected.[13,33] Our youngest patient was 6 weeks old. Up to one-third of cases begin in teenagers or adults.[3,21] Males and females are equally frequently affected.

Manifestations (Table 3.6)

Fever. A typical fever pattern has been described (quotidian) with one or two daily hectic spikes, sometimes to 105°F, and return to 98.6°F or below.[25,34] Our experience suggests that return to subnormal temperature (<98°F) usually occurs only in those given aspirin at the time of the peak.[34] Children given no medication at the height of the spike tend to have hectic fever without return to below normal (Fig. 3.4). The fever spikes often take place late in the afternoon or in early evening and may be accompanied by shaking chills. Children who do not have pleurisy, pericarditis, or myocarditis often look surprisingly well at the time they are febrile as compared to children febrile with acute disorders.

Rash. A distinctive evanescent salmon-pink macular or maculopapular rash, most commonly on the trunk or overlying joints, occurs in most children with systemic JRA (Fig. 3.5).[35,36] As one looks at the rash, it seems to change slightly, with new spots appearing while others disappear. Rubbing or scratching the skin may elicit the rash (Koebner phenomenon); in about 25% of cases, the rash itches. If one is sufficiently familiar with the rash, a presumptive diagnosis can be made on the basis of the rash and fever alone. However, occasionally, catecholamine-

Table 3.6. Manifestations of Systemic JRA

Hectic fever
Salmon-pink evanescent rash
Arthritis and torticollis
Myalgia
Hepatosplenomegaly and lymphadenopathy
Tenosynovitis
Pericarditis and myocarditis
Pleurisy and lung infiltrates
Abdominal pain
Irritability, drowsiness, meningismus
Acute laryngeal stridor
Anemia, leukocytosis, thrombocytosis, greatly elevated ESR

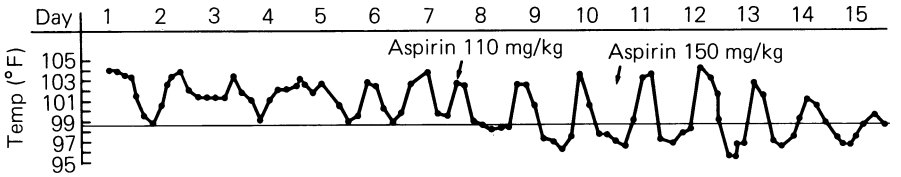


Figure 3.4. Typical hectic fever pattern of systemic JRA (patient pictured in Fig. 3.5). The temperature does not generally fall below 98.6° unless aspirin is given, as shown during the week of observation without therapy. Some response is noted soon after aspirin is begun, but satisfactory control of fever is dependent on achieving a therapeutic level of salicylate. Steady-state salicylate levels are not achieved until about the ninth day of therapy.

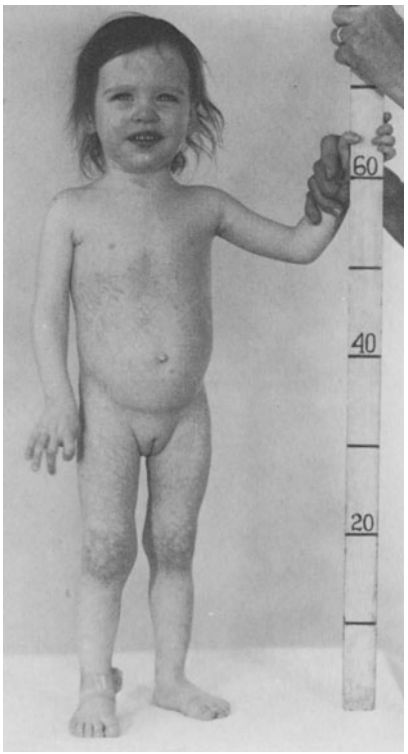


Figure 3.5. Typical rheumatoid rash in a 2-year-old dwarfed child who had a year of fever and rash before arthritis was apparent. The Koebner phenomenon is apparent where she has scratched the abdomen. On the thighs, the rash is associated with a livedo reticularis pattern. (See also frontispiece.)

secreting tumors or other disorders may present with a similar rash, so that the presence of typical rash does not relieve the physician from the need to exclude other diagnostic possibilities.

The rash of JRA is often most pronounced at the time of the fever spikes. If these are limited to evenings, it may be worthwhile for the physician to reexamine the child at that time, as the fleeting rash may not have been noticed by the family or hospital staff. The rash of JRA may come and go during the course of treatment even though fever and arthritis are controlled with medication.

Biopsy of the rash is not necessary since it is the clinical characteristics rather than the pathologic features that are useful to the physician. Where biopsies have been performed for academic study, the primary finding has been edema, as in urticaria. In florid cases, mild perivascular infiltrates of lymphocytes or polymorphonuclear cells may be seen in the loose connective tissue of the subepithelial layer.[36,37] When fever and arthritis are accompanied by a rash suggesting impetigo or psoriasis, Reiter's syndrome is the most likely diagnosis (see Chapter 4).

Arthritis. Children with systemic JRA fall into two groups: (1) those with obvious severe, unremitting polyarticular disease who have a rather poor prognosis for ultimate joint function and who account for the major crippling and death in

JRA and (2) those with arthralgia without much arthritis who have an excellent prognosis for future joint function and often must represent a different disorder from the severe polyarticular systemics.[18,38] While the severe polyarticular systemic-onset JRA population represents a discouraging challenge to the pediatric rheumatologist and a fearful prospect to parents of children called JRA, it constitutes a very small percentage of children with arthritis, perhaps 2% of those registered in our consultation clinic.

Torticollis. During the acute attack, more than half the children have neck pain and torticollis. Neck pain is often the most prominent arthritic manifestation in systemic-onset patients.[5] Cervical spine pain, therefore, may be a good clue to diagnosis in children with relatively little visible arthritis.

Myalgia. Myalgia is often a prominent symptom in Still's disease, especially in children with little arthritis.[39] Elevations of creatinine phosphokinase are generally mild, if present at all.[40] The severity and quality of the muscle pain in systemic JRA resembles that of adult polymyalgia rheumatica and presumably is a manifestation of vasculitis in muscle. Lumbar, cervical, and thigh muscles are most commonly affected. Muscle weakness is not seen. Muscle biopsies are obtained only in children thought to have polyarteritis nodosa or some other form of systemic vasculitis. In Still's disease, biopsies have usually been normal, but occasionally a perivascular accumulation of round cells has been found in connective tissues surrounding muscle.[33]

Hepatosplenomegaly. Systemic JRA is frequently accompanied by enlargement of the liver and spleen. Minor abnormalities in SGOT and SGPT are common.[40] Sometimes the hepatomegaly is alarming, extending 10 cm below the costal margin. When liver biopsies have been obtained, only nonspecific inflammation in the periportal areas has been seen.[41]

Lympadenopathy. Nondiagnostic lymphoid reactive follicular hyperplasia is also most always present in systemic JRA: at times, the nontender and freely movable lymph nodes may reach 5 cm in diameter.[42]

Tenosynovitis. Proliferative inflammation about the wrist commonly creates dorsal synovial pouches (Fig. 3.6). Sometimes these "masses" are mistaken for "tumors." Synovial pouches are also occasionally seen in other joints. An unusual manifestation of tenosynovitis that we have seen in one child with systemic JRA is tenovaginitis of the superior oblique tendon of the eye, resulting in Brown's syndrome. This syndrome is characterized by intermittent vertical diplopia and a clicking sensation on trying to move the eye up and inward; the click is followed by resumption of normal vision. This syndrome has also been reported in adults with arthritis.[43]

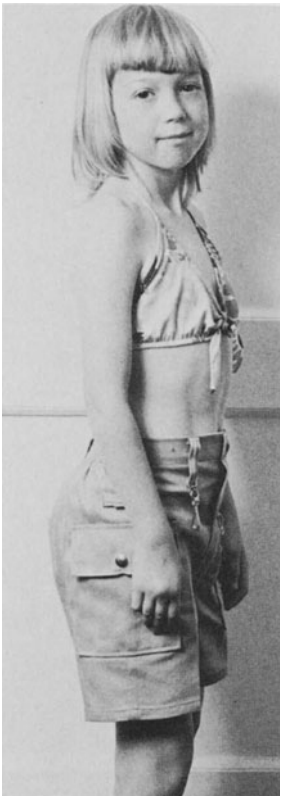


Figure 3.6. Proliferative polyarticular JRA with cystic "synovial pouches" at the wrists and shoulders. Stance indicates flexion contracture at the elbow with limited supination, often an early but unrecognized arthritic manifestation in children. The accentuated lordotic posture is a clue to disease in the hips and is accommodated by standing with the knee bent. Some of these girls do not complain of pain (as initially observed by Still[10] and emphasized by Grokoest et al.[18]), and an early diagnosis may not be made at the time of routine pediatric examiniation unless the joints are carefully examined.

Pericarditis and Myocarditis. About one-half of children with systemic JRA have pericarditis during the initial attack. Usually, the pericarditis is asymptomatic or manifested only by minimal chest pain, and diagnosis depends on the demonstration of echocardiographic, radiographic, and electrocardiographic abnormalities (Fig. 3.7). Occasionally, the pericarditis is associated with myocarditis, cardiac tamponade, and severe congestive heart failure (Fig. 3.8).[44,45] Attacks of pericarditis and myocarditis usually last between 1 and 15 weeks, with an average of 2 months. However, some patients tend to have recurrent attacks.[46] These patients resemble patients with recurrent Coxsackie B viral pericarditis and myocarditis.[47] In one adult with this syndrome, Coxsackie B3 virus could still be demonstrated in the pericardial fluid 1½ years after the first of many recurrent episodes.[48] Adenovirus has also been demonstrated in the pericardial fluid of one child at the onset of systemic JRA,[49] and we are aware of adenovirus isolation from bone marrow and pleural fluid in two other patients at the onset of systemic JRA. A similar vasculitis syndrome has also been associated with the demonstration of high titers of hepatitis B virus antigen in pericardial fluid.[50] These are isolated cases, however, and in most patients with pericarditis the pathogenesis of the episode is unknown.

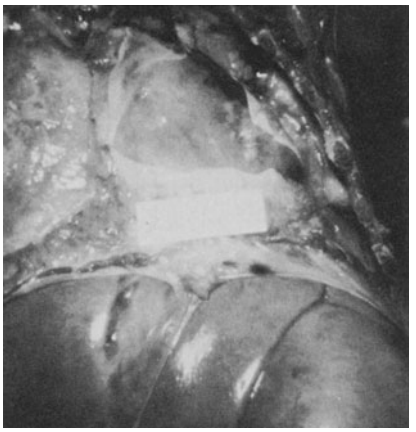


Figure 3.7. Fibrinous pericarditis was found at autopsy in a child with systemic JRA who died following the second injection of gold (see Fig. 3.41). The pericarditis was clinically silent and unrecognized.

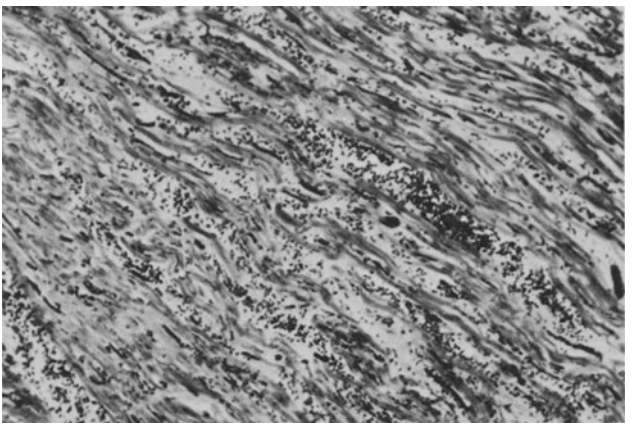


Figure 3.8. Flagrant myocarditis noted in the same patient (Fig. 3.7) was also "silent."

Although symptomatic constrictive pericarditis has not been reported in childhood JRA, adhesive pericarditis is a common finding in the select population of children with JRA who are examined postmortem.[10,46] Myocarditis that was not recognized during life may be demonstrated at postmortem examination (Figs. 3.7 and 3.8).

Rheumatoid nodules on the heart valves and chordae tendineae have not been reported in children, but we have seen one child with seropositive RA associated with tuberculosis in whom rheumatoid nodules were demonstrated in the lung, heart, and meninges at the time of postmortem examination (Fig. 3.9).These findings were analogous to those seen in the animal model of arthritis called "adjuvant arthritis" (see Chapter 9).

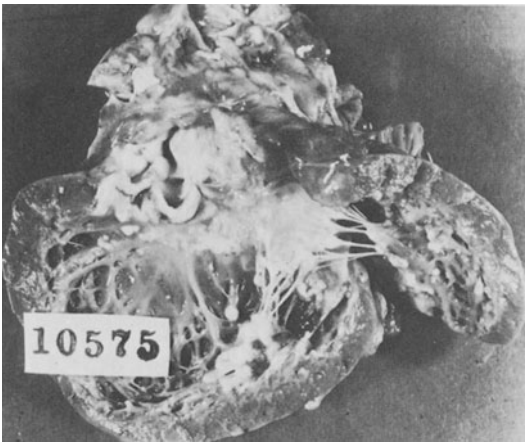


Figure 3.9. Endocardial rheumatoid nodules found at autopsy in a 6-year-old girl with seropositive JRA who died of congestive heart failure. Left ventricle, mitral and aortic valve granulomas caused stiff valves and extended to the chordae tendineae and the endocardium of the papillary muscles, trabeculae carneae, and adjacent ventricular endocardium. Patient also had arrested tuberculosis.

Pleurisy and Lung Infiltrates. One-third of children with systemic-onset JRA have radiographic evidence of pleural effusions during the acute episode. These are often associated with pericarditis and are sometimes also accompanied by transient lung infiltrates that disappear along with the pericarditis and pleurisy as the disease comes under control.[3] Still's disease is an important consideration in the differential diagnosis of the syndrome of recurrent pleurisy and pericarditis in childhood. Occasional cases of fibrosing alveolitis and of rheumatoid nodules in the lung have been seen in children with arthritis.[51,52] A recent report suggests that subclinical abnormalities of pulmonary function may be common in JRA.[53]

Abdominal Pain. Diffuse abdominal pain suggestive of serositis is a prominent symptom in about 10% of children with systemic JRA.[42]

Laryngeal Stridor. Systemic JRA occasionally presents with stridor as the most apparent symptom, a result of life-threatening acute cricoarytenoid arthritis.[37,54] Although arthritis may also be demonstrable elsewhere, it is usually not noted in the context of caring for the child with a compromised airway.

Cerebral Manifestations. Irritability, drowsiness, meningismus, and nonspecific electroencephalographic changes are all frequently observed in systemic JRA.[55] An episode of cerebral vasculitis has been documented by cerebral angiogram in one child with JRA.[56] O'Connor recently reported one child with hemiparesis, and we have had one patient with a transient hemiparesis.[57] Occasional children have been reported with either febrile or afebrile seizures. Perivascular mononuclear-cell infiltrates in the brain and mononuclear inflammation of the meninges were demonstrated in all patients whose brains were examined in a recent postmortem study.[57] Immune complexes were found in the spinal fluid of one of those children. Central nervous system (CNS) involvement is probably more frequent than has been previously recognized in Still's disease. However, it

is not as frequent as suggested by postmortem material, which reflects the incidence only in the most severely ill patients.

Renal Disease. Significant renal pathology is not a part of JRA except in those few children who develop amyloidosis. However, transient albuminuria, leukocyturia, erythrocyturia, and decreased creatinine clearance are reported to occur in about one-third of especially carefully followed patients if repeated examinations were performed looking for these abnormalities.[58] Minor changes may also be seen on renal-biopsy specimens.[58] While some of the renal findings must be a result of damage by drugs (see below), it also seems likely that some may be a manifestation of the disease itself, albeit generally a manifestation of seemingly little consequence.

Amyloidosis. Amyloidosis may be a complication of any chronic disease and in the past accounted for up to 50% of deaths from childhood arthritis.[18,59,60] Transient proteinuria is the first manifestation, but the diagnosis is usually not suspected until more persistent proteinuria occurs. Associated symptoms include nephrotic edema, hypertension, hepatosplenomegaly, abdominal pain, diarrhea, and congestive heart failure. Diagnosis is usually achieved by rectal biopsy. Amyloidosis is very rare in children in the United States; the reason for the increased incidence in European pediatric rheumatology clinics is unknown but may be related to the tendency of such clinics to serve disproportionate numbers of severely affected individuals.

Amyloidosis has been reported in equal numbers of male and female arthritic children and is not limited to those with systemic disease.[59] One might suspect from this observation that there is at least equal risk of amyloidosis in severely affected childhood-onset male spondyloarthritis, although data to confirm such a hypothesis are not available at present.

Renal Papillary Necrosis. Renal papillary necrosis (RPN), a known complication of analgesic use, has not been associated with the use of aspirin alone in JRA.[60A] Recently, Wortmann et al. reported RPN in three severe JRA patients treated with many drugs.[61] The children had unexplained hypertension or hematuria; IVPs demonstrated filling of an entire papillary region, typical of RPN. The authors emphasized that all of their patients were chronically dehydrated, which may cause RPN and which would certainly increase the risk of RPN with anti-inflammatory drug therapy. Care should be taken to avoid chronic dehydration in children receiving analgesic therapy.

Anemia. Hemoglobin of less than 10 g has been reported to occur in 39% of children with JRA at some time during their course.[42] The anemia seems to be a result of a combination of factors, including iron deficiency[62] (poor diet, increased losses as a result of medications, malabsorption of oral iron,[63,64] impaired release of iron stores), shortened life-span of red blood cells, and impaired release of erythrocytes from a hyperplastic bone marrow.[12] Erythroid hypoplasia has also been

reported in one child,[65] and we have seen one child with generalized marrow hypoplasia in our clinic.

Case Report

A 3-year-old boy was admitted to the Babies Hospital in April 1972 with a 2-week history of fever and polyarthritis. A diagnosis of JRA was made, and treatment was begun with aspirin with only partial control of his symptoms. His hemoglobin fell to 5.6 g, his WBC to 1400/mm^3, and his platelet count to 52,000. The bone marrow was hypoplastic. His symptoms were controlled with the addition of tiny doses of prednisone (3 mg daily) to his aspirin regimen, and the hematologic parameters returned to normal as his symptoms subsided. Four months later, he had an exacerbation of symptoms while receiving a lowered dose of aspirin. Three weeks later, he was readmitted with pancytopenia (hemoglobin, 6.3 g; WBC, 800; platelet count, 32,000). At this time, he was found to have pneumococcal bacteremia. He was treated with appropriate antibiotics, blood and platelet transfusions, and, after control of the infection, with prednisone, 30 mg daily. Aspirin treatment was subsequently reinstituted and prednisone gradually withdrawn without ill effect. After 2 years, his arthritis remitted, and aspirin treatment was discontinued. However, 2 years later, he again developed high spiking fever and polyarthritis. Although the arthritic symptoms responded to aspirin, he again developed pancytopenia with a severely hypoplastic marrow, which again responded to prednisone therapy. Manifestations of systemic JRA have persisted since that time, requiring treatment with prednisone as well as many other antirheumatic medications, including choline salicylate. He remains somewhat anemic, but his WBC and platelet count are normal.

Although children with G6PD deficiency are generally instructed not to take salicylates, recent studies suggest that a therapeutic level of salicylate in G6PD-deficient individuals does not produce hemolysis.[66]

It is often impossible to utilize ordinary laboratory methods to document iron deficiency in children with severe JRA. Serum iron and iron binding capacity determinations are altered by chronic disease. Serum ferritin is often elevated in children with active arthritis even if they are iron deficient, and so it cannot be used as a guide to iron deficiency.[67] Bone marrow stains for iron are a satisfactory method of proving iron deficiency but are impractical except in special circumstances. Although a therapeutic trial of iron therapy is not the ideal method of diagnosing iron deficiency, it is often the only practical approach in children with JRA.[62]

Other nutritional anemias have not been documented in JRA. However, some nutritional anemias may be drug induced, and all deficiency anemias may be intertwined biochemically and pathologically.[68] Further study of the possible role of deficiencies of vitamins and minerals in these children is needed.

That part of the anemia that is due to iron deficiency generally responds to proper oral iron administration. However, occasionally oral iron is not absorbed and parenteral iron administration is required.[63,65] Severe anemia unresponsive to iron therapy is sometimes a major manifestation of the systemically ill patient. When systemic disease is controlled with aspirin, anemia often disappears. Occasionally, very ill patients will require alternate-day prednisone therapy to control otherwise intolerable anemia.

Disturbances of Linear Growth (Dwarfing). Somatic growth arrest was reported as an important feature of systemic or severe polyarticular JRA by Still,[10] and was reemphasized by Kuhns and Swain[69] and by Coss and Boots (Fig. 3.5).[70] This subject has been more recently reviewed by Ansell and Bywaters[71] and by Bernstein et al.[72] Growth-arrest lines in the metaphyses of ill children are a reflection of the cessation of growth due to end-organ inability of the bones to respond to growth hormone and/or a direct inhibitory effect of illness on growing cartilage. Growth-hormone deficiency is not a part of JRA,[73] and remission or control of the disease is associated with prompt catch-up growth (Fig. 3.10);[71] permanent dwarfing results only from disease that begins early and is uncontrolled throughout childhood or from steroid therapy (Fig. 3.10).[71,74] While large daily doses of corticosteroids may result in some irreversible stunting of growth, morning alternate-

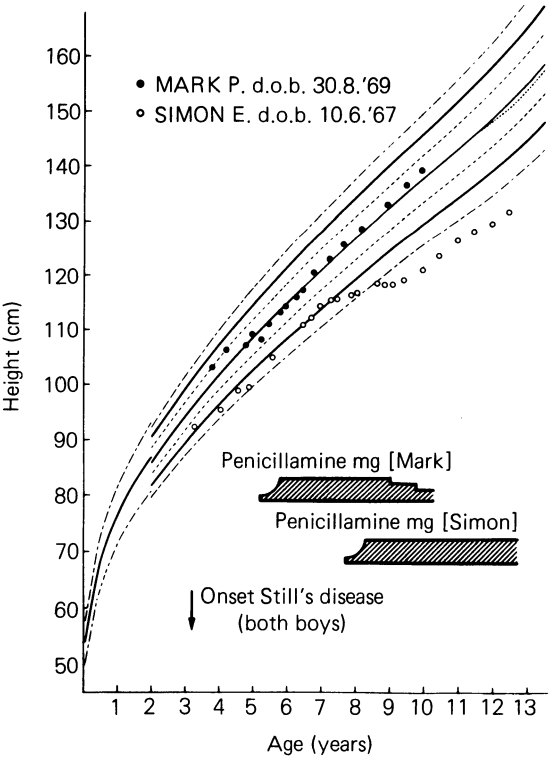


Figure 3.10. Fall-off in linear growth associated with poorly controlled JRA. Patient Mark P. had quick resumption of growth as his disease came under control but will not quite achieve his original anticipated adult height. Patient Simon E., with an inadequate response to drug therapy, will remain dwarfed despite recent control of disease. (From Ansell and Hall, ref. 166. Reproduced with permission.)

day steroid or corticotropin therapy may actually foster linear growth if the systemic manifestations associated with growth failure are controlled by a dose of corticosteroids that does not inhibit growth.[74–76] Height may also be adversely affected by collapse of vertebral bodies secondary to steroid therapy and immobility, and by flexion contractures at the hips and knees.[71,72]

Other causes of growth failure, including hypothyroidism and autoimmune polyendocrinopathy, have been reported in association with JRA and must be excluded in arthritic children with growth failure.[77–79]

Ectopic Ossification. Occasionally, children with severe long-standing JRA develop new-bone formation in tissues that do not normally ossify.[18,42,80] This is most often in subcutaneous tissues adjacent to affected large joints or in areas subject to pressure from splints or shoes but has also been noted in the eye, brain, and spinal cord. Spur-like calcifications in ligaments, previously reported as a feature of JRA, were more likely manifestations of spondyloarthritis, and most of these children with ectopic calcification may represent examples of severe spondyloarthritis.[80]

The Course of Still's Disease

Children with systemic-onset disease separate themselves out into two categories. In one group (about 40% of systemic JRA), there is very little arthritis. Therapy tends to completely control the arthritis, which disappears when the febrile episode subsides. While severe, the illness has a relatively brief course. Febrile episodes rarely last more than 6 months at a time but frequently recur at least once.[3,34,38] These patients usually ultimately recover without sequelae or with minimal joint dysfunction.

A second group of patients develops arthritis that does not remit when the systemic symptoms are controlled. This includes the 25% of systemic-onset patients who develop incessant intractable polyarticular disease that is progressively destructive; permanent handicap is inevitable. In most older published series, this group was selectively overrepresented and equaled about 5% of the total childhood arthritis population. Recent registrations in our clinic indicate that most arthritis in childhood is pauciarticular, and the proportion of these terribly ill, unremitting crippled children has decreased to less than 2% of all arthritis in children. The remaining 35% of systemic-onset patients tend to have a spectrum of polyarticular disease that may ultimately remit, leaving some scars but a normally functioning adult.

Death in Still's Disease

The incidence of death has decreased from 7% reported in earlier series[18] to 5% in 30-year series[81] and 2% in the past 20 years.[92] Since almost all deaths in the United States now are in the systemic polyarticular group, however, the incidence of death in that population in the past 20 years seems to have been around 14%.[7,82] The

most common causes of death have been amyloidosis, infection, intractable heart failure, and accidents.[60,81,82] Some accidents are related to the presence of arthritis.

Death rates from all causes are diminishing in all pediatric rheumatology clinics.[60] In our own hospital, during the decade 1961–1970, there were five deaths. In the last decade, despite a greatly increased number of patients, there have been only two deaths, one septic (gold neutropenia) and one arthritis-related accident. Both deaths were theoretically avoidable.

Treatment of Still's Disease

Treatment of Fever and Arthritis. Salicylates were obtained from plants and used as antipyretics and for analgesia by Hippocrates over 2000 years ago.[83] Easily dissolved palatable 81-mg tablets are available and very convenient for parents of infants and young children. Ordinary 325-mg generic aspirin tablets provide the cheapest nonsteroidal anti-inflammatory therapy (Table 3.7). Buffering often prevents the achievement of constant therapeutic salicylate levels (Fig. 3.11)[84] and has not been shown to prevent gastric erosion.[85]

The mechanisms of action of aspirin remain a great mystery. In 1971, Vane reported that aspirin inhibits the synthesis of prostaglandins, hormone-like substances that can cause redness, swelling, and fever.[86] Other anti-inflammatory actions of aspirin are probably directed at lymphokine action on target cells or

Table 3.7. Relative Cost of Antirheumatic Drugs

Drug	*Size (mg)*	*Cost per 100 ($)*	*Daily Dose (40 kg)*	*Daily Cost to Patient*
Salicylates				
Aspirin	325	$.60	8	$.05
Bayer timed-release aspirin	650	6.35	4	.23
Ecotrin		3.95	8	.32
Bufferin	325	2.98	8+	.25+*
Baby aspirin	75	1.36	35	.48
Arthropan	650/tsp	7.96 (240 cc)	4 tsp	.66
NSAIDs				
Indocin	25	12.28	3	.36
Naprosyn	250	22.14	2	.44
Clinoril	150	26.13	2	.52
Nalfon	300	9.47	6	.54
Motrin	400	14.28	4	.56
Meclomen	50	14.98	4	.60
Tolectin	200	12.82	6	.78

*Rapid excretion may result in the need for increased dosage.

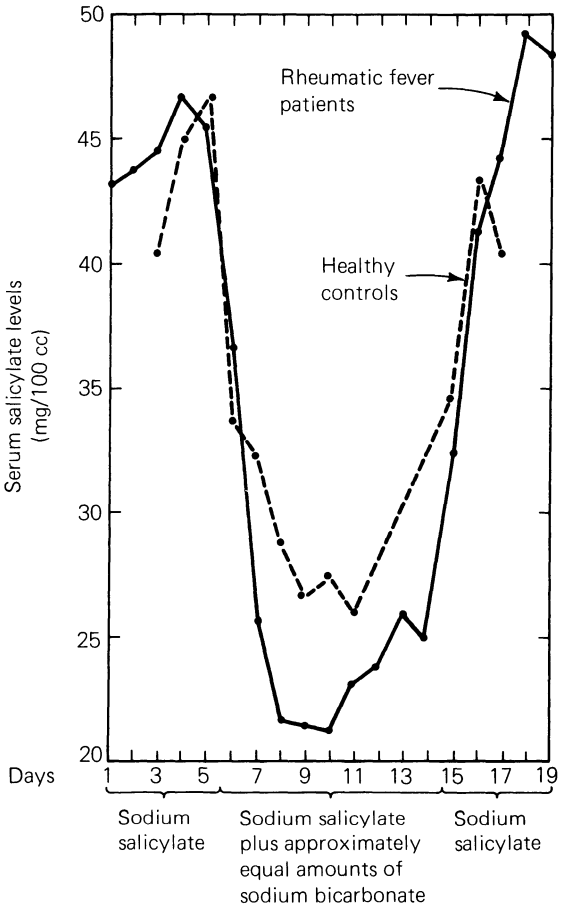


Figure 3.11. Dramatic decrease in salicylate levels caused by buffering with equal amounts of sodium bicarbonate. (Based on data of Smull et al., JAMA 125:1173–1174, 1944. From Gross M, Greenberg LA: The Salicylates: A Critical Bibliographic Review. Hillhouse Press, New Haven, Connecticut, 1948.)

lymphokine production by lymphocytes.[87] It is unlikely that any one action accounts for the total response.

The anti-inflammatory effects of aspirin in arthritis are only demonstrable at high dosage.[88] In adults, 4 g daily is required; similar studies have not been performed in children. Analgesia is achieved by considerably lower doses.

Aspirin remains the most commonly used treatment in Still's disease and is usually effective in controlling fever and arthritis after a salicylate level of between 25 and 30 mg/dl is achieved. A few patients require and tolerate slightly higher levels (Figs. 3.12 and 3.13).[89,90] In systemically ill patients, these levels are rarely if ever obtained with less than 110 mg/kg/day, which is the customary starting dose (up to 3.6 g daily). Often a higher per kilogram dose is required in young children. Some systemically ill children require and tolerate much higher doses to achieve a therapeutic level; this is especially true in children receiving concomitant prednisone therapy (Fig. 3.14). One of our sickest patients with malabsorption and concomitant steroid therapy required 300 mg/kg/day; some children require six doses daily for control of fever.

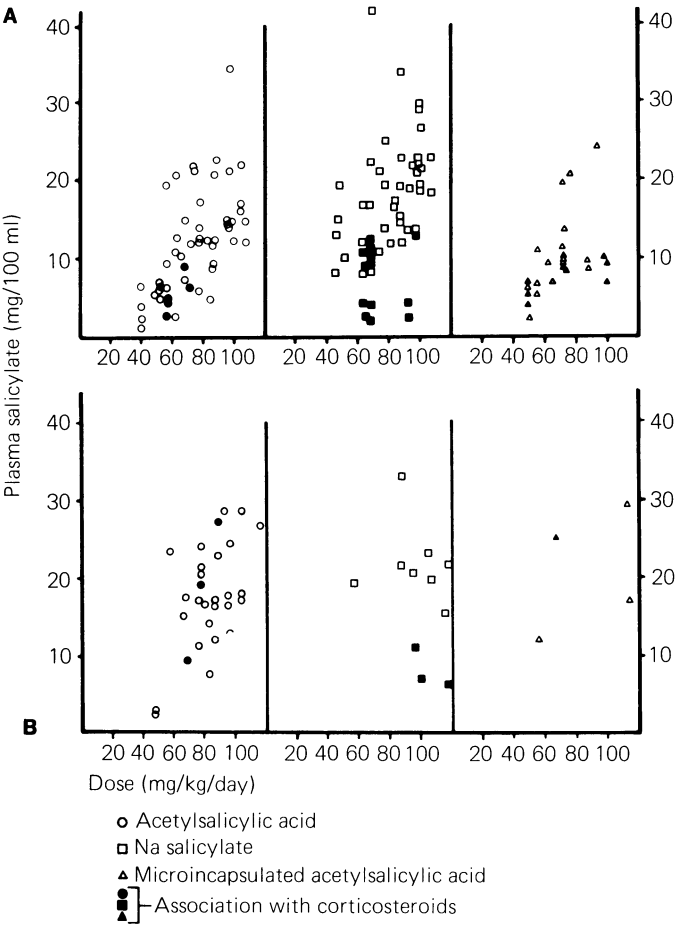


Figure 3.12. Great interindividual variability of plasma salicylate levels is shown in children receiving the same dose, both as outpatients (**A**) and inpatients (**B.**) For example, in 14 patients taking sodium salicylate as outpatients, a daily dose between 99 and 106 mg/kg (mean, 101 mg) yielded plasma salicylate concentrations ranging from 15 to 30 mg/dl in different individuals; similarly, a daily dose of acetylsalicylic acid (ASA) between 78 and 83 mg/kg (mean, 80 mg) in outpatients gave plasma salicylate levels varying from 6 to 24 mg/dl in different children. Note lowering of levels caused by additions of corticosteroids. (From Bardare et al., ref. 92. Reproduced with permission of the authors and editor of Archives of Disease in Childhood.)

In patients who tolerate an average dose without adverse symptoms and whose disease is controlled with that dose, salicylate levels need not be measured. However, in patients requiring dosage regulation to achieve control of the disease or in those who develop signs of salicylism, blood levels are measured[91,92] and the dose adjusted. Salicylate levels reach their peak 9 days after the initiation of steady-dose therapy and tend to fall off slightly thereafter.[93] At high serum levels, small-

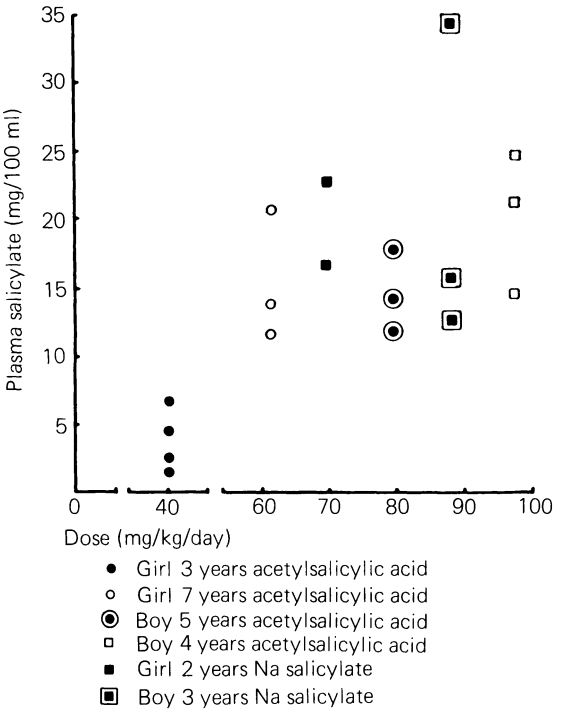


Figure 3.13. Daily plasma salicylate levels differ greatly in the same individual receiving the same dose as shown; in a 3-year-old boy, the level varied from 12 to 34 mg/dl despite steady dosing with 90 mg/kg and obtaining specimens under identical circumstances regarding time after last dose. (From Bardare et al., ref 92. Reproduced with permission of the authors and editor of Archives of Disease in Childhood.)

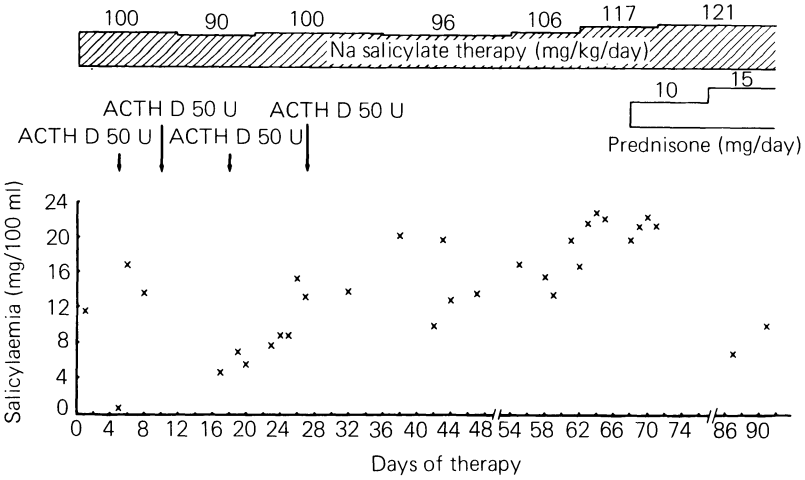


Figure 3.14. The addition of corticosteroids causes a prompt reduction in plasma salicylate levels. In a patient receiving daily prednisone, a high dose of salicylate (121 mg/kg/day) yields only a very low salicylate level (9 mg/dl). It is impossible to prescribe appropriate amounts of salicylate to patients receiving concomitant corticosteroid therapy without measuring the salicylate level until the patient is receiving a steady dose of both drugs. (From Bardare et al., ref. 92. Reproduced with permission of the authors and editor of Archives of Disease in Childhood.)

dosage increments may result in considerable increases in serum levels.[94] We generally increase by no more than 10% at one time. Similarly, if toxicity occurs, a reduction in dosage of 10% is often adequate to reach a tolerable therapeutic level. Levels vary widely in the same patients,[92,94] often related to activity. More activity seems to reduce the serum level in a given individual. Noncompliance is also a common cause of variable levels.[42] Careful regulation of salicylate levels protects the child from unnecessary exposure to more toxic agents. The important pharmacokinetic considerations for achieving optimal salicylate dosage are listed in Table 3.8.

Slower-acting Agents and Nonsteroidal Anti-inflammatory Drugs. If, despite maximally tolerated salicylate treatment, a patient cannot attend school or lead a relatively normal life, a second agent is necessary (Fig. 3.15). Standard "slower-acting" agents, discussed in the section on polyarticular disease, may also help in the control of arthritis in systemic-onset patients.[95] Supplemental use of nonsteroidal anti-inflammatory agents sometimes may contribute to the control of both arthritis and fever.

Corticosteroids. When fever and polyarthritis cannot be controlled with maximum regimens of nonsteroidal anti-inflammatory agents, it may be necessary to add prednisone to the regimen (Table 3.9). It is always preferable and usually possible to use an alternate-day regimen. Very sick children who cannot be controlled with alternate-day steroid supplements usually will respond to surprisingly

Table 3.8. Important Pharmacokinetic Considerations for Achieving Optimal Salicylate Dosage

Pharmacokinetic studies show half-life varies with tissue saturation.
High-dose steady state not achieved for 7–9 days.
At high levels, small dosage changes cause large variations in serum levels.
Urinary excretion varies greatly with small changes in urine pH.
Serum levels are greatly increased by small decreases in urine pH.
Serum levels are greatly decreased by small increases in urine pH.
Great interindividual variation in dose is required to achieve the same level.
Great intraindividual variation in serum levels at different times in the same patient on the same dose.
Great variation in tolerated and effective levels in different children.
Addition of corticosteroids to therapeutic regimen causes reduction in the salicylate level and requires considerable increase in salicylate dose to achieve prior level.
Removal of corticosteroids from the therapeutic regimen causes increase in the salicylate level and poisoning if not carefully monitored.
Systemically ill and anemic patients often require high doses due to malabsorption and/or altered metabolism of salicylate.

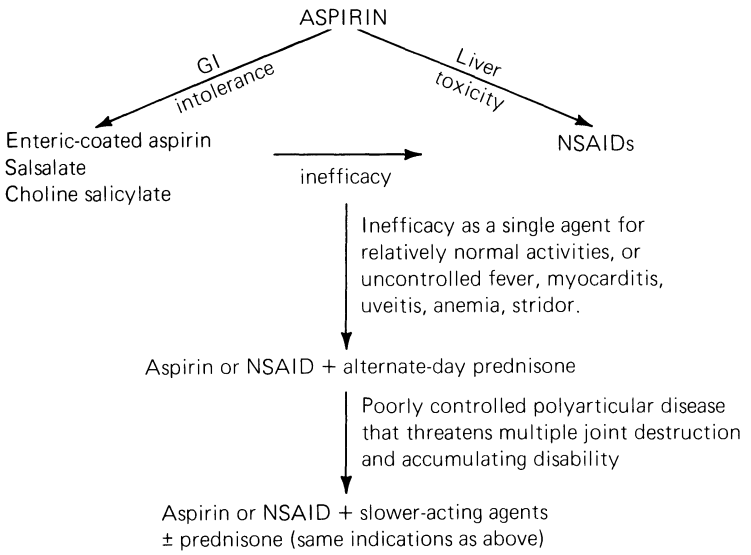


Figure 3.15. Treatment module for childhood arthritis.

Table 3.9. Indications for Systemic Corticosteroid Therapy in JRA

Fever that cannot be controlled with any NSAID
Myocarditis
Tamponade not controlled with intrapericardial steroid injection
Uveitis not controlled with local steroids
Intolerable anemia
Inability to ambulate
Acute laryngeal stridor

tiny doses of prednisone (1 mg) but may require as many as six doses throughout the day and night to control their unimaginable pain, fever, and anemia. Most children with disease that requires steroids, however, can be adequately managed with full doses of aspirin and a "boost" of a small dose of prednisone every second morning (10–15 mg qod). The regimen must be individualized for each child. Monitoring of prednisone blood levels is complicated and not yet generally available.[96]

The adverse effects of long-term glucocorticoid therapy are well known to the clinician (Table 3.10).[97] Alternate-day steroid therapy has provided the physician with the ability to avoid bed-chair crippling with an acceptable amount of steroid toxicity. Frequent tiny doses of prednisone have sufficed for almost all our other patients until they, too, can be switched to an alternate-day regimen. Corticosteroids, therefore, if administered skillfully, are the tool that avoids bed-chair crippling, whereas if misused, these same drugs can cause increased crippling or even death.

Table 3.10. Adverse Effects of Glucocorticoid Therapy

Metabolic
Central obesity
Glucose intolerance
Hyperosmolar nonketotic coma
Hyperlipidemia
Endocrine
Hypothalamic-pituitary-adrenal axis suppression
Growth failure in children
Menstrual irregularities
Musculoskeletal
Osteoporosis
Aseptic necrosis of bone
Myopathy
Cutaneous
Thin, fragile skin
Purpura
Striae
Acne
Hirsutism
Impaired wound healing
Ocular
Posterior subcapsular cataracts
Glaucoma
Central nervous system
Psychiatric disorders
Pseudotumor cerebri
Cardiovascular-renal
Sodium and water retention
Hypokalemic alkalosis
Hypertension
Gastrointestinal
Pancreatitis
Peptic ulcer
Intestinal perforation
Impaired immune response
Bacterial, viral, fungal, and parasitic infections

From Nelson and Conn, ref. 97, p. 766, with permission.

Alterations in Salicylate Dosage Required after Introduction of Supplemental Corticosteroids. It has been repeatedly demonstrated that salicylate levels fall after the introduction of corticosteroids to the therapeutic regimen (Figs. 3.12, 3.14, and 3.16). Therefore, when adding prednisone, it is necessary to redetermine the salicylate level and increase the dose of salicylates to maintain maximum-tolerated serum level.[92,98] If the physician is not alert to this phenomenon, there may be a tendency to continuously increase the prednisone dosage, resulting in further lowering of the salicylate level and the need for more pred-

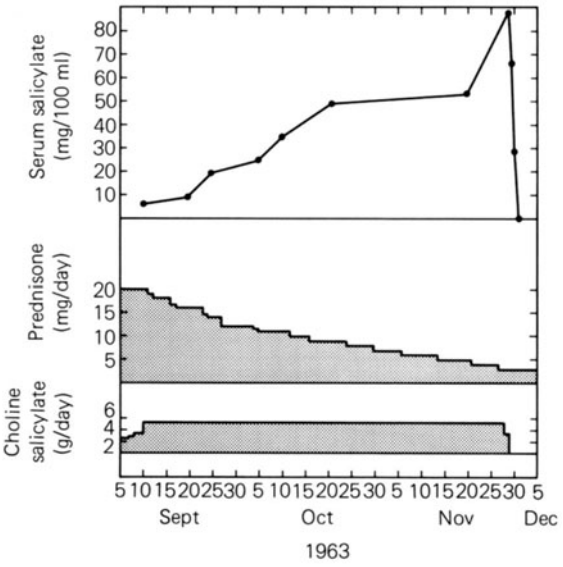


Figure 3.16. Dramatic progressive salicylate poisoning of a 5-year-old boy with JRA produced by gradual withdrawal of prednisone while maintaining a steady dose of salicylate. Note that initially, while receiving prednisone (1 mg/kg/day), a salicylate level of only 10 mg/dl was achieved despite the administration of about 250 mg of salicylate/kg/day. (From Klinenberg and Miller, ref. 98, with permission. Copyright 1965, American Medical Association.)

nisone. Although this principle has been repeatedly emphasized, our experience suggests that it is repeatedly neglected even by experienced rheumatologists.

It is equally important to be alert to the potential for salicylate poisoning when lowering the dose of prednisone administered to children also receiving aspirin. In this circumstance, salicylate levels rise, and the dose of aspirin may have to be adjusted downward to avoid poisoning (Fig. 3.16).[92,98] We teach these principles to the parents of our patients, who can then determine when to measure the levels and are often able to make the necessary adjustments in dosage without instructions from the physician.

Salicylate Toxicity. Children tolerate aspirin well, and dyspepsia is rare. However, for many children with systemic and polyarticular disease, effective treatment demands a salicylate level close to toxicity.[89–91]

If adequate control of a child's arthritis requires maximum-tolerated doses of aspirin, it goes without saying that the parent must be aware of the signs of salicylate poisoning. When aspirin treatment is begun, we advise the parent of the three cardinal signs of too much aspirin (Table 3.11):

1. *Change in personality for the worse.* In general, after institution of aspirin therapy in the arthritic child, there is improvement in disposition with relief of pain and inflammation. After a week, if aspirin levels increase to toxic proportions, there will be a behavioral regression, with irritability and emotional lability, requiring measurement of the level, prompt report (2 h), and reduction in dosage.

Table 3.11. Cardinal Signs of Salicylate Toxicity

Change in personality for the worse (irritability, lability, depression, withdrawal)
Fast breathing ("croup")
Nausea (anorexia) or vomiting

2. *Fast breathing.* Although all children with high salicylate levels breathe more rapidly than normal, a greatly increased respiratory rate simulating dyspnea or croup should be assumed, in these children, to represent salicylate poisoning, requiring prompt measurement of the serum level prior to any further salicylate administration.
3. *Nausea and vomiting.* Most children with systemic JRA requiring maximum salicylate levels will have improved appetites as fever and pain are controlled. However, if the salicylate level then climbs to toxic proportions, the improvement in appetite will be replaced by anorexia followed by nausea and, if the dosage is not then reduced, by repetitive vomiting. Sometimes a child vomits only occasionally, usually shortly after taking the medicine, as the sole manifestation of too much aspirin, presumably because levels are too high only intermittently. Parents and physicians can be alert to this potential by recognizing that any vomiting requires measurement of the salicylate level. Parents often assume vomiting to be a result of a viral illness. No such assumption is permissible unless the salicylate level has been measured and demonstrated to be nontoxic. Viral illnesses are common in children and may result in lowering of salicylate levels due to vomiting of medications or increases in levels due to relative dehydration from the illness; we cannot distinguish one from the other without the salicylate level. Our office and hospital staff is trained to obtain these levels at any time at the request of any of our patients (without formality) and to promptly provide the results in our absence to the parents, who are aware of the desired therapeutic levels and the technique of dosage omission and regulation. In order to care for arthritic children adequately, salicylate levels must be available 24 h/day with 2-h reporting. Less than this will result in increased use of more toxic secondary agents in these children. A technique for microsalicylate determinations ensures greater patient/parent compliance in toddlers.[91]

Bleeding as Result of Salicylate Administration. This particular toxic side effect of aspirin administration deserves special consideration. Tiny doses of aspirin have long been recognized to have the potential to cause bleeding in those with hemophilia.[99] Occasionally, patients with bleeding disorders secondary to abnormalities of platelet aggregation report bleeding with aspirin.[100] What was not initially recognized was that this might be paradoxically dose-related. Recent evidence suggests that this effect may not be seen in patients receiving high doses of aspirin.[101] Bleeding time may also not be further increased in such patients by

the nonacetylated salicylate preparations, salicylsalicylic acid (salsalate; Disalcid) and choline salicylate (Arthropan, Trilisate; see below).[102]

Easy bruisability may result from prolongation of the prothrombin time in children receiving chronic aspirin therapy.[103] Even in children in whom the determination of prothrombin time is normal, vitamin K, 5 mg orally daily, may be reported by patients to reduce bruisability and nosebleeds.

Significant gastrointestinal hemorrhage is a rare complication of aspirin administration in children. Controversy exists over whether such hemorrhage occurs only in those with primary coagulation defects or whether it can occur in normals as well.[104,105] When such hemorrhage occurs in children treated with aspirin alone, it is generally a result of gastric bleeding and is best treated, after cessation of aspirin, with transfusions of *freshly drawn platelets* and *fresh* whole blood.

Salicylates and the Liver. When the SGOT/SGPT tests became available, it was observed that patients with rheumatic fever being treated with large doses of aspirin frequently had elevated levels of these "liver" enzymes. No harmful effects were reported associated with these chance laboratory observations.[106] Subsequent studies in arthritic children, coincident with the institution of machine determinations of multiple blood chemistries, revealed that unrecognized asymptomatic elevations of "liver" enzyme (below 400 units) occurred with aspirin therapy in 25% of children with arthritis, was often dose-related, tended to disappear with reduction of dose or with time alone, and generally seemed to have no pathologic consequences.[107] Nevertheless, it remains possible that subtle symptoms or liver damage might occur in such children.[108] It seems reasonable not to discontinue aspirin and institute more toxic agents solely because of chance laboratory observations, but if equal control of the arthritis can be achieved with agents of equal or less toxicity without these abnormalities, it would seem the prudent course to change to those agents. Thus, only in the case of severe life-threatening elevations in enzymes would it be worth instituting daily corticosteroids as an alternative to aspirin, but at even lower levels of enzyme abnormality, consideration should be given to trying other nonsteroidal anti-inflammatory agents that do not raise the level of SGOT/SGPT. These drugs may be instituted on the same day the aspirin is withdrawn, and the liver enzyme abnormalities, if caused by aspirin, generally are eliminated within a few days.[109]

A small number of children develop symptomatic hepatotoxic effects of salicylate with elevations of SGOT/SGPT over 1000 units, tender hepatomegaly, vomiting, and a prolonged prothrombin time. Continuation of aspirin therapy may result in serious, even fatal, hepatotoxicity. In most studies, this intolerance occurs more frequently in systemically ill patients, especially those with little or no arthritis, who may represent a different subset with more primary hepatic involvement.

It is our policy to measure SGOT/SGPT in all patients prior to instituting therapy and during the period of dosage regulation. These enzymes are also measured in patients with abdominal pain or malaise and in those manifesting symptoms of salicylate toxicity.

Occasionally, using choline salicylate in lieu of other salicylate preparation

results in less hepatotoxicity.[90] In some children who cannot tolerate salicylates, other nonsteroidal anti-inflammatory agents can be substituted successfully without hepatoxicity. However, while these agents are rarely hepatotoxic, the same patients who cannot tolerate salicylates sometimes cannot tolerate these agents, either. In other children, adequate control of fever is not achieved with these agents, at least with currently accepted dosage and with our inability to measure serum levels to identify those who might require a higher dose to achieve a meaningful serum level (due to altered absorption, metabolism, or excretion). A stratagem that we generally find effective in very difficult situations in which serious salicylate hepatotoxicity occurs and no other agent provides adequate control is the use of alternate-day steroids plus aspirin. Some children will tolerate a required and otherwise intolerable salicylate level when taking relatively small doses (1 mg/kg) of alternate-day prednisone in addition to salicylate. The mechanism by which the prednisone protects the liver in this situation is speculative.

Gastritis and Ulcers. Within a few minutes of aspirin ingestion, gastric acidity increases, presumably as a result of back-diffusion of hydrogen ions in the mucosa. Whether salicylate administered systemically has a similar effect is controversial.[110] Animal experiments suggest that the mucosa develops some resistance to this effect with chronic administration.[105]

The weight of evidence suggests that gastric but not duodenal ulcers are associated with heavy aspirin usage.[105] There is some evidence of increased susceptibility to ulcers in patients with RA even without salicylate treatment. In our experience, duodenal ulcers are not uncommon in arthritic children. While the role of aspirin in the causation of these ulcers may be controversial, there is no question that patients with peptic or duodenal ulcer disease are less tolerant of aspirin than normal and suffer from worse dyspepsia than others.[105]

We have seen no instance of major gastrointestinal bleeding from duodenal ulcer in an arthritic child treated with aspirin alone; the same cannot be said for combinations of aspirin with corticosteroids and indomethacin, which have in one instance each resulted in uncontrollable hemorrhage requiring gastrectomy in two children under the age of 5. These experiences have sensitized us so that we treat ulcer symptoms by changing to enteric-coated aspirin and providing frequent milk feeds and nocturnal antispasmodics and antacids if there is nocturnal ulcer pain.

The toxic effects of salicylates have been overemphasized when compared to their therapeutic benefits and the billions of tablets consumed each year.[105] Aspirin has been accused of causing analgesic nephropathy, but there is no proof of a single case in a child receiving aspirin alone.[60A,61,111] Although hearing may be temporarily reduced, especially at high frequencies, there is no evidence that permanent hearing loss results from chronic aspirin administration. There are a great many other metabolic, endocrinologic, hematologic, and immunologic effects of aspirin administration that are adequately reviewed elsewhere.[83,112]

Special Aspirin Preparations. There is increasing evidence that enteric-coated aspirin produces fewer gastroduodenal erosions.[113] Some children with dyspepsia who cannot tolerate regular aspirin will tolerate enteric-coated aspirin and

absorb it well, attaining adequate and reliably constant salicylate levels.[114] In these youngsters, there is no reason not to use enteric-coated tablets. Not all enteric-coated tablets are equally well absorbed.[115] In one study, Ecotrin was best absorbed, and this is the sole enteric-coated tablet in use in our clinic. We have sometimes seen even these tablets undigested and whole in the stool of our patients.

Sustained-Release Aspirin. These tablets are constructed so as to provide sustained release over an 8-h period, presumably providing better nighttime and early-morning blood levels and fewer peaks and troughs. This is achieved by partial absorption in the stomach and the rest in the small intestine.[116] Controversy exists as to whether sustained serum salicylate levels are really better achieved during chronic administration of these costly tablets. However, some patients with dyspepsia who do not absorb enteric-coated tablets will do well with sustained-release tablets.

Older children hate to take medicines in school both because the other children will "see" and because many schools require the children to go to the nurse's office to have their medicine administered to them. These antiquated countertherapeutic school regulations infantilize and isolate our handicapped children, who we wish to become responsible for their own care and self-sufficient despite their handicaps.[117] Formal pleas to the American Academy of Pediatrics have not so far succeeded in producing an exception to these rules for our patients or enlightened school policies, although we have been successful in getting the rules modified in individually enlightened school systems.[117] Where these rules are enforced, any medication with a long enough half-life or a sustained-release tablet, which allows teenagers to avoid taking medicines in school, may be advantageous and worth considerable additional expense. In adults, better compliance has been shown to be achieved with less frequent dosage schedules, resulting in better control of arthritis by drugs with a long half-life when compared with equipotent medications that require more frequent administration.[118]

Other Forms of Salicylate. We have experience with only three other preparations (salsalate, choline salicylate, choline magnesium trisalicylate) that are hydrolyzed in vivo to salicylic acid and so presumably have comparable activity to aspirin. All are nonacetylated and therefore presumably do not affect platelet aggregation.[102] Salicylate levels can be determined and regulated just as when aspirin is administered, providing a mechanism to determine compliance and optimal dosage. These preparations are much more expensive than aspirin (Table 3.7) but have provided control of disease in some children who could not take aspirin.

Salsalate (salicylsalicylic acid), marketed in the United States under the trade name Disalcid, is available only in nondissolvable tablet form, with each tablet equal to 500 mg of salicylate. Dosage regulation is the same as for aspirin; presumably, medication can be administered at 8-h intervals.

Choline salicylate is a very useful form of salicylate, available in the United States as a liquid (Arthropan), with 650 mg of active ingredient in each teaspoon, equal to 130 mg of active ingredient in each cubic centimeter. Choline salicylate is sometimes tolerated when dyspepsia prohibits the administration of aspirin, and

some older children who cannot swallow tablets prefer it to taking dissolved "baby aspirin." It is possible but not proved that the choline radical helps prevent the liver enzyme abnormalities sometimes seen with aspirin administration.[90,119] While choline salicylate liquid has been very useful to this author in pediatric rheumatologic practice, its presence in the household is akin to the threat of oil of wintergreen, another potent salicylate liquid that has resulted in death from toddler ingestion. We tend not to prescribe choline salicylate when there are toddlers in the home who may accidentally ingest it and are careful to warn parents to keep it locked up at all times.

Choline salicylate is also available in tablet form as choline magnesium trisalicylate. This product (Trilisate) is reported to be useful in some patients who cannot tolerate aspirin but has not been tested in children. Tablets (500 mg and 750 mg of active ingredient) contain more than half of the salicylate as the magnesium salt, which might cause diarrhea in some children. A syrup (500 mg/tsp) has just been marketed.

Treatment of Pericarditis and Myocarditis

Mild pericarditis can often be successfully treated with aspirin alone.[42–46] However, when pericarditis and myocarditis are life-threatening (Fig. 3.17), prednisone should be instituted promptly (2 mg/kg/day in four divided doses).[42–45]

When steroids are to be administered to patients in congestive heart failure, it is useful to give an injection of furosemide 1 h prior to the first dose of steroid. This helps avoid further fluid overload. Potassium losses may be increased by both diuretics and steroids. Supplemental potassium may be given if necessary. Miller has suggested that death may result from digitalis-induced arrhythmia in these children.[45] Patients with myocarditis are very prone to arrhythmia, and digitalis should, therefore, be avoided.

Aspirin is not given initially to these patients because of the risk of increasing cardiac failure due to the increased metabolic rate induced by aspirin. After congestive heart failure has been controlled with prednisone, aspirin therapy is instituted. During concomitant steroid therapy, large doses of aspirin may be required to achieve an adequate salicylate level. The change to alternate-day prednisone (usually 150 mg qod) is then made. The salicylate dosage may have to be gradually reduced if, due to reduction in steroid dosage (see above), serum salicylate begins to rise to toxic levels. This regimen allows rather prompt discharge from the hospital with gradual reduction of alternate-day prednisone (maintaining steady serum salicylate levels) over a period of several months, avoiding rebound exacerbations.

We have experience so far with only one case treated with intrapericardial injection of corticosteroids as the sole treatment for pericardial tamponade in an arthritic child. This regimen was reported initially by Scharf et al. in 1976[120] and is based on considerable reported experience in adults with tamponade associated with renal dialysis.[121,122] In our single case, we injected 200 mg of triamcinolone hexacetonide (Aristospan 20 mg/cc) at the time of tamponade, continuing high-dose oral aspirin but giving no systemic steroids. Removal of fluid at the time of

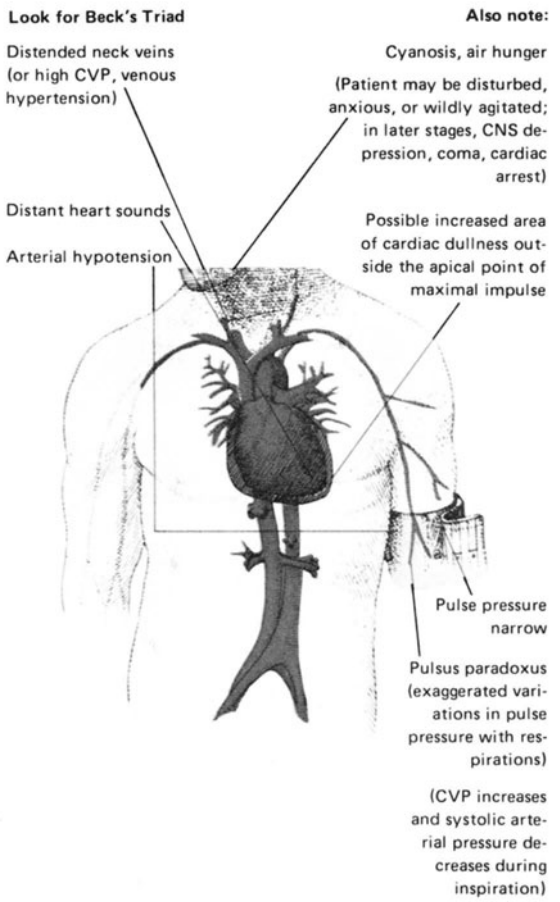


Figure 3.17. Pericardial tamponade may occur in children with systemic JRA and demands prompt diagnosis and therapy. Of 80 patients with tamponade reported by Shoemaker, 87% had one or more signs of Beck's triad, but only 35% showed all three. These findings may occur rather late in the course. If treatment is delayed until all the classic signs of the triad are present, cardiac arrest is likely to intervene. (From Hospital Medicine, November 1978, copyright 1978, with permission of Hospital Publications, Inc.)

the pericardiocentesis relieved the immediate problem; following the injection of steroids, there was no reaccumulation of fluid (Fig. 3.18). Had there been reaccumulation, we were prepared to offer a second injection. While this treatment is new, it does seem to offer a simple, safe, and effective bedside procedure in place of months of oral prednisone administration. We are determined to use it as our first approach to all children with tamponade from JRA.

Treatment of Laryngeal Stridor

When systemic JRA presents with airway (cricoarytenoid) obstruction, corticosteroids should be promptly administered. After the obstruction has been relieved, salicylates are introduced and steroids gradually weaned away.[54]

Polyarticular Juvenile Rheumatoid Arthritis

All forms of arthritis may be polyarticular both in onset or course. The real significance of "polyarticular" is the implication of symmetrical destructive disease

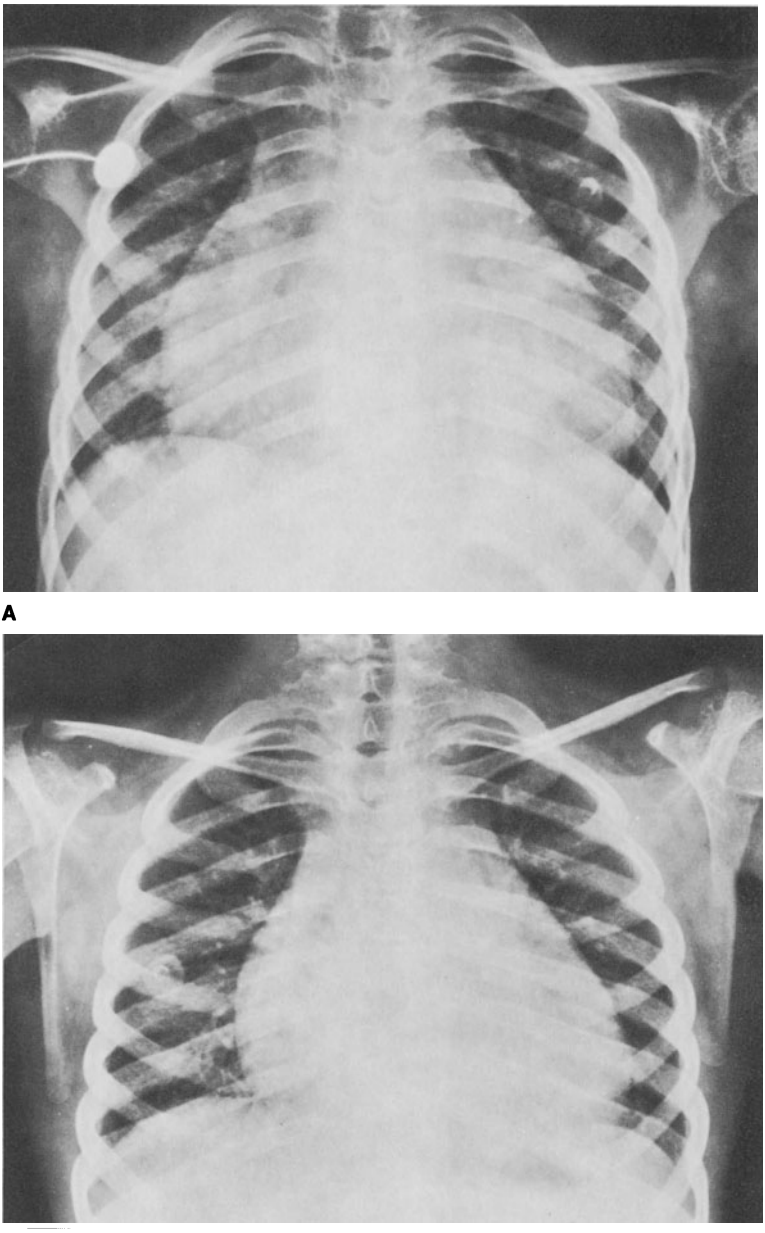


Figure 3.18. (**A**) Severe cardiomegaly shown in a chest film of a child with systemic JRA with pericarditis and tamponade despite aspirin therapy. (**B**) Repeat film 2 days later, after injection of depot steroids into the pericardial sac. No other treatment was necessary; the patient continued to receive aspirin, and all evidence of pericarditis gradually disappeared.

in many joints (Fig. 3.19). Later age of onset and involvement of many joints of the fingers, hands, and wrists are associated with poorer prognosis than polyarticular disease primarily limited to the lower extremities.[123,124] These prognostic determinants are the same in JRA and in young adult arthritics.[123]

Adverse prognosis in polyarticular JRA is most closely correlated with the *consistent* presence of *significant amounts* of rheumatoid factor.[4] It is thus useful to subdivide polyarticular-onset JRA into "seropositive" and "seronegative" subsets.

Epidemiology and Prognosis

Polyarticular Seropositive JRA. Most arthritic children with consistently significantly positive tests for rheumatoid factor are girls, have the onset of disease after age 8, have rheumatoid nodules, and have severe progressive disease with extensive radiographic changes. In one series, after an average of less than 5 years, 50% had reached class III or IV disability[4] (Table 3.12). The childhood early onset of this adult form of RA is thus associated with a very poor functional prognosis, indicating that girls affected this early have a special propensity for the disorder. This group represents less than 7% of the total JRA population in older reports and less than 3% of arthritic children currently being registered in our clinic. In adults, this subset of RA has been associated with HLA-DR4, and this

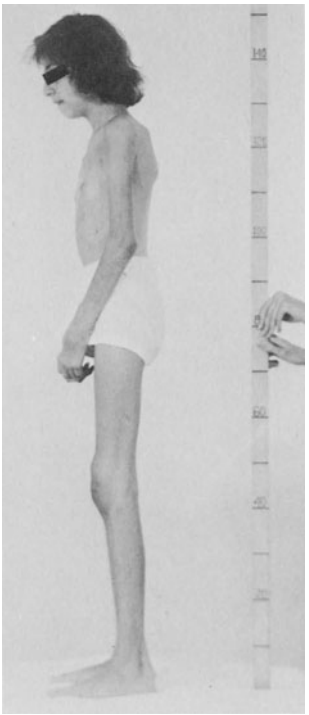


Figure 3.19. Poorly controlled polyarticular JRA affecting essentially all joints symmetrically and causing depression, delayed puberty, and dwarfing of this 13-year-old girl.

Table 3.12. Classification of Functional Impairment in Rheumatoid Arthritis (ARA)

Class	*Characteristics*
1	Performs all usual activities without handicap
2	Performs adequately for normal activities despite discomfort or limited mobility of one or more joints
3	Limited to little or no activities and self-care
4	Largely or wholly incapacitated—bedridden or confined to wheelchair

association has recently also been established in those with childhood-onset seropositive arthritis.

Polyarticular Seronegative JRA. Previously reported series of seronegative polyarticular JRA include some patients who have what we would now term HLA-B27–associated spondyloarthritis with more joints involved than usual (see Chapter 4) and some patients with slightly more severe forms of pauciarticular JRA. However, we mean primarily to include in this group a population whose disease most resembles seropositive early-onset adult RA but who do not have rheumatoid factor. Girls are more frequently affected. The ANA test is positive in 25% of these patients. Rheumatoid nodules are rare. After an average of 7 years of disease, 15% of these children had entered functional class III or IV as a result of very severe joint destruction.[4] While the prognosis is not good for the children, it is much better than that of the seropositive group.

Clinical Features

Onset. By the time they get to the rheumatologist, most of these youngsters have obvious arthritis. However, prior to diagnosis, there is often a period of months during which arthritis is present but not recognized, although the physician knows they are ill with low-grade fever, lethargy, weight loss, and morning stiffness. In addition to symmetrical involvement of many large joints, especially the wrists, these children almost always have distal small joint symmetrical arthritis involving the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. Other frequently affected joints include the interphalangeal toe joints, cervical spine, and temporomandibular joints. Synovial outpocketings or pouches are frequently seen overlying the wrists (tenosynovitis) (Fig. 3.6). Joints are frequently warm but usually not tender. Effusions are easily demonstrated, and limitation of extention is apparent in many joints. Occasionally, patients have "dry" arthritis without effusions or warmth but with progressive flexion contractures. If routine pediatric examinations do not include examining the range of motion of joints, the diagnosis may be missed for years. Some of these patients, primarily girls, do not complain of pain despite obvious arthritis.[18,125]

Rheumatoid Nodules. Subcutaneous nodules near the olecranon process at the elbow are frequently palpable in seropositive arthritic children (Fig. 3.38B). Microscopic examination shows central necrosis and palisading fibroblasts, identical to the pathology in seropositive adult nodules (Fig. 3.20). Polyarticular arthritic children also sometimes have transient nodules over the interphalangeal joints of the fingers and toes. These tend to come and go with exacerbations of the disease. Some authors indicate slight pathologic differences between these nodules and those of adult RA.[126,127]

Course

Structure of the Joints. Rheumatoid arthritis primarily affects the synovial joints which are diarthroses; that is, a joint resembling a hinge, with a cavity and free movement.[128] The articulating bones are covered by a hyaline (glasslike) lining, the articular cartilage. The marginal nonarticulating connective tissue is called the synovial membrane (Fig. 3.21). This membrane provides the substances necessary for metabolism of articular cartilage and is the source of synovial fluid.

The joint is surrounded by a fibrous capsule. The bone is lined by a thin connective tissue membrane—the periosteum. Ligaments secure opposing bone surfaces and may attach to bone inside or outside the capsule. Tendons attach muscle to bone inside the capsule. The site of attachment of a ligament or tendon to bone is called an enthesis. The motion of tendons and muscles over bony prominences is facilitated by bursae, closed sacs lined with a protruding bursal (synovial) membrane. There are at least 156 bursae in the body.

All of these structures may become inflamed and contribute to pathology in and around the joints.[127] Although the potential exists for varying types of inflamma-

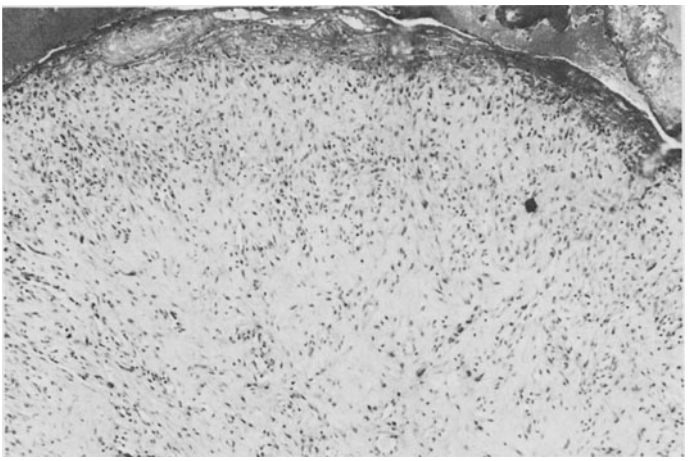


Figure 3.20. Rheumatoid nodule showing typical palisading granuloma. This patient was a 16-year-old boy with cystic fibrosis of the pancreas who developed seropositive rheumatoid arthritis.

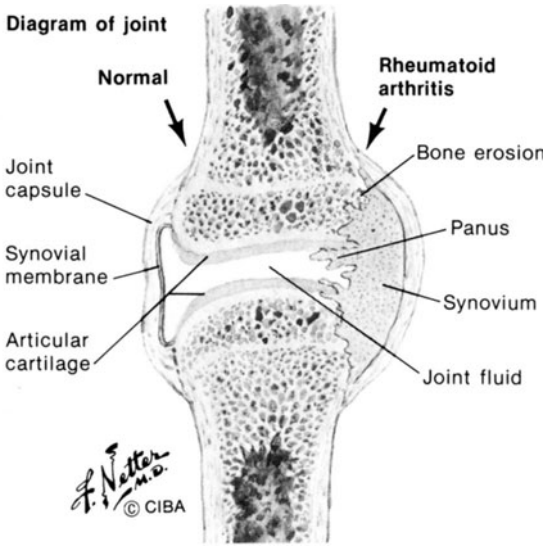


Figure 3.21. Diagrammatic representation of joint in rheumatoid arthritis. (From Clinical Symposia 31(4):23, 1979, with permission of CIBA Laboratories.)

tion to constitute different forms of arthritis, sorting out these differences remains to be accomplished. However, the recognition of the importance of the more frequent, severe, and calcifying inflammation at the enthesis in HLA-B27–associated spondyloarthritis provides a clue indicating that immunogenetic techniques may help in identifying different pathophysiologic processes now grouped under one umbrella (JRA or RA) (see Chapter 4).

Pathologic Considerations

The diverse group of diseases we call JRA, induced by a variety of genetically controlled responses to different environmental stimuli, all have in common inflammation in and around the joint. This inflammation seems to be perpetuated by immunologic events rather than by continued active infection.[129]

Synovium. The inflammatory reaction in the synovium begins with congestion and edema (Table 3.13). This is followed by cellular infiltration, at first with polymorphonuclear leukocytes, then with small lymphocytes, and in advanced cases with plasma cells and multinucleated giant cells. The synovial lining cells multiply, elongate, and palisade. Lymphoid follicles with germinal centers (Allison-Gormley nodules) form in some cases. Blood vessels proliferate and form granulation tissue. The synovium thickens in a villous fashion (Figs. 3.1, 3.21).

Articular Cartilage. In more severe cases, the inflammation extends from the synovium into the articular cartilage. A mantle of granulation tissue, a pannus, forms covering the bone and connecting the inflamed cartilage to the inflamed synovium (Fig. 3.21).

Table 3.13. Synovitis

Characteristics	*Effects*
Proliferation of synovial lining cells	Stretching of the capsule, ligaments, tendons
Infiltration of synovium by inflammatory cells	Granulomatous proliferation and villus formation
Effusion of fluid containing inflammatory cells	Invasion of tendons, cartilage, and bone by pannus and destruction by proteolytic enzymes
	Increased connective tissue producing stiffness and reduced range of motion
	Either capsuloligamentous laxity and hypermobility or fibrous ankylosis and ultimately bony ankylosis

Destruction of cartilage by this inflammation leads to bony erosions. If the pannus continues to grow, the cartilage may be continually eroded until it disappears altogether.

Subchondral Bone. Continuous with the inflammation in the synovial tissue is osteitis, inflammation in the bone itself. Periarticular demineralization (osteolysis) is common in epiphyseal bone. If the epiphyseal plate is involved, growth is retarded, and dwarfism may result. Erosions and cyst-like areas of destruction may be apparent. Osteoporosis also occurs from disuse.

Periosteum. The synovial recesses in the phalanges are large and extend for long distances along the phalanges. Therefore, synovitis in the proximal interphalangeal joints may be associated with concomitant periostitis in the immediately adjacent bone shaft. Periostitis without synovitis is not characteristic of JRA, although it may be seen in a variety of other disorders including syphilis and HLA-B27-associated spondyloarthritis. Periostitis is rare in JRA.

Ankylosis. Newly formed connective tissue, which constitutes the scar resulting from granulation tissue in and around the joints, may form fibrous contractures and articulations or may rarely even calcify, producing bony ankylosis.

Joint Deformities

Detailed description of the pathomechanics in each joint are beyond the scope of this monograph. In every joint, a balance exists between the muscles and tendons and the bones through which they exert their action. At first, capsular distension and bulging of the synovium may initiate deformity. If the invasive inflammatory synovium grows into the cartilage, tendons, and ligaments, the capsular and liga-

mentous supports weaken. Inflamed tendons may contract or rupture. Articular surfaces remodel under the forces of abnormal muscle pull. The healthy balance of forces is lost. Soft tissues contract, and there is fibrosis involving the capsule and periarticular tissues, resulting in loss of mobility of the joint. Subluxation may occur in severe disease (Figs. 3.22 and 3.23).

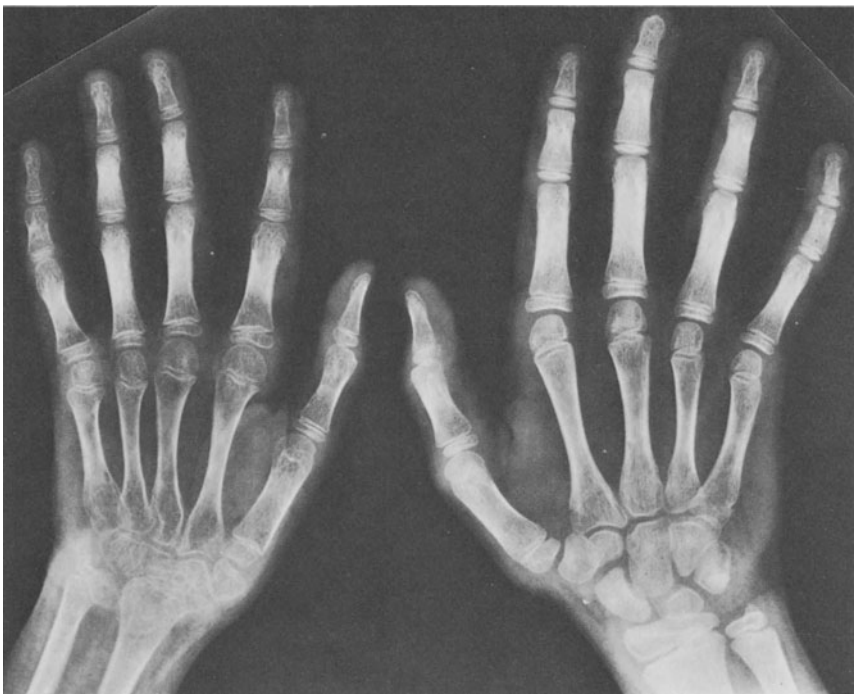


Figure 3.22. Severe arthritis of the left wrist in a 9-year-old girl with onset of pauciarticular seronegative, B27-negative arthritis at age 2 years.

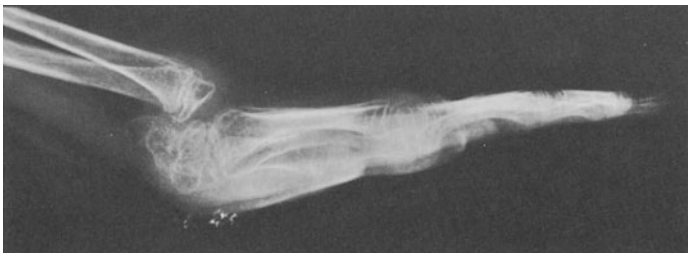
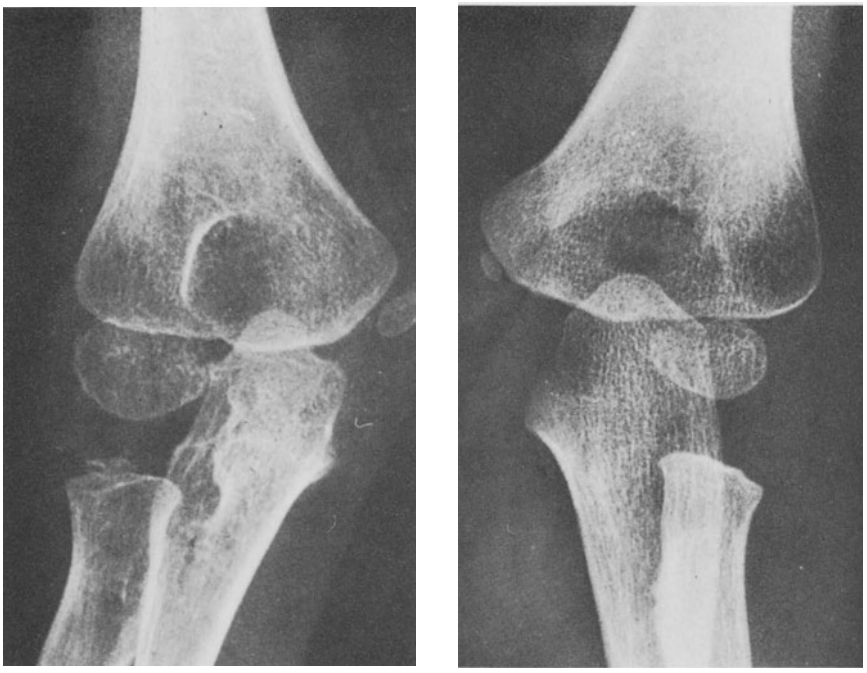


Figure 3.23. Lateral view of wrist shown in Fig. 3.22. This child, with minimal disease elsewhere, has "disappearing bones" (the "opera-glass hand") with severe subluxation.

Bone Deformities

Unique deformities may occur in the growing skeleton. Chronic hyperemia may result in accelerated growth in affected growth centers (Fig. 3.24). An extremity or appendage may be elongated (Figs. 3.25 and 3.26). In the short bones, growth arrest may occur, resulting in permanent underdevelopment of a bone. If accelerated maturity results in asymmetric premature fusion of an epiphysis, the extremity may ultimately be shortened (Fig. 3.38B).

Systemic disease of all sorts inhibits growth, presumably as a result of end-organ inability to respond to growth hormone. Inflammation at the growth plate and deformities may also contribute to short stature. The administration of daily corticosteroids also arrests growth, presumably by a suppressive effect on cell proliferation in peripheral tissues. Large doses of alternate-morning steroids (>1 mg/kg/day) may also stunt growth, whereas small doses may accelerate growth by controlling systemic disease.



A B

Figure 3.24. Growth disturbance in JRA with advanced skeletal maturation on the involved side and retarded maturation on the opposite side. Patient is a female, aged 3 years 9 months. Involved elbow (**A**) shows advanced skeletal maturation, 5 years, in involved areas. Uninvolved elbow (**B**) shows retardation in skeletal maturation, 2 years 8 months, in corresponding areas without local disease. (From Grokoest et al., ref. 18, with permission of the publisher.)

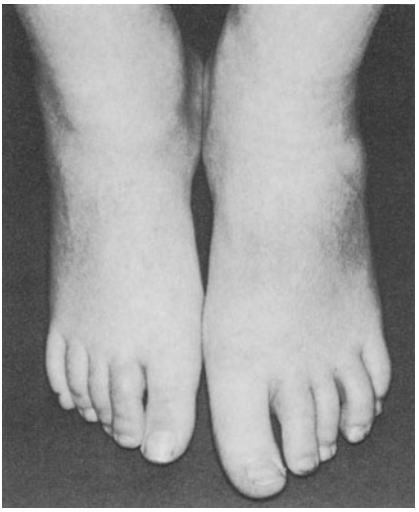


Figure 3.25. Enlargement and accelerated growth of the left foot in JRA.

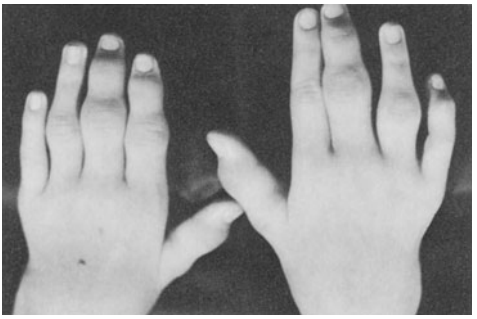


Figure 3.26. The right second finger has linear overgrowth, the left fifth finger is foreshortened.

Bone erosions are a late finding in JRA, resemble those of adult RA, and are first seen on intra-articular bone surfaces unprotected by cartilage (Fig. 3.27). Joint narrowing and fibrous and bony ankylosis are seen in severe cases (Fig. 3.24).

Specific Joint Involvement

Temporomandibular Joint. Temporomandibular joint (TMJ) disease is common in all forms of childhood arthritis. It may be asymptomatic and overlooked on routine examination. Interference with the normal growth pattern in the mandible results in a shortened ramus. In rare patients, the mandibular dysplasia is asymmetric.

The soft-tissue profile of the face is determined by the triad of nose, lips, and chin. Although the chin is only a part of the mandible, it is the most conspicuous frontal component in man. A pleasing and harmonious profile is often lost in JRA. (Fig. 3.28A).[18,130]

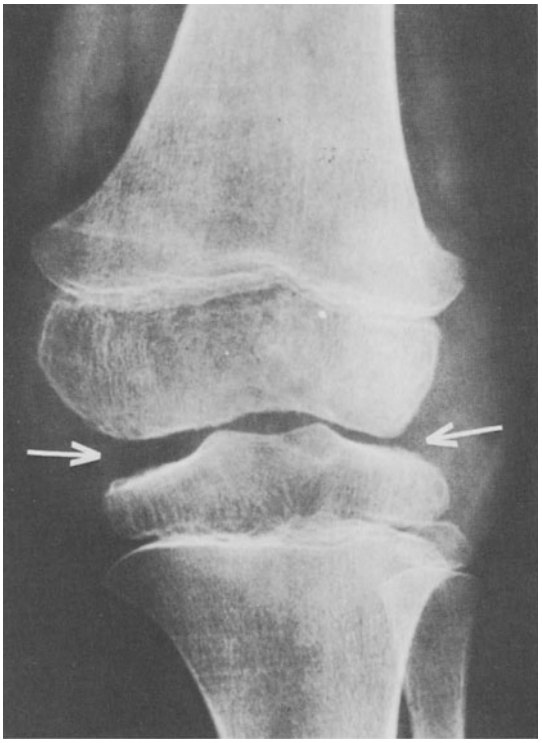
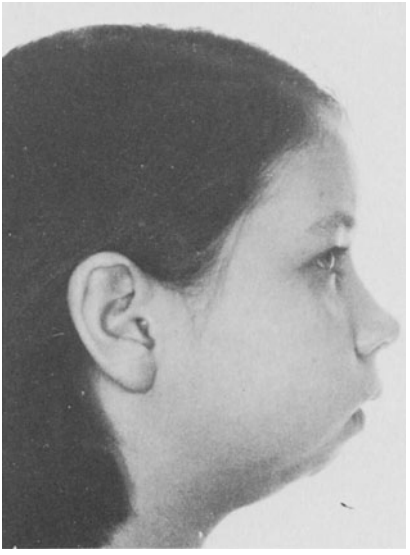


Figure 3.27. Knee in severe systemic polyarticular JRA (age 7 years; onset at age 3 years) showing erosions and narrowed joint space *(arrow)* (see also Fig. 3. 42).



A **B**

Figure 3.28. (**A**) Mandibular dysplasia (HLA-B27–associated spondyloarthritis) also shown in polyarticular JRA in Fig. 3.39. (**B**) Bone-graft reconstruction of the chin produced an obvious change in affect.

The micrognathia of JRA is also often associated with gross dental malocclusion. There may be difficulty in chewing food, and the patient may speak with a lisp. Only the second molar teeth may contact when the patient closes her mouth. Tendinous insertions of the lateral pterygoid muscles may be destroyed along with the condyle, which is flattened, eroded, and rarefied. The mouth is then opened as if it were a hinge, with little or no gliding motion.

Elongation osteotomy of the body of the mandible and restoration of the contour of the jaw by iliac bone grafting or silicone implant may result in great cosmetic improvement[131] and contribute to the psychological well-being of the arthritic teenager (Fig. 3.28B). In rare instances, the interincisal opening decreases to a dangerously small orifice due to ankylosis of the TMJ. A vitallium plate may then be inserted to restore joint motion to normal.

Cervical Spine. Clinical manifestations of cervical spine involvement are common in systemic and polyarticular arthritis in childhood and also in persistent early-onset spondyloarthritis. Loss of the sharp margins of the articular facets of the C-2–C-3 apophyseal joint may first be seen radiologically after years of clinical disease (see Fig. 4.25).[18,20,132] If the disease progresses, erosions occur, followed in even more severe cases by bony bridging and fusion of the cervical segments. Intervertebral disk spaces may be narrowed and the stature and anterior-posterior diameter of the vertebral bodies diminished.

Growth deformities in the cervical spine result in a short neck with increased cervical lordosis, dorsal kyphosis, and compensatory overgrowth of the lumbar vertebrae (Figs. 3.19 and 3.29).[132] Although cervical spine involvement almost always starts at the C-2–C-3 level, it may occasionally extend down to the thoracic spine

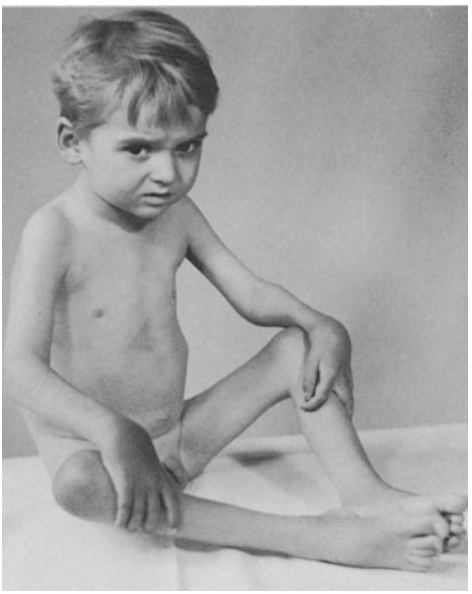


Figure 3.29. Growth deformities in the cervical spine result in a short neck with increased cervical lordosis and dorsal kyphosis (see also Fig. 3.19).

(Figs. 3.30 and 3.31).[18,20] Subluxation of the atlas on the axis, as is seen in severe adult RA, may occur in the worst cases.

Anesthesiologists must be aware of potential difficulty with intubation and of the additional hazards (dislocation, fracture, and cord injuries) that may occur during anesthesia.[133]

Cricoarytenoid Arthritis. Schlesinger first called attention to laryngeal arthritis causing stridor, dyspnea, and cyanosis in JRA. Occasionally, life-threatening stridor is the presenting manifestation of systemic-onset JRA.[37,54] Tracheostomy may be avoided by prompt institution of prednisone therapy, which can usually subsequently be weaned away after adequate salicylates have been administered. The acute swelling that produces the dramatic initial symptom subsides without apparent significant residua. Hoarseness may result from chronic laryngeal arthritis in polyarticular patients. Laryngeal ankylosis has not been reported

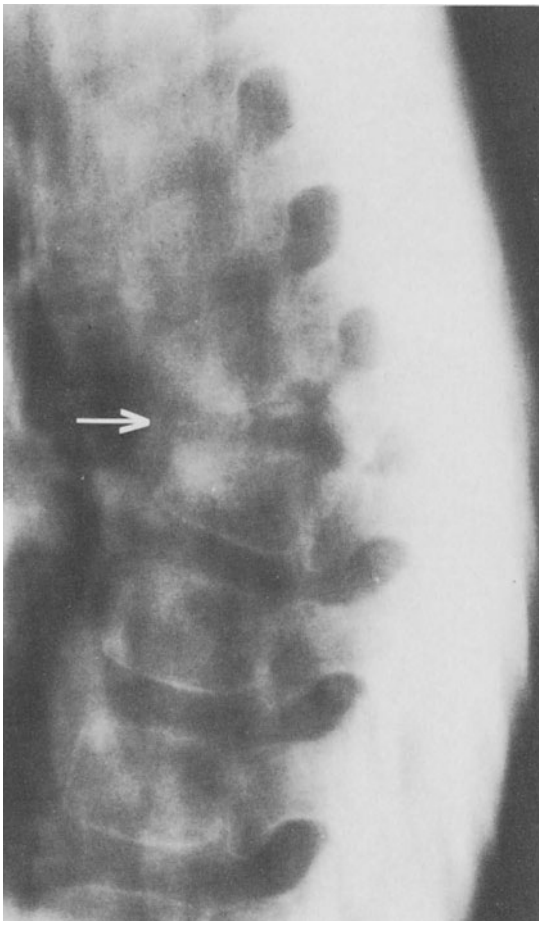
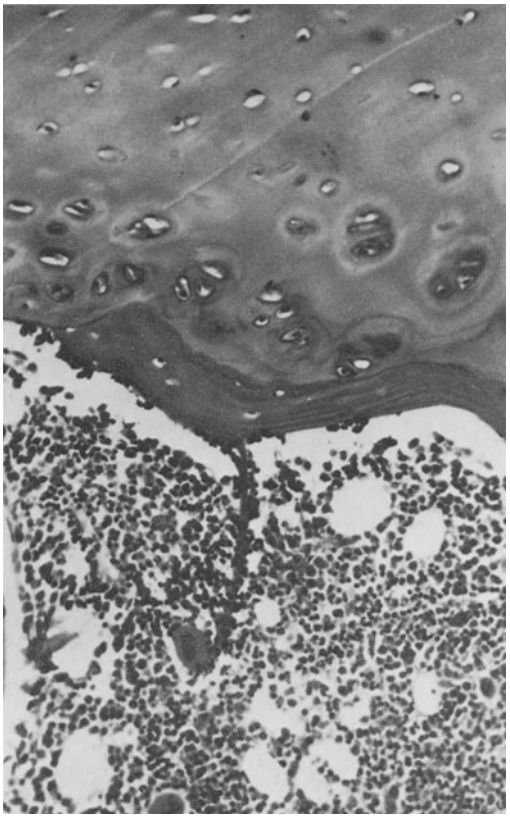
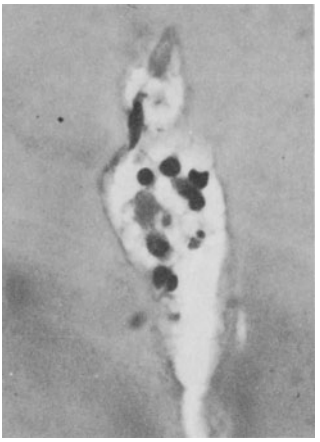


Figure 3.30. Complete destruction of middorsal vertebra with gibbus deformity resembling tuberculosis in a 9-year-old boy with severe systemic polyarticular JRA. Needle biopsy demonstrated "rheumatoid inflammation" (Fig. 3.31).



A



B

Figure 3.31. Needle biopsy of the apophyseal joint (T-7) in patient (Fig. 3.30) showing chondromucinous changes in the deeper layers of articular cartilage (**A**), causing destruction (hyperplastic bone marrow below); in a high-power view (**B**) lymphocytes can be seen invading a bone lacuna in articular cartilage. (**A**) ×40; (**B**) ×128.

in childhood, but fibrosis can make intubation for surgery difficult in older children.[133]

Peripheral Joint Manifestations. A detailed description of the combined results of inflammation and destruction of each individual joint of the growing child is available elsewhere[134] and is beyond the scope of this monograph. Articular and periarticular pain and swelling are followed promptly by juxta-articular demineralization. Muscular wasting is soon apparent in affected areas. Overgrowth of the epiphyses may produce gross enlargement of the rapidly developing ends of the long bones, while the shafts may be thinned. Small bones may be underdeveloped. Specific radiographic and clinical findings may include:[18,20,134]

Hands and Wrists. Altered length and width of digits and individual bones, crenation, crowding and fusion of carpal and carpometacarpal joints and bones into solid masses, proximal interphalangeal joint contractures and fusion, spindle and pencil-tip appearance of the fingers. In the hand and wrist, there is normally a

complicated balance between the forces of a multitude of tendons and ligaments. As this is lost, collapse deformities occur with hyperextension of one joint and compensatory flexion of another. Classic deformities include "swan neck" and "bouttonière" deformities of the fingers, palmar subluxation, and radial or ulnar deviation of the MCP joints (Fig. 3.32). Use of the hand in activities of daily living may accentuate the deformity, and a vicious cycle of deforming forces may be established.

Knees. Flexion contracture at the knee is common (Fig. 3.33). In addition to all of the usual manifestations of arthritic inflammation at the knee, children often develop an impressive valgus deformity. This may result from overgrowth of the leg at the knee, requiring the child to assume the valgus position to walk with less limp (Fig. 3.34). However, it may also result from hip disease when limitation of external rotation of the hip causes assumption of the valgus position at the knee. Since we have adopted a policy of providing both lifts to the short leg and vigorous physiotherapy aimed at correcting limited hip rotation, we have not had to do stapling procedures or osteotomies to correct the knee valgus.

Hips. Hip involvement is common in all forms of childhood arthritis and is characterized by both a flexion contracture and by simultaneous limitation of full flex-

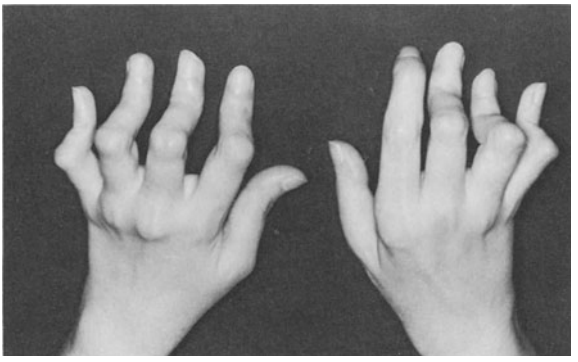


Figure 3.32. "Boutonnière" deformities (left, 2–5; right 3–5) characterized by flexion deformities of the proximal interphalangeal joints and extension deformities of the distal interphalangeal joints. "Swan-neck" deformities consisting of hyperextension of the proximal interphalangeal joint and flexion of the distal interphalangeal joint are also developing in the right second finger. Patient had the onset of polyarticular seropositive JRA at age 9, without multisystem disease but with positive antinuclear antibodies, low serum total hemolytic complement, and elevated anti-DNA antibodies. Now age 22, she continues to have destructive arthritis as her only symptom. The deforities resemble those seen in the "lupus hand" but are not correctable and are accompanied by radiologic evidence of severe destructive changes. More common finger abnormalities in severe long-standing JRA are shown in Figure 3.26.

Figure 3.33. Hip and knee contractures typical of the child allowed to become wheelchair-bound; the child sits all day with the knees and hips flexed. Rehabilitation requires surgical release of iliotibial bands and other soft-tissue contractures about the hips and knees with a vigorous immediate postoperative exercise program and prohibition of the wheelchair.

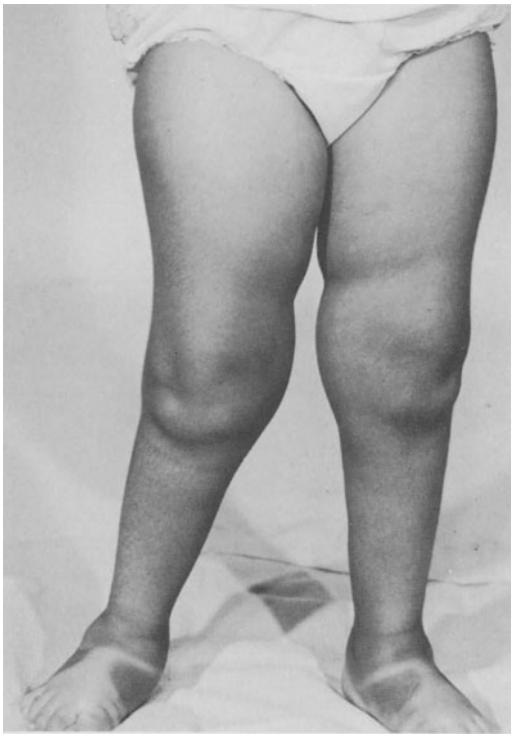
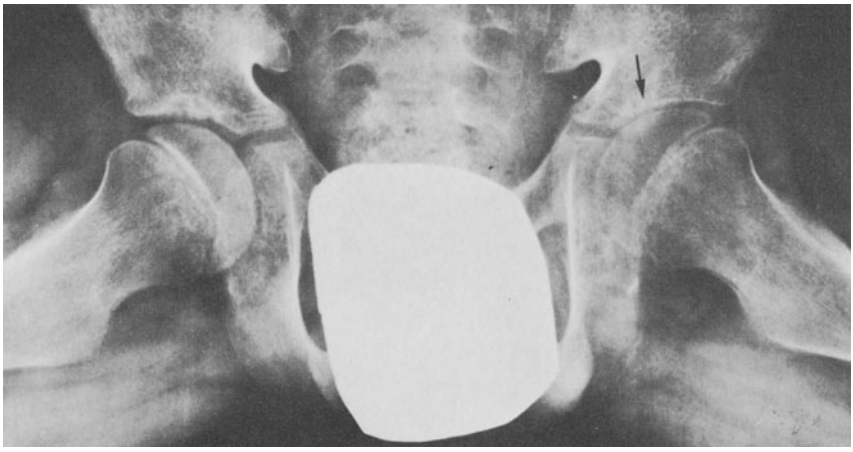


Figure 3.34. Although the patient has bilateral knee (and ankle) effusions, the right leg has overgrown, resulting in the child's having to stand with the knee in valgus; the deformity is progressive. Surgical correction (stapling or osteotomy) is avoided by lifting the opposite (good) heel by building up the oppposite shoe. This deformity is also caused by hip disease resulting in limited external rotation of the hip with compensatory assumption of the valgus knee posture to walk; this may be treated with physical therapy to maximize external rotation at the diseased hip.

ion, abduction, and rotation (Fig. 3.33). Some of the findings are a result of iliopsoas and adductor spasm. The hip pathology is sometimes masked by a typical compensatory increased lumbar lordosis, which, if noted, provides a clue to its existence (Figs. 3.6, 3.39).

There is loss of substance and broadening of the femoral head. The neck is often poorly developed, and cystic changes appear in the head and neck. Later, marked



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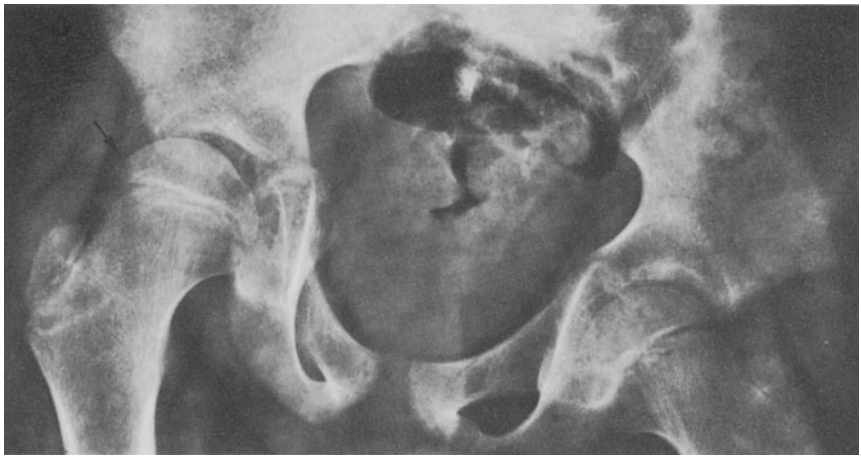

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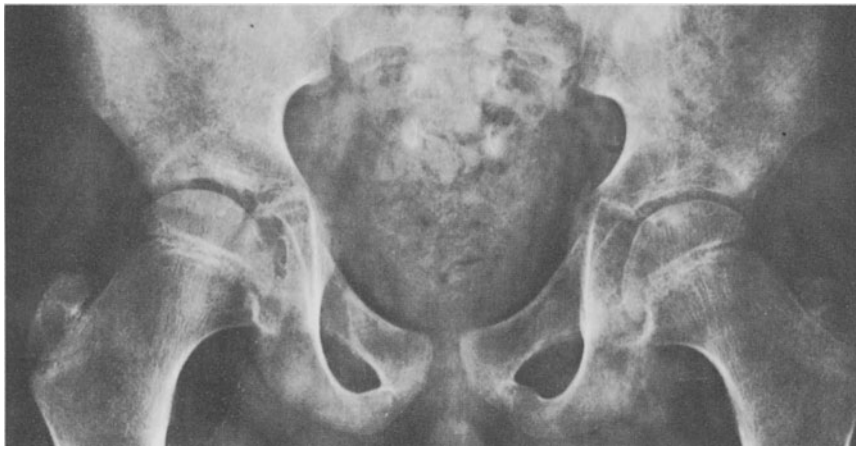


C

narrowing of the joint space may be accompanied by secondary degenerative changes and aseptic necrosis of the femoral head. Acetabular destruction and protrusio, coxa magna, and dislocation may occur (Figs. 3.35, 3.48, 3.51, and 3.52).

Feet. Although the knee is the most frequently involved joint in all forms of childhood arthritis, significant scarring is more frequent at the ankle and tarsus (Fig. 3.36). The foot is a complex articulation involving many joints in several planes. In addition to the many synovial joints, many bursae and tendon sheaths may be diseased, just as in the hand (Fig. 3.37). Fibrous, cartilaginous, or bony fusion of tarsal bones (tarsal coalition) may be mistaken for a congenital anomaly.

Deformities of the hips and knees may also cause compensatory deformities in the feet. Valgus deformity is more common than varus, but both may occur. Valgus foot deformities are sometimes compensatory for valgus knee deformities.

Elbows. Limitation of supination of the elbow is one of the most common and subtle diagnostic signs of childhood arthritis and may occur without flexion contracture. Most severely affected arthritic children have limitation of both extension and supination (Fig. 3.38).

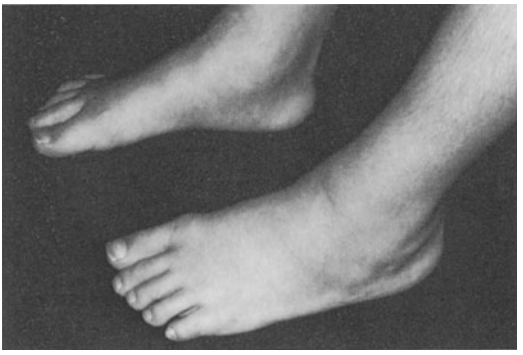


Figure 3.36. Inability to dorsiflex the ankles and limited eversion are common findings in polyarticular JRA.

Figure 3.35. Bilateral hip disease in an 8-year-old boy with systemic JRA (onset at age 3). (**A**) Following a jump into the swimming pool, there was acute chondrolysis of the left hip, illustrated here by sudden joint-space narrowing *(arrow)* not seen previously (see Chapter 2, Acute Chondrolysis of the Hip, and Fig. 2.47). (**B**) Six weeks later joint-space restoration is apparent in the left hip (similar to that seen in patients without arthritis who suffer acute lamellar coxitis, Fig. 2.47) but the right hip is seen to be subluxed, apparently as a compensation for the painful left hip. Without treatment (other than continuing aspirin), the subluxation disappeared on the right side, and the joint space in the left hip returned to normal (**C.**) The patient has continued to have severe arthritis and, following a recent flare of systemic manifestations (age 15), had accelerated bilateral destruction of the hip joints that will eventually require surgical replacement.

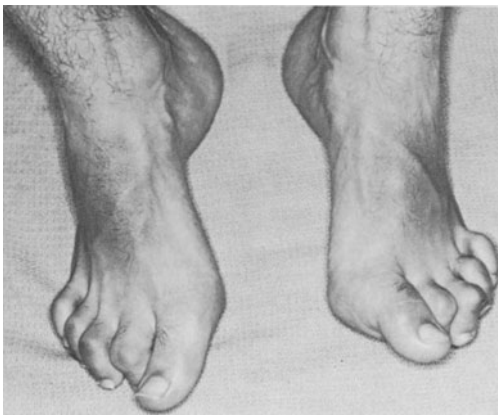
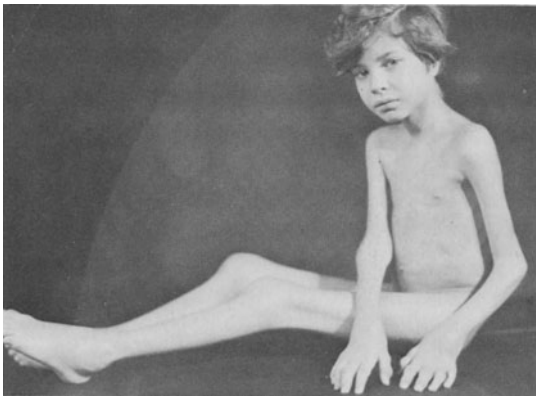


Figure 3.37. Hallux valgus and flexion contractures of the toes in a teenage boy with polyarticular JRA. The toe abnormalities are the same as those seen in the fingers.



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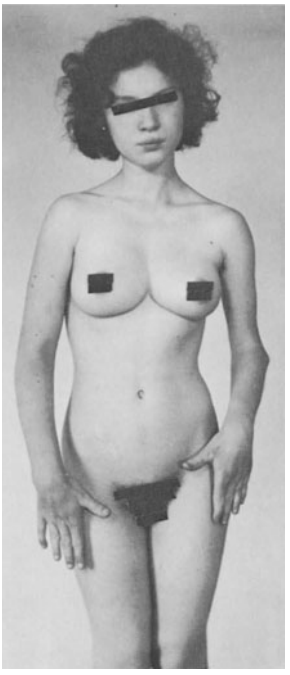


B

Figure 3.38. (**A**) At age 9, this youngster with extensive seropositive polyarticular disease has apparently equal arm length. However, by age 15 (**B**) the entire left upper extremity is seen to be foreshortened. A rheumatoid nodule is visible below the left elbow. Flexion contractures are visible in many joints.

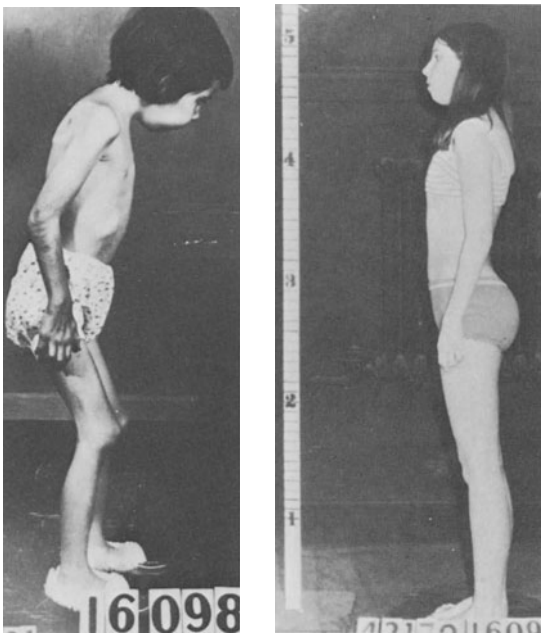
Shoulders. The shoulders are frequently affected in severe polyarticular disease. Both the acromioclavicular joint and the glenohumeral joint may be affected; the latter may be accompanied by necrosis of the humeral head and growth disturbances in the humerus. Severe disease may produce painful swelling of the joint and all the surrounding bursae (Fig. 3.38).

Treatment of Polyarticular JRA

Drugs are only one part of the prescription for children with rheumatic disease. Drugs are important, however, and talented prescribing indicates knowledge and competence. Physical and occupational therapy help to maintain strength and function. The attitudes of the prescriber and the therapeutic team may determine compliance, maintain morale of the child and family, and enable growth and development to proceed despite the soul-sapping nature of chronic sickness. The physician and the patient/parent become partners in control of the disease. A sense of control, albeit even less control than one would wish, is ego rewarding and helps combat depression. Part of prescribing for these children involves teaching the parent and eventually the child the purposes of each medication, its potential benefits and side effects, and the methods used to regulate the dose so as to achieve maximum benefit and minimum side effects. The maximum potential benefit from drugs can only be achieved with such teamwork (Fig. 3.39).

Anti-inflammatory Drugs

Salicylates. Aspirin remains the primary therapeutic agent in all forms of RA because it is generally equally effective and much cheaper than any currently available, equally safe alternative therapy.[135] In addition, experience with the new nonsteroidal anti-inflammatory agents in children has been very limited. There may be unanticipated long-term side effects that make chronic administration of



A **B**

Figure 3.39. Example of the accomplishments of a therapeutic team in the care of a child with severe polyarticular JRA. At age 6, both hips were said to be dislocated (**A**). Nine years later, although she still had severe arthritis with delayed puberty and short stature, she could function in normal teenage society (**B**). (From the Arthritis Reporter, Spring 1972, with permission of the Arthritis Foundation, New York Chapter, and Dr. J. S. Stillman.)

these agents to children inadvisable unless salicylates do not provide satisfactory control of the disease. The principles and techniques of aspirin therapy have already been discussed in the section on systemic JRA. Alternative salicylate preparations may be used where intolerance prevents adequate treatment with regular aspirin.

Other Nonsteroidal Anti-inflammatory Drugs (NSAIDs). The salicylate radical has been chemically modified to produce an ever-increasing number of agents that have as their goal better efficacy and fewer side effects (Table 3.14).[135]

Table 3.14. Drugs Used for the Treatment of Arthritis in Children

Nonsteroidal Anti-inflammatory Agents: Salicylate Preparations	
Aspirin, 325-mg or 82-mg tablets	80+ mg/kg/day—salicylate level measured to achieve efficacy or maximum tolerated level (4–6)
Enteric-coated aspirin, 325-mg tablets	
Sustained-release aspirin, 650-mg tablets	
Choline salicylate, 1 tsp = 650-mg equivalent	
Choline magnesium trisalicylate, 1 tsp = 500-mg equivalent, 500- and 750-mg tablets	
Salsalate (salicylsalicylic acid), 500-mg tablets	
Nonsalicylate NSAIDs Approved by U.S. FDA for Use in Children	
Tolmetin (Tolectin), 20–30 mg/kg/day (4); 2000 mg max dose	
Naproxen (Naprosyn), 10–15 mg/kg/day (2); 750 mg max dose	
NSAIDs Not Yet Approved by U.S. FDA for Use in Children	
Indomethacin (Indocin), 1–3 mg/kg/day (3–4); 200 mg max dose	
Ibuprofen (Motrin), 20–50 mg/kg/day (4); 2400 mg max dose	
Fenoprofen (Nalfon), 40–50 mg/kg/day (4); 3200 mg max dose	
Pirprofen (Rengasil), 10–15 mg/kg/day (4); 1000 mg max dose	
Ketoprofen (Orudis), 3–5 mg/kg/day (4); 300 mg max dose	
Proquazone (Barsan),* 10–20 mg/kg/day (4); 1000 mg max dose	
Meclofenamate (Meclomen),† 4–6 mg/kg/day (3); 300 mg max dose	
Sulindac (Clinoril),‡ 4–6 mg/kg/day (2); 400 mg max dose	
Slower-Acting Antirheumatic Drugs	
Hydroxychloroquine, 7 mg/kg/day; 300 mg max dose	
Gold (injectable), 0.5–1 mg/kg/week; 50 mg max dose	
Gold (oral—under study), 0.1 mg/kg/day; 6 mg max dose	
Penicillamine, 5–10 mg/kg/day; 500 mg max dose	

*Preliminary trials in children showed low efficacy.
†Preliminary trials in children showed excessive toxicity.
‡Not studied in children.
Numbers in parentheses indicate usual number of daily doses.

More than 50 antirheumatic compounds are reported to be currently under investigation. None have been proved to retard the rate of cartilage destruction or to induce remission of disease. So far, no one agent has proved to be superior for all patients.[135,136] In general, however, indomethacin, tolmetin, naproxen, and sulindac appear to be more effective in HLA-B27–associated spondyloarthritis.[135,137,138] Agents with a long half-life such as naproxen, which requires administration only twice daily, achieve better compliance and may be more effective on this basis alone in all forms of arthritis.[118] Objective comparisons of efficacy and tolerance of all these agents and their comparison to aspirin and the other salicylates have been handicapped by the general lack of availability of serum levels. Therapeutic trials have been conducted with arbitrary dosage, making no allowance for differences in individual absorption, metabolism, and excretion. Pharmacokinetic principles, which had led to improvement in the care of asthmatic and epileptic children, have not yet been applied to the use of these agents in children.[139]

A paucity of clinics with sufficient numbers of patients and staff to conduct controlled clinical trials has also delayed the accumulation of knowledge about these drugs in children. Most tests with adults have included primarily seropositive patients; the number of children to whom the conclusions are directly applicable is small. The few reported studies in children have made no effort to separately determine efficacy among the various subsets of childhood arthritis.[109] In the United States, at the time of this writing, only two of these agents (tolmetin and naproxen) have been tested sufficiently to satisfy the requirements of the Food and Drug Administration (FDA) for licensing for use in arthritic children. This dilemma is not easily solved. On the one hand, it is well established that the results of drug studies in adults should not be applied to children without testing in children. On the other hand, some sick children are being deprived of medications that would undoubtedly be of benefit to them and are available to adults with identical conditions. Both the children and the drugs are thus "orphaned."

However, availability of these agents has led to a new approach in our management of older arthritic children. If aspirin does not provide adequate control, we often have the youngster try a number of different agents briefly. Within a few days, many youngsters can report their individual preference based on subjective relief of symptoms and tolerance of side effects (Table 3.15). We have been slower in using these agents in the very young because of the lack of long-term experience with them. Nevertheless, they are useful in the care of arthritic children.

Tolmetin Sodium. The U.S. JRA Cooperative Drug Study Group demonstrated, within the limitations stated above, that tolmetin sodium, 20–30 mg/kg/day in three or four divided doses, was equal or better than aspirin, 80–100 mg/kg/day in four doses, in terms of anti-inflammatory effect and was slightly better tolerated than aspirin.[109] Recent studies suggest a half-life in adults of 4–6 h and peak serum levels 40 min after single doses.[140] In adult nonarticular rheumatism and soft-tissue disease, common in pauciarticular JRA, tolmetin surpassed aspirin in efficacy. We find it very useful in mild spondyloarthritic children. In the pedi-

Table 3.15. Adverse Reactions Associated with the Use of Nonsteroidal Anti-inflammatory Drugs.

Incidence Generally Greater than 1%	*Incidence Generally Less than 1%*
Gastrointestinal	*Gastrointestinal*
Gastrointestinal pain (10%)	Gastritis or gastroenteritis
Dyspepsia*	Peptic ulcer
Nausea* with or without vomiting	Gastrointestinal bleeding
Diarrhea*	GI perforation
Constipation*	Liver function abnormalities
Flatulence	Jaundice, sometimes with fever
Anorexia	Cholestasis
Gastrointestinal cramps	Hepatitis
	Pancreatitis
Dermatologic	
Rash*	*Dermatologic*
Pruritus	Stomatitis
	Sore or dry mucous membranes
Central Nervous System	Erythema multiforme
Dizziness*	Toxic epidermal necrolysis
Headache*	Stevens-Johnson syndrome
Nervousness	
Drowsiness*	*Cardiovascular*
	Congestive heart failure in patients with marginal cardiac function
Special Senses	Palpitation, arrhythmia
Tinnitus	
	Hematologic
Renal	Thrombocytopenia
Edema	Leukopenia
Hematuria*	Increased prothrombin time in patients on oral anticoagulants
Proteinuria*	Hemolytic anemia
Hematologic	
Hematocrit lowered more than 10%†	*Central Nervous System*
	Vertigo
Miscellaneous	Altered mental state
Edema	
	Special Senses
	Blurred vision
	Hypersensitivity Reactions
	Anaphylaxis
	Angioneurotic edema
	Hypersensitivity syndrome consisting of some or all of the following: fever, chills, skin rash, changes in liver function, jaundice, leukopenia, and eosinophilia; rarely, fatalities have been reported
	Renal
	Acute renal failure

*Incidence generally between 3 and 9%. (Those reactions occurring in less than 3% of patients are unmarked.)

†Incidence generally 42% in children.

atric clinical trial, liver enzyme abnormalities related to aspirin therapy promptly returned to normal.[109] Licensing of the drug in the United States includes children, so that informed consent and therapeutic trial protocols are not required, and the drug may be used in children by general physicians. It is available only in bad-tasting 200-mg tablets that must be divided and disguised for children who cannot swallow tablets. It is about 10 times as expensive as ordinary aspirin but only twice as expensive as flavored soluble "baby" aspirin tablets administered in similarly efficacious dosage.

Naproxen. Although not tested in the United States, experience in Europe showed sufficient efficacy and tolerance in children to warrant FDA licensing for children in the United States.[141,142] A long half-life of 13 h has been confirmed in children, providing greatly increased convenience, better compliance, and perhaps improved control of disease. In adults with RA, preference was expressed for naproxen and other anti-inflammatory drugs compared with aspirin, but this effect was entirely explained by better compliance.[118] However, in ankylosing spondylitis (AS), naproxen was a considerably better agent than aspirin and was even slightly preferred over indomethacin, the agent previously found to be more effective in AS.[118] I have found it generally well tolerated and an excellent agent for use in teenagers with spondyloarthritis, both HLA-B27-positive and -negative.[137] In small children, it has been tested at 10 mg/kg/day in two divided doses.[141,142] In teenagers, we generally start with 250 mg twice daily and increase the evening dose to 375 or 500 mg as needed and tolerated. Some children cannot tolerate naproxen due to lethargy or psychic effects ("like being on a trip"), and one youngster who was greatly benefited could not tolerate the palpatations it occasionally produces.

Indomethacin. Indomethacin, 2 mg/kg/day in four divided doses, has been used safely in children with control of fever and arthritis.[89] There is great variability in half-life; twice-a-day dosage, advocated in adults, has not been reported in children. This drug was better than aspirin in most trials involving patients with AS and related disorders.[118,143] However, naproxen is preferred by many patients who cannot tolerate the headaches, dizziness, and fatigue caused by indomethacin. Higher than recommended doses have been reported in association with death from liver disease and infection in children.[144] The drug seems safe in proper dosage and is, in some patients with HLA-B27–associated spondyloarthritis, preferred to all others.

Ibuprofen. Ibuprofen, 20 mg/kg/day, has been shown to be safe and efficacious in children, but the half-life is short and divided doses necessary.[145] The drug is extremely well tolerated and has sometimes been helpful in children who could not tolerate other drugs (Fig. 3.40). However, liver enzyme abnormalities seen with aspirin therapy may or may not return to normal with ibuprofen. Higher doses are generally required for control of fever in children with systemic JRA (40 mg/kg/day).

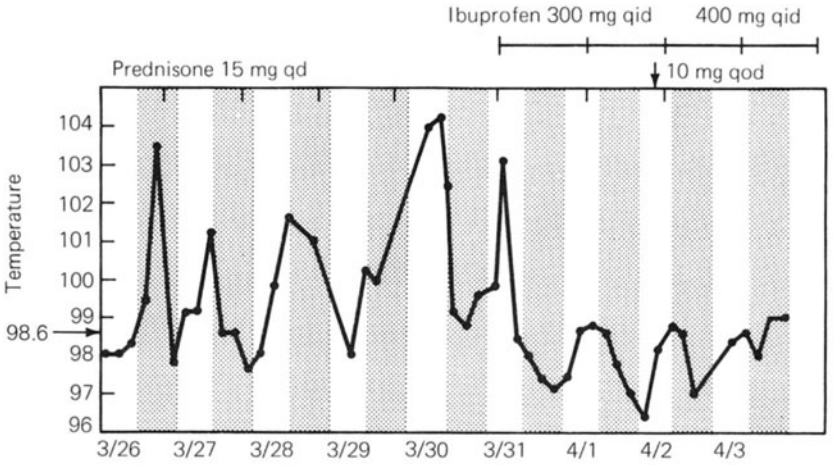


Figure 3.40. Steroid sparing effect of NSAIDs. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, may be used to control fever in children with systemic JRA who are unable to tolerate salicylates. NSAIDs may be used together with alternate-day steroids in patients whose fever cannot be controlled with NSAIDs alone. Alternate-day prednisone plus a NSAID may be more effective in controlling fever than daily prednisone alone, as shown in this illustration. (From Brewer EJ: Nonsteroidal antiinflammatory agents. Arthritis Rheum 20:513–525, 1977; with permission of the American Rheumatism Association.)

Fenoprofen. Preliminary study by the Pediatric Rheumatology Drug Study Group has shown this drug to be safe and effective in a dose of 30 mg/kg/day. Divided doses are necessary.[146]

Undoubtedly, further studies will demonstrate usefulness and safety of other new NSAIDs, including other profens and sulindac, now widely used in adults. Some, like flufenamic acid, mefanamic acid, and phenylbutazone, have, in our opinion, already been demonstrated to be too toxic for use in children. The pace of new developments in the field of NSAIDs has tended to make reviews outdated by the time of publication. Unfortunately, there is a paucity of scientific study of NSAIDs in children.[147]

Hazards of NSAIDs. These new drugs have all of the potential toxic side effects of aspirin[135] plus a higher incidence of anaphylactic-type reactions. Our early experience suggested that extraordinarily high doses of indomethacin might be associated with increased susceptibility to infection, but this has not been a problem with more appropriate doses.[144] The major symptoms limiting use of these drugs in children are central nervous system manifestations, including headache, drowsiness, depression, and depersonalization reactions. These reactions may occur after taking a single tablet.[146] Other worrisome problems with these agents include the reported reduction in renal function, the potential to cause interstitial nephritis and renal papillary necrosis (analgesic nephropathy) and the rare occurrence of the nephrotic syndrome and irreversible renal failure.[60A,135,148–150] The

major limiting fact in the use of these drugs in children, therefore, is uncertainty about the frequency of severe unanticipated toxicity, especially renal toxicity, which might first become manifest after years of chronic administration.[60A]

Our current approach to the use of NSAIDs in children may be summarized as follows:

1. We begin all systemic and polyarticular JRA patients on aspirin and offer NSAIDs as an alternative or supplement only if the disease is not adequately controlled with aspirin.
2. All teenage HLA-B27–associated spondyloarthritics are started on aspirin and urged to try naproxen, tolmetin, and sulindac for a few days each if they are not perfectly satisfied with the aspirin.[151] Some of these youngsters prefer aspirin to all of these new agents. Within a few days, most youngsters can report their individual preference based on subjective relief of symptoms and tolerance of side effects.
3. Children with pauciarticular disease are generally started on aspirin. However, if young children with prominent enthesopathy can swallow tablets, naproxen or tolmetin are sometimes the optimal agents. Older children with prominent enthesial symptoms often prefer naproxen to other medications.
4. Studies of interactions between NSAIDs have produced conflicting results.[135] To avoid interference and a lower net effect, only one anti-inflammatory drug is generally used at one time in any patient. In a few special circumstances, the combination of aspirin and another NSAID such as indomethacin or naproxen seems to have been helpful to our patients.[146] However, such combinations may increase the risk of analgesic nephropathy.[60A]

Slower-Acting Antirheumatic Drugs. Gold, chloroquine, and penicillamine, the drugs included in this category, do not have the standard laboratory properties of anti-inflammatory drugs and generally are rather specific for rheumatic diseases. Weeks to months of therapy are required before a beneficial effect may be expected. While it is possible they may in some cases induce remission of the disease and inhibit cartilage destruction, they have not been proved to do so.

The indication for use of the slower-acting drugs is generally considered to be persistently poorly controlled polyarticular disease that threatens multiple joint destruction and accumulating disability (Fig. 3.15). Potential therapeutic benefits must be balanced against the potentially serious side effects of treatment with these agents. The number of children requiring these medications is small, their potential toxicity is great, and considerable clinical experience is necessary for their safe and effective use. The care of such children should be either in or supervised by pediatric rheumatology clinics. Their use should be discontinued after 6 months unless there is objective evidence of improvement by that time.

Chrysotherapy. Gold evolved as a therapeutic agent for RA as a result of Koch's demonstration that the in vitro growth of tubercle bacilli was inhibited by gold and Forestier's erroneous assumption that tuberculosis was related to RA.

Despite a multitude of studies, the mechanism of action of gold in RA remains unknown.[152]

Chrysotherapy was in wide use for 30 years before the controlled study of the Empire Rheumatism Council managed to demonstrate that it was more effective than placebo; the difference in effect was not overwhelming, and the advantage of 20 weeks of gold therapy was lost at the time of 2-year follow-up.[153] No similar study has been performed in children. However, many experienced physicians have reported the efficacy of gold in some pediatric cases and the need for continued maintenance therapy to maintain the clinical effect.[95,146,154] Scientific studies do not prove the commonly stated clinical dictum that gold has the capability of inducing a remission. Naturally, in any disease characterized by exacerbations and remissions, any long-term therapy will coincide on occasion with remission.

Fifteen to thirty percent of children started on gold therapy must discontinue treatment because of adverse side effects.[155] Gold salts are reported to be 10 times more toxic than any other therapy used in Great Britain and over a 7-year period accounted for 16 deaths in the U.K.[156] Death is most commonly from narrow aplasia and its complications, especially overwhelming sepsis. Other side effects include severe mucocutaneous reactions, autoimmune thrombocytopenia, and membranous nephropathy. We have seen one child with fatal disseminated intravascular coagulation and reviewed the record of another (not fatal) after the *second* test-dose injection of gold and are now aware of eight other similar cases (Fig. 3.41).[107,108]

Some toxic reactions to gold seem to be immunologically mediated. For example, proteinuria is 32 times more common in patients with HLA-DRw3 and so seems to be genetically controlled.[157]

When the decision to give gold is made, a complete blood count, platelet count, blood chemistry determination, and urinalysis are obtained, and a test dose of gold is given as soon as the results are available. The total weekly dose is calculated as 0.5–1 mg/kg/dose (50-mg maximum for adults).[95,146] We start with a test dose equal to one-fifth the weekly dose and increase equally weekly so that the full dose

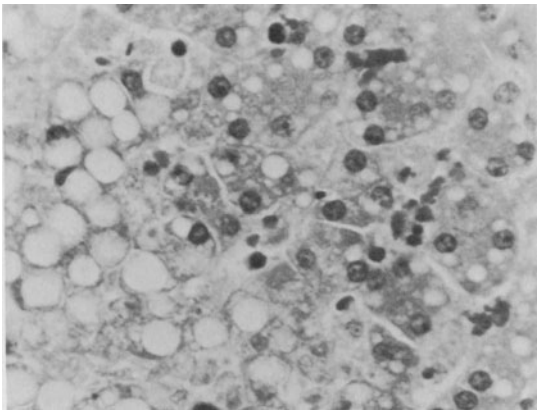


Figure 3.41. Disseminated intravascular coagulation (clogging blood vessels with red blood cells) with necrosis and fatty metamorphosis of the liver following the second injection of gold.

is achieved on the fifth injection. A complete blood count, platelet count, and urinalysis are obtained on the day of each dose, and the gold is not given until the results are checked by the physician. The injection is omitted if there is any rash or laboratory abnormality. Unexplained fever early in the course of gold therapy suggests the possibility of sepsis due to neutropenia and requires immediate evaluation. Serum gold levels are generally unavailable and have not yet been proved to be useful.

To avoid long waits in the clinic, we have taught responsible parents to give the intramuscular injections at home after they get our telephone approval indicating that the laboratory studies that day were normal. With this system, they may have the blood and urine studies in their own neighborhoods, and some of the inconvenience of gold injections is removed. So long as the child is improving, we continue the gold weekly, usually for a period of 1 year. If the youngster is in remission, we gradually reduce the gold injections to every 2, 3, and then 4 weeks and, if still in remission, discontinue the injections after about 2 years. If there is no improvement with gold, we give up the therapy after 6–9 months. If the arthritis worsens soon after reducing the frequency of gold administration, we resume the weekly injections. A number of different intramuscular gold preparations are marketed, without any clear-cut distinctions between them. Most of the injected gold is excreted via the kidneys and some through the gastrointestinal tract.[158] However, with time, there are increasing deposits in all tissues, which remain for years after cessation of therapy. Oral preparations of gold are being tried in adults, and it is hoped that ultimately a controlled trial will show oral gold to be safe and efficacious in children.[159]

Penicillamine. Penicillamine was initially found to be of use in Wilson's disease and has been used in lead poisoning and cystinuria in children. The discovery that penicillamine helps some adults with RA resulted from a trial by Jaffe in a patient with high-titer rheumatoid factor.[160] Based on laboratory evidence that the drug could dissociate human macroglobulins in vitro, he hypothesized that penicillamine would cause intravascular dissociation of IgM rheumatoid factor. The patient apparently benefited, and the level of rheumatoid factor was reduced, but for unknown reasons. Despite a great many studies, the mechanism leading to improvement remains unknown. Unlike gold, whose efficacy can be demonstrated in experimental models of arthritis such as adjuvant disease, penicillamine is ineffective in any such model. About all that can be said is that based on the extraordinarily wide range of serious drug-induced "autoimmune" disorders penicillamine can produce as side effects of its use,[161] it must act on some very basic immunologic mechanism(s).[160]

Multicenter controlled trials with penicillamine in adults have demonstrated statistically significant improvement in such measures of arthritic activity as grip strength, hemoglobin, and ESR. The results were not all that impressive. For example, in one such study, the average ESR in the treated group was reduced from 53 mm/h to 46 mm/h.[162] Twenty-six percent of the patients had to discon-

tinue the therapy because of side effects. However, experienced clinicians continue to be enthusiastic about penicillamine as a therapeutic agent in patients whose severe active RA is inadequately responsive to conventional therapy.[163,164] The drug has been used in a few hundred children with polyarthritis without systemic manifestations and is said to be about as effective as gold, equally toxic to gold, but preferred because it can be taken orally.[165,166] In an uncontrolled series using a dose of 15–30 mg/kg/day, 69% of children receiving the drug as their first slow-acting agent were said to benefit; 53% of children being treated with penicillamine after receiving gold without benefit were said to benefit from penicillamine.[166] No controlled studies against placebo have so far been reported in children, but one such international study (of 10 mg/kg/day) is now being conducted by the JRA Cooperative Drug Study Group together with a group of pediatric rheumatologists in the Soviet Union.

In the United States, most parents prefer to try the drug with the longest clinical experience over the newer agent, so here gold is usually chosen first over penicillamine, the latter being reserved for children who have not had an adequate response to gold. Whether this is the best regimen cannot be known without a controlled clinical trial of penicillamine versus gold versus placebo; no such trial has been arranged because of the reluctance of the parents of these sick children to accept the placebo sham injections for a 1-year trial period.

Side effects of penicillamine administration may include thrombocytopenia, agranulocytosis, aplastic anemia; membranous nephropathy with nephrotic syndrome; less common but more serious, rapidly progressive glomerulonephritis; Goodpasture's syndrome; hemolytic anemia; cholestatic hepatitis; serious rashes including pemphigus; myasthenia gravis; polymyositis; thyroiditis; and lupus erythematosus.[160,161] Vitamin B_6 deficiency may be combated by simultaneous administration of 25 mg of vitamin B_6 daily at a different time than the medication. No harmful effects of coincident heavy-metal chelation have been noted, but they could be unrecognized, as could other effects of its lathyrogenic and collagen basement-membrane–altering properties. Serious proteinuria is more likely to occur in the same patients who develop proteinuria with gold, especially those with HLA-DRw3.[157]

Dosage regulation of penicillamine cannot be based on serum levels, which are not available. In adults, increased side effects and few benefits have been achieved with doses in excess of 600 mg daily. In Europe, many children have received 15 mg/kg/day or even more if they did not respond.[165] We have generally limited our young patients to a single 250-mg tablet daily, beginning with a dose of 50 mg daily and increasing every 2 weeks until the maximum dosage is achieved. Better gastrointestinal tolerance has been achieved in adults with this "go low, go slow" regimen. A complete blood count, platelet count, urinalysis, and chemistries are obtained prior to each increase and monthly thereafter. Urinary protein determination with filter-paper strips can be done more frequently by the parent at home. The reported incidence of side effects requiring withdrawal of medications varies from 10 to 30%. Other antirheumatic medications have to be continued since a beneficial effect may not be noted for months. Other drugs with potential for sim-

ilar side effects (gold and immunosuppressive agents) should not be given concomitantly.

Penicillamine is continued until the patient has been in total remission for 1 year. If no beneficial effect is seen after 6 months of administration of the full dosage, there is no purpose in continuing unless one wishes to take the risk of a trial at a higher dosage. We discontinue the drug at the first sign of any toxic effect.

Hydroxychloroquine. This antimalarial compound has been reported to be equally effective to gold in adults with RA but fell into disfavor when irreversible retinal toxicity was reported.[167] Two large pediatric groups have continued to use it and report it to be an effective agent with greater ease of administration and less toxicity than gold or penicillamine.[168,169] At a dosage of 5–7 mg/kg/day (maximum 200 mg daily) given as a single dose, the most frequent side effect is reported to be corneal deposition, which is reversible and said to be dose-related. The most worrisome side effect is macular degeneration, which may progress after the drug is withdrawn. Patients with known familial tendency to macular degeneration may be at higher risk. With careful frequent ocular monitoring and drug withdrawal, the incidence of significant retinopathy threatening vision may be kept to 1%.[169,170] The lack of popularity of this drug represents doubts about efficacy in the face of this ocular hazard in a disorder with increased ocular risk from uveitis. If a controlled trial showed efficacy, this agent would be more widely used and has the potential for combined use with penicillamine or gold. Such a trial is being conducted by the Pediatric Rheumatology Drug Study Group.

When hydroxychloroquine is used with success, the drug is generally continued in full dosage for 6 months and then gradually reduced over a 2-year period. Chloroquine must be kept locked in the medicine cabinet. Death has been reported after childhood ingestion of as little as 1 g.[146]

Corticosteroid Treatment of Severe Polyarticular JRA

If properly used in JRA, corticosteroids may prevent blindness; enable function as opposed to the alternative of a bed-chair existence with all that implies for the child and family; and prevent death from overwhelming myopericarditis. With improper use, they may foster crippling or death.[146]

For some severely affected children, a small dose of prednisone on alternate mornings (together with their nonsteroidal drug and slow-acting agent) may make the difference between going to school and a reasonably normal life or becoming a bed-chair cripple (Fig. 3.42).[76,171] The risks of alternate-day prednisone are small when weighed against the alternatives.[172] Animal studies and clinical evidence in these children indicate that loss of weight bearing is associated with worse cartilage destruction (see Figs. 3.48 and 3.49).[173–177] Occasionally, we see the rare child who comes to us already wheelchair-bound, demineralized and weak, and with characteristic absence of cartilage at the knees and hips out of proportion to anything we ever see in our own most severely affected children (see Fig. 3.48). Much

Figure 3.42. Severe systemic JRA (age 9 years, onset at age 3 years). Patient has large effusions in all joints and requires 3.9 g of aspirin daily plus 17 mg of prednisone on alternate mornings for control of fever and arthritis. She has had a cerebrovascular accident from which she has fully recovered and required a gastrectomy for uncontrollable hemorrhage caused by a penetrating duodenal ulcer at a time she was receiving indomethacin, aspirin, and steroids. She has failed to be helped by hydroxychloroquine, gold, pencillamine, or plasmapheresis. The alternate-day steroids enable her to attend school and summer camp and lead an almost normal life despite progressive joint destruction (see Fig. 3.27).

of this is secondary to entering the wheelchair. All of our patients attend regular school daily and none are ever allowed in a wheelchair. In our opinion, if prednisone is required to achieve that goal, it is well used for that purpose.

Small divided doses of prednisone can also be used in very severe polyarticular JRA (1 mg four times daily). However, we have not used daily prednisone except in systemic JRA for many years and have found alternate-day regimens to be preferable. While we try to use the smallest dose possible on alternate days (10 mg), we use whatever is needed for continued ambulation.

Pulse Corticosteroid Therapy. Massive intravenous doses of corticosteroids administered over a short period of time ("pulse" therapy) have been reported to sometimes be helpful in renal graft rejection reactions, SLE, and other rheumatic diseases.[178] Experience with a few arthritic children suggests that this technique may be helpful on rare occasions but that in general too frequent injections are required. Doses of 20–30 mg/kg of methylprednisone have generally been used.[146,179]

Immunosuppressive Agents. The incidence of death from JRA is about 7% in reported series.[60] While this is probably an overestimate, based on disproportionately severe cases being seen in large referral centers, it constitutes an underestimate for the select group in which almost all deaths occur: the severe polyarticular group characterized by persistent unremitting disease. It seems reasonable

to suppose that these agents, despite their potential for early or late significant or even fatal side effects, might be appropriate for the treatment of those youngsters who are potentially threatened with severe and permanent wheelchair crippling or death. However, there have been no controlled studies to support such a hypothesis, and little data are available. Chlorambucil has been reported to be the best agent for treatment of arthritic children with amyloidosis.[59] It is not known whether this implies improvement following better control of the arthritis or a specific effect of chlorambucil on renal amyloid.[180] Melphalan, another nitrogen mustard derivative, might also be worthy of trial in JRA with amyloidosis.

Azathioprine, cyclophosphamide, and chlorambucil have all been reported to be helpful in severe adult RA and in severe JRA unresponsive to other agents.[146,181] It is hoped but not proved that these highly toxic agents[182–184] could be used safely and alter the course of JRA rather than just offer symptomatic treatment. If this were proved, they certainly would have wider use in those children threatened with becoming "twisted wreckage."

Levamisole. This potent antihelmintic has some anti-inflammatory effects at high dosage and has thymominetic effects on T lymphocytes.[185] The beneficial effects in adults with RA are said to be similar to gold and penicillamine. A high incidence of fatal agranulocytosis, seizures, and coma has prevented adequate study in children and suggests that levamisole is unlikely to be useful in JRA.[186,187] However, unusually high doses were given to some of the children. New agents derived from levamisole or with similar pharmacologic properties and less toxicity may be discovered and be of more use in childhood arthritis.[187]

Plasma Exchange and Lymphocyte Depletion. Reducing the amounts of circulating antibody and immune complexes in antibody- or immune-complex–mediated diseases by plasma exchange is a technique used in Goodpasture's syndrome, SLE, and myasthenia gravis. Initial reports, based on somewhat sketchy evidence, have been enthusiastic. Plasmapheresis, lymphoplasmapheresis, and lymphapheresis have been tried in RA with varying success.[188–190] In one report of plasma exchange in JRA, success was dependent on the simultaneous administration of fresh-frozen plasma and was associated with an accidental death.[191] Apheresis at present must be considered a research procedure rather than an accepted mode of therapy.

Since high titers of rheumatoid factor or significant immune complexes have usually not been demonstrated in JRA, the mode of action of plasma exchange, if it worked, would be entirely unknown. We have tried plasmapheresis in one terribly ill systemic JRA patient. A femoral vein catheter was required. Blood transfusions were also required since the child was too small to provide blood for "priming" of the machine. Prompt improvement was seen in terms of arthritis, serum levels of immune globulins, and ESR. However, within a few weeks, the patient had resumed her prior state. The technical difficulties and repetitive hazards of doing this procedure in this small child outweighed its small benefits.

The use of total body lymphoid irradiation to achieve lymphocyte depletion in adult RA has not provided long-term improvement sufficient to warrant trials in children.

Pauciarticular Juvenile Rheumatoid Arthritis

It has long been recognized that arthritis in childhood frequently affects only one or a few joints.[2,11] In 1977, the ARA-JRA criteria committee agreed to classify children who, at 6 months after onset of arthritis, have disease limited to one to four joints as a pauciarticular subset.[12] This is the most frequent form of arthritis in childhood and accounts for an increasing proportion of patients seen in large childhood arthritis clinics (Table 3.4). Large joints, especially those of the lower extremities, are most frequently affected, and involvement is often asymmetrical and spotty.

The pauciarticular group has a better prognosis than either the systemic or polyarticular groups. Most patients will make a full recovery from the arthritis and have no disability. However, 11–37% of pauciarticular onset children will ultimately have a polyarticular course, and some significant disability in individual joints may occur. Visual impairment from chronic uveitis is also a significant risk in this group.[39]

Just as it has become apparent that it is difficult to make general statements about children with JRA without dividing them into clinical subsets, it has become obvious that what has been called pauciarticular JRA is an amalgam of different disorders. However, no two authorities agree at this moment on how to subdivide this group. Everyone recognizes the need to identify those patients who really have the disorder AS.[39,137,192] In our current schema of subdividing JRA, we have used histocompatibility testing as an aid to subset characterization. For purposes of study and prognosis as well as a useful guide to drug management, we find it most helpful to identify all HLA-B27 patients and consider them a separate disorder. Similar patients have been reported elsewhere as one subset of pauciarticular JRA.[39] HLA-B27–associated arthritis is discussed in Chapter 4.

All authors agree on a second clinical subset of pauciarticular disease, which is often characterized as "little girls with one swollen knee, a positive test for antinuclear antibody, and a high risk of chronic uveitis."[15,39] In one study, 10% of arthritic children belonged to this subset. (Only 65% of these were ANA-positive.)[39] Some authors have included all patients with chronic uveitis as a single subset (i.e., not limited to females). Children with the onset of pauciarticular arthritis prior to age 5 tend to be in this subset. Recent studies in our laboratories and others have shown that HLA-B27-negative, early-onset pauciarticular JRA with uveitis is associated with HLA-DRw5.[9,15,193]

The characterization of pauciarticular JRA into subsets is not just of clinical interest. With recent evidence suggesting that JRA may represent a series of disorders with T-cell defects, it is reasonable to presume that different patterns of

disease may be a reflection of different variations in immunologic function.[194] For purposes of study, we are now dividing the HLA-B27-negative pauciarticular patients into two subsets: DRw5-positive and DRw5-negative.

HLA-DRw5–Associated Pauciarticular JRA

Among 39 pauciarticular-onset patients known to be HLA-B27-negative, we found 23 DRw5-positive patients.[9,193] The tested population was not unselected and was weighted for uveitis, so it may not be a totally accurate representation of the constituency of the total B27-negative pauciarticular group. Seven DRw5 patients were males; one of these had uveitis. Thus, while males (7 of 23) are not as frequently affected as females (16 of 23), they did not constitute an insignificant part of this population. The number of affected joints at onset averaged only 1.3. In 17 of 23 patients (74%), the onset was monarticular. The knee was most frequently affected (12 of 23), with hip and ankle the other relatively frequently affected joints (5 of 23). Elbow, finger, foot, and TMJ were all affected in single instances; in no cases were the wrists or shoulders affected at the time of onset of arthritis in this population. The arthritis tended to be very mild, to respond to aspirin, and to remit relatively quickly. Recurrent attacks were common, however, and two patients developed a polyarticular course.

The age at onset of this arthritis differs in association with the presence or absence of uveitis. The average age at onset in girls with uveitis was 3.8 years (in the single boy, 3 years), while in girls without uveitis, it was 8.2 years, and in boys without uveitis, 7.5 years. The pattern of arthritis did not vary with age.

This association of DRw5 with pauciarticular JRA and especially with girls with JRA and uveitis has since been confirmed by Glass et al.[15] After discussion with us, they selected 45 pauciarticular JRA patients, heavily weighted for females (41) and uveitis (24). Of the 45, 28 were HLA-DRw5; 17 of 24 with uveitis were HLA-DRw5. As expected from prior reports, ANA was found especially frequently in the DRw5-positive girls with uveitis. The relationship between DRw5 and this subset of childhood arthritis has been found in all populations so far examined. Our preliminary data suggest that other DR association found only in individual geographic areas may represent population-biased samples. However, further study is required.

Non-B27, non-DRw5 Pauciarticular JRA

Of the 39 HLA-B27-negative patients tested, 16 were also DRw5-negative; of these, 6 were boys and 10 were girls. The average age at onset of arthritis was 6.4 years for boys and 5.9 for girls. There were no apparent differences to distinguish the pattern of arthritis in this subset from the total pauciarticular group, but individual patients might most resemble one of the other subsets, that is, HLA-B27–associated disease, DRw5-associated disease, or polyarticular seropositive RA associated with DRw4.

Prognosis

The overall prognosis for the entire pauciarticular JRA group is good, with relatively little scarring except in the eyes (see below). However, more severe involvement requiring joint replacement occurs in the B27 group (see Chapter 4), and recent studies indicate that the prognosis for the knees of the DRw5 uveitis group may not be as good as we had previously thought. While in our short-term follow-up period the prognosis for joint function seemed good, in a larger long-term series of patients with chronic iritis reported by Kanski, 20% of patients had "severe disease" and ultimately required surgical joint replacement.[195] We can expect to learn more as a result of a prospective study of this subset.

Treatment

In most pauciarticular patients, aspirin, 90 mg/kg/day (max. 3.6 g daily) in four divided doses, provides excellent control of the arthritis. A few children respond better to tolmetin or naproxen or tolerate it better. Teenagers may prefer other nonsteroidal anti-inflammatory agents. In our clinic gold, penicillamine, and hydroxychloroquine are not used in the treatment of pauciarticular disease since the toxic hazards of these agents would seem to outweigh their potential therapeutic promise.

Antirheumatic medication is continued until the patient has been asymptomatic and has normal laboratory studies for 6 months. Remission is defined by being asymptomatic and having normal laboratory studies for a period of 6 months after cessation of all treatment.

Intra-articular Corticosteroid Injections. Children do not like injections into their joints; the beneficial effect, if there is any, tends to wear off in days. Intrasynovial injections are occasionally complicated by the introduction of bacteria into the arthritic joint, creating a very difficult diagnostic and therapeutic problem. Experimental evidence suggests hydrocortisone may have a deleterious effect on damaged cartilage in young animals. Repeated injections may foster total joint destruction. Leakage of steroid around the needle tract may cause permanent unattractive atrophy of skin and subcutaneous tissues. Nevertheless, there are occasions where one injection of long-acting steroid of a single large knee effusion, after removal of fluid, provides great relief of pain, allowing mobilization of the stiff joint and correction of deformity.[12,146,196] The beneficial effect, in some rare instances, may be extremely long-lasting. The risk of a single injection is small, but we do not give repeated injections.

Iridocyclitis (Anterior Uveitis)

The association of iritis with arthritis in children, the distinction of this subacute or chronic iritis, which was persistent from the form of iritis that was acute and

paroxysmal, and the observation that the parents of children with iritis usually had arthritis were all reported by Jonathan Hutchinson in *Lancet* in 1873,[197] a quarter of a century prior to Still's description of JRA and over a century before we again recognized the heritable tendency.

Subacute or chronic inflammation of the iris and ciliary body occurs in 20% of all children with JRA (Fig. 3.43). Both eyes are ultimately affected in 70% of children with uveitis. Patients tend to have recurrent attacks; in 21% of cases, the duration of eye disease exceeds 10 years.[195] Arthritis precedes the onset of uveitis in almost all (92%) cases.[195,198]

The Susceptible Population

If the B27 subset is excluded, about 90% of arthritic children with uveitis are girls. In some series, 60–90% of them have antinuclear antibodies.[199,200] Although the disease is almost always pauciarticular (often monarticular) at onset, it need not remain pauciarticular, and some severely incapacitated patients have uveitis. The mean age at onset of arthritis in the uveitis population is 3.7 years.[195] The knee is the single most commonly affected joint. The arthritic population characterized as little girls with swollen knees and a positive ANA test has a greater than 40% risk of uveitis.[4] In our preliminary studies, 90% of arthritic children with subacute or chronic uveitis were of a single HLA-DRw type—DRw5.[193] Patients with pauciarticular-onset arthritis remain at risk for uveitis for many years. In 21% of cases, uveitis began more than 5 years after the onset of arthritis.[195]

Diagnosis

Most patients are asymptomatic early in the course of their disease, although mild redness of the eye or visual complaints occur occasionally (Fig. 3.43). Thus, early

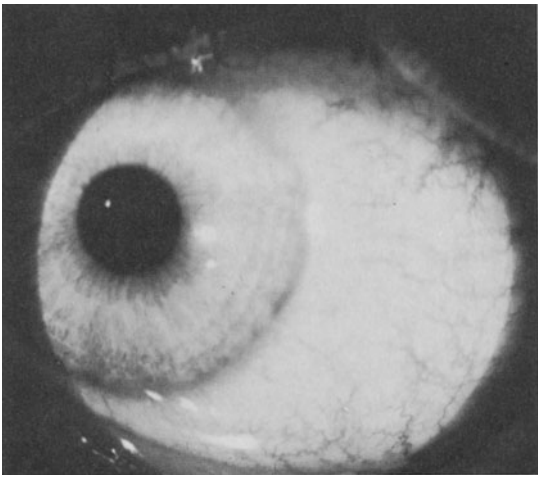


Figure 3.43. Although the subacute or chronic uveitis associated primarily with pauciarticular JRA (especially common in little girls with antinuclear antibodies) is generally found only by routine screening slit-lamp examinations, occasionally patients will have a "ciliary flush" indicating inflammation.

diagnosis depends on routine slit-lamp screening of all arthritic children. This is carried out at 6-month intervals in our clinic but may be more appropriate at 3-month intervals in the most susceptible population or monthly in those known to have had a prior attack. HLA-DR typing can be expected to help identify the group to be more carefully screened.

The ophthalmologist notes the number of cells in the anterior chamber and the amount of protein precipitate (flare), using a standard grading system. Fresh keratic precipitates are noted if present. Unfortunately, in published reports, 18% of patients already had band keratopathy, and 9% had cataracts at the time of initial diagnosis;[195] it is hoped that these figures reflect the experience of the past 30 years rather than the present.

Course

If the disease is unilateral when first seen and the second eye becomes involved, it generally is affected within a year. Although attacks of uveitis may be brief, they tend to recur.[195]

All patients are not equally severely affected, and it seems unlikely that all have the same potential for scarring and blindness. Our routine screening procedure identifies some patients with inconsequential disease. However, in the largest published experience (160 cases), Kanski reported some loss of vision in 43% of affected eyes.[195] Twenty-six percent of affected eyes in his series lost all vision or retained only light perception or the ability to count fingers; 17% of affected children were totally blind. It is hoped that with earlier diagnosis and treatment and modern surgical techniques, these figures are a reflection of the past rather than current experience.[198]

Medical Treatment

Uveitis is treated with mydriatics and topical corticosteroid drops administered at frequent intervals.[198,201] If a prompt response is not obtained, systemic steroids are instituted (Fig. 3.44). We use prednisone, 1–2 mg/kg/day in divided doses, until the inflammation is completely controlled (usually a few weeks) and then change to an alternate-day regimen (2–5 mg/kg/dose). If the inflammation is controlled, the dose is gradually reduced with careful monitoring of the eyes. The regimen is aimed at preventing visual scars and accepts steroid side effects in an effort to prevent blindness.

This program, together with frequent monitoring of asymptomatic arthritic children, has the potential to prevent blindness totally from late-diagnosed or inadequately controlled uveitis.[198] Nevertheless, we continue to see patients who are blinded by complicated cataracts secondary to inadequately treated uveitis.

While in our clinic with this regimen we have had no loss of visual acuity in 86% of children with uveitis in whom the diagnosis was made prior to loss of visual acuity,[198] others have not had similar success and report limited steroid responsiveness.[195] There has been too little experience with immunosuppressive drugs in steroid-resistance uveitis to allow meaningful comment.

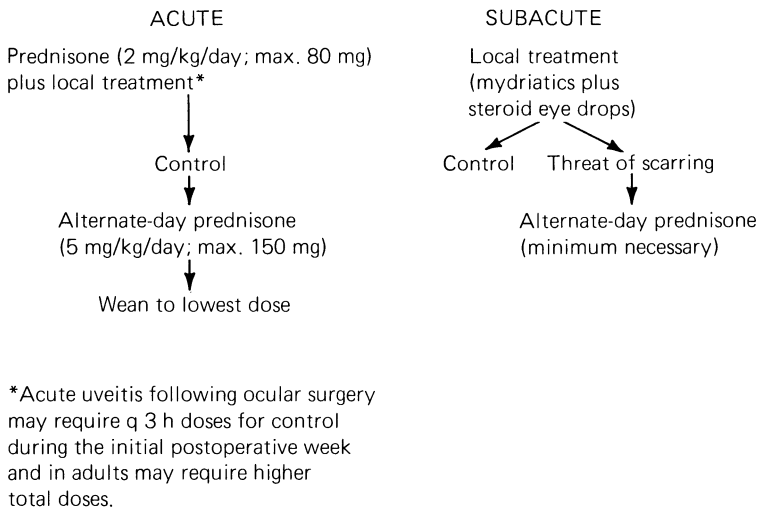


Figure 3.44. Treatment module for uveitis.

Surgery for Band Keratopathy

When vision is obstructed by calcium deposits in the cornea, removal of the band keratopathy by chelation and curretage is a simple and generally successful procedure.[202]

Cataract Surgery in Patients with Uveitis

Until recently, the surgical removal of a complicated cataract in arthritic children was generally followed by blindness (Table 3.16, Fig. 3.45).[202–204] In 1976, we reported a two-phase new approach to these cataracts; removal with the new surgical technique of phacoemulsification and intraoperative and postoperative medical support with daily high-dose steroid therapy.[204] In Dr. Praeger's hands, this

Table 3.16. Results of Cataract Surgery in JRA

Visual Acuity	*Smiley and Kanski*[202]	*Chylack et al.*[201]	*Key and Kimura*[202]	*Praeger et al.*[204]	*Kanski and Crick*[203]*	*Diamond and Kaplan*[205]*
20/200 or less	8	6	11	4†	14	5
20/40–20/120	3	2	9	0	5	2
20/30 or better	1	0	3	13	15	8
Totals	12	8	23	17	34	15

*Acuity groupings slightly different: Kanski and Crick: 20/120 or less, 20/60–20/80, 20/40 or better; Diamond and Kaplan: 20/100 or less, 20/70, 20/25, or better.
†One failure related to amblyopia exanopsia and three to uncontrolled glaucoma.

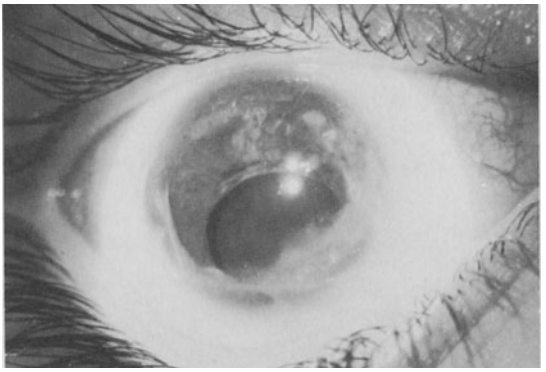


Figure 3.45. Appearance of eye following surgery with old techniques aimed at removing the complicated cataract that results from uveitis. Very few patients we operated on retained useful vision (Table 3.16).

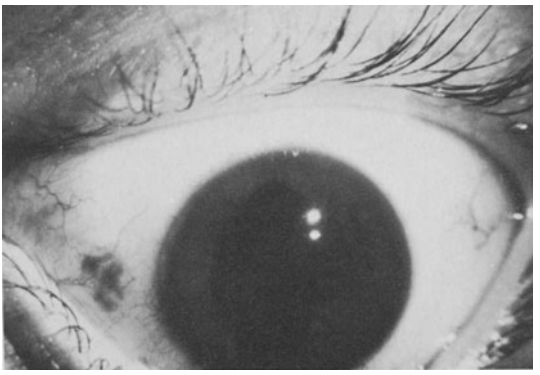


Figure 3.46. Note clear appearance of the eye a few months after surgery using phacoemulsification and high-dose perioperative steroids. Photo shows superior sphincterectomy and inferior iris sphincterotomy with pericentral opacification of intact posterior capsule. Note iris synechia to lens capsule. (Courtesy of Dr. D. Praeger.)

technique has now been entirely satisfactory in 13 of 17 cases (Table 3.16, Fig. 3.46). Improved results with new techniques for lensectomy rather than phacoemulsification, but without systemic steroids have been reported by Smiley and Kanski.[202,203] The published results do not equal the combination of phacoemulsification and aggressive steroid therapy. Recently, Kaplan and Diamond, after demonstrating that postvitrectomy uveitis in the rabbit was prevented by vigorous steroid therapy, used a steroid regimen similar to ours but with a different surgical procedure (lensectomy with vitrectomy) for patients with complicated cataracts.[205] Their results also do not equal those with phacoemulsification, but their patient population did not include children and may not have been analogous to ours. We have also used our steroid regimen with lensectomy and vitrectomy without phacoemulsification in two children. Both operations were successful in restoring vision, but more steroids seemed to be required than have been required in those cases done with phacoemulsification. Recently, Chylack has also reported phacoemulsification to be the procedure of choice in these children.[201] Thus, pending further study, my recommendation would be administration of steroids to completely control inflammation on the day prior to and during surgery and in sufficient

dosage to control inflammation postoperatively with cataract removal by phacoemulsification. The surgical technique and steroid regimen are detailed elsewhere.[204] Unilaterally, blind eyes in young children must be operated on promptly to avoid amblyopia exanopsia. Glaucoma must be adequately treated when present or a blind eye will result despite successful cataract surgery.

Arthritis with Psoriasis

All forms of arthritis may occur coincident with psoriasis, but arthritis that mainly involves the distal interphalangeal joints of the hands is most distinctive and is usually called "psoriatic" (Fig. 3.47). Half of arthritic children with psoriasis have this form of arthritis.[206,207] In one recent study, the presence of HLA-B8 was associated with more severe disease in arthritic children with psoriasis, whereas HLA-

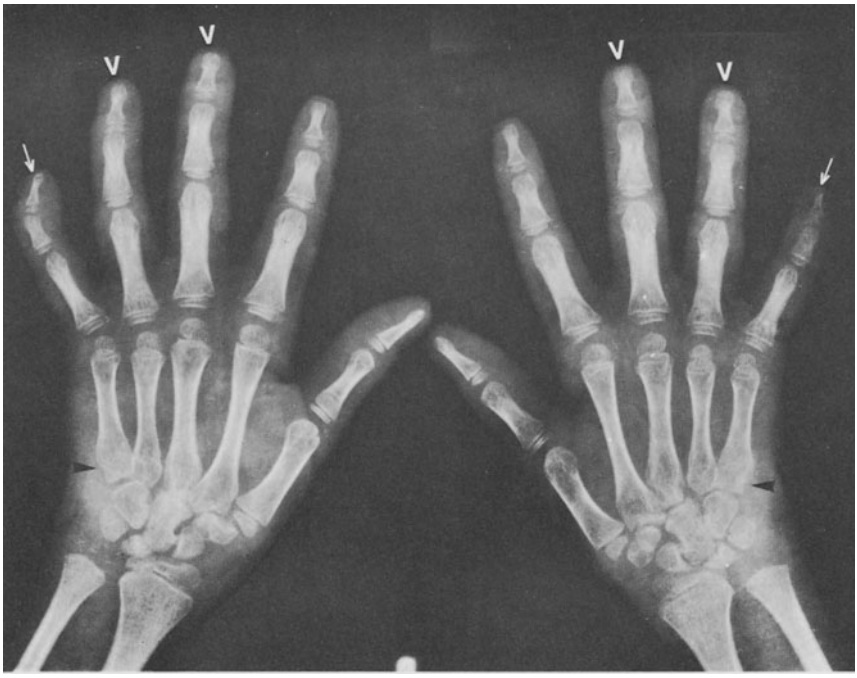


Figure 3.47. Hands of a 9-year-old boy with congenital familiar psoriatic erythroderma, showing loss of soft tissues in the distal finger tufts *(arrow heads),* with beginning loss of bone substance and DIP-joint arthritis in the fifth fingers *(arrows).* There are extensive arthritic changes at the wrists with crenation of the carpal bones and loss of joint space. Note severe erosions visible at the lateral bases of the fifth metacarpal bones (*black arrow heads).* The findings are typical of those seen in other forms of psoriasis.

B17 was more frequently found in children with milder forms of childhood arthritis associated with psoriasis.[208] Sacroiliitis occurs in 30% of children with psoriasis and arthritis and, when present, is generally associated with the presence of HLA-B27.

Females are more commonly affected with arthritis/psoriasis (2.6:1). The mean age of onset is high for childhood arthritis (9–10 years of age). Arthritis usually precedes the appearance of the psoriatic skin lesions.

Although psoriatic arthritis in childhood is generally a mild disease, it tends to continue into adult life and, in some cases, is associated with rapid joint destruction. Management is similar to other forms of childhood arthritis and depends on the extent of the joint involvement.

Exercises as Therapy in Childhood Arthritis

Movement and weight bearing are important in preventing accelerated destruction of cartilage. Evidence from animal studies shows that experimentally damaged cartilage suffers worse destruction if prohibited from weight bearing and exercise.[173] Radiographic regrowth of hip cartilage/fibrous tissue allowing improved function has similarly been demonstrated following ambulation of bedridden children with hip destruction from JRA (Fig. 3.48).[177] It is also generally not understood that joint capsular structures and muscle undergo adaptive shortening during immobilization even in the absence of inflammation.[176] When combined with inflammation in the synovium and all the periarticular structures, immobilization results in the most aggressive functional impairment of hips and knees, resulting in a bedridden condition (Fig. 3.49). Once bedridden, cartilage destruction and contractures about the joints accelerate.

The reason for the ghastly radiographic appearance of the hips and knees of bedridden JRA patients is not just JRA but the vicious cycle of JRA combined with immobility and lack of weight bearing (Fig. 3.48).[177] Sometimes this cycle is begun by well-meaning physicians who do not understand these physiological mechanisms. The natural tendency is to avoid use of painful joints. It is often hard to convince physicians of the crucial importance of walking on damaged legs in JRA. Convincing parents and children in pain requires a thorough understanding of the critical necessity for ambulation and of the horrendous physical crippling created by immobility in chronic polyarticular JRA.[177]

Complete immobilization of the arthritic joint (as in circular plaster) is never indicated and may result in accelerated loss of muscle strength and prolonged or permanent loss of function. We continue to see children who are put in plaster by orthopedists even though x-rays are normal "just in case" they mave missed a fracture. This practice is to be discouraged.

The primary goal of the physical and occupational therapist in JRA is the *maintenance of function* of individual *joints,* of the *child,* and of the *family.* Phys-

ical measures to help relieve pain and deformity and to preserve and restore motion and strength are the most often emphasized tools of the physicians and allied health personnel in the department of physical medicine and rehabilitation. Their role in the care of these children is greater than the sum of the parts. They exude confidence and show their commitment to function; they emphasize the positive—what the child can do—and fight to minimize what he or she cannot do. The interdisciplinary team exudes optimism, helps to break communication barriers between the primary physician and the family, and contributes, by example to the family, a sense of buoyancy and control over the disease.

Getting Started in the Morning

Gelling and stiffness make early morning one of the worst times of day for the arthritic child. Arising at 6:00 A.M., taking the medicine, then reading in bed or getting a bit more sleep, followed by a warm bath or shower, help in getting started. A simple set of limbering-up exercises is performed, and the child assumes straight posture in front of the mirror. Later in the day, the detailed exercise program is continued.

The Specific Exercise Program

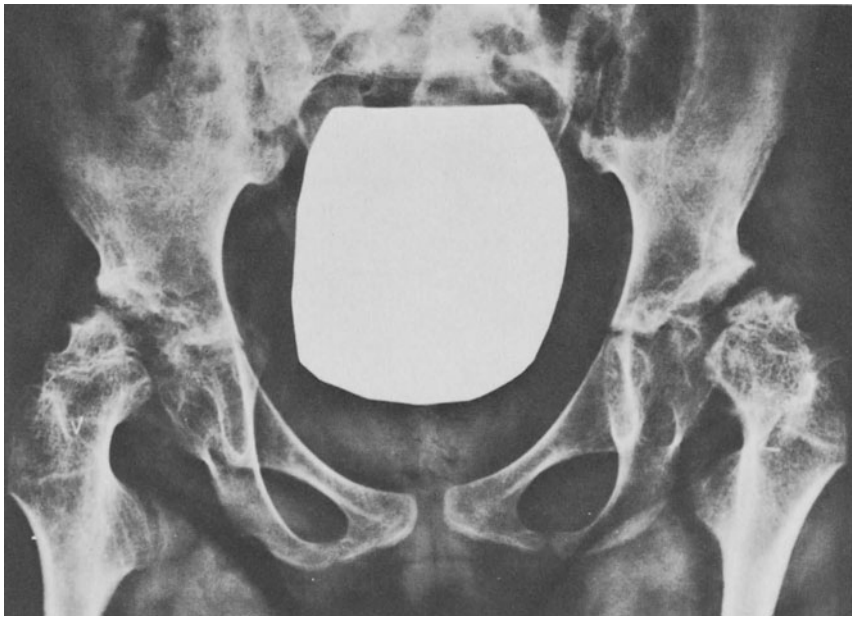
If pain is severe, heat in the form of hot baths or local application of towels or soaks may be helpful. The maintenance of motion is achieved by putting every joint of the body, whether involved or uninvolved, through a full range of motion using positions that require as little resistance as possible. The child and parent are shown how to compare normal joint motion with that of affected joints, how to examine the joints, and the visual clues of joint involvement.

A detailed, individually written program is provided to each family as they are taught the exercises. After the program has been taught, it is performed by the child and parent with praise and suggestions from the therapist. This is reviewed and reinforced at several subsequent visits to the rheumatologist. The optimal arrangement is for the physical and occupational therapists to be present in the clinic or office to work with the patients at the regularly scheduled visits. We try to avoid separate visits to the therapist except for patients requiring rehabilitation.

Although gentle passive stretching exercises are used, active and resistance exercises, especially with resistance applied by the child himself, are more effective. Strength of weak muscles may be improved with muscle-tensing exercises that do not involve joint motion (isometric exercises). Many exercises may be performed while in school or in front of the television.

Gravity is used when possible to prevent or correct deformity. Watching TV in the prone position helps to prevent hip-flexion contractures. Children are also encouraged to sleep in this position.

Sleeping splints may be useful as a means of increasing joint mobility (exten-



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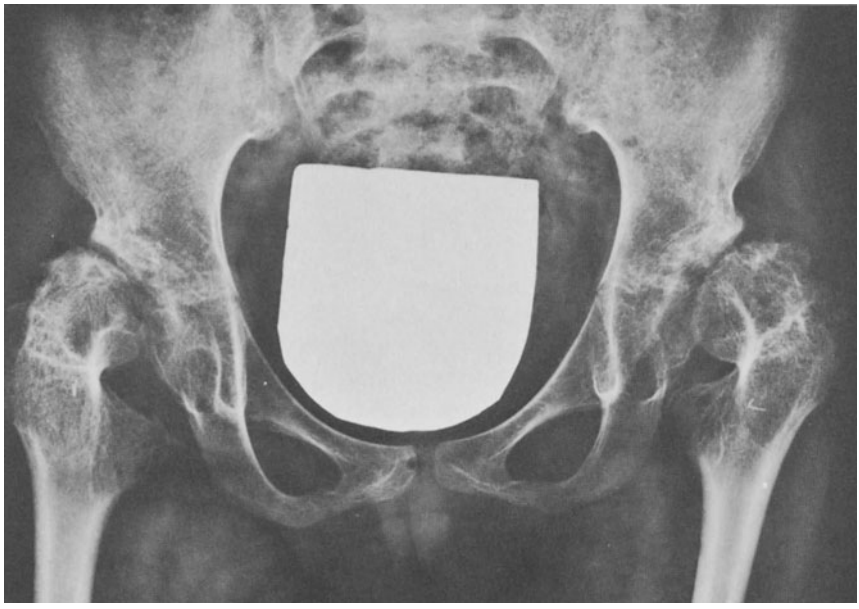
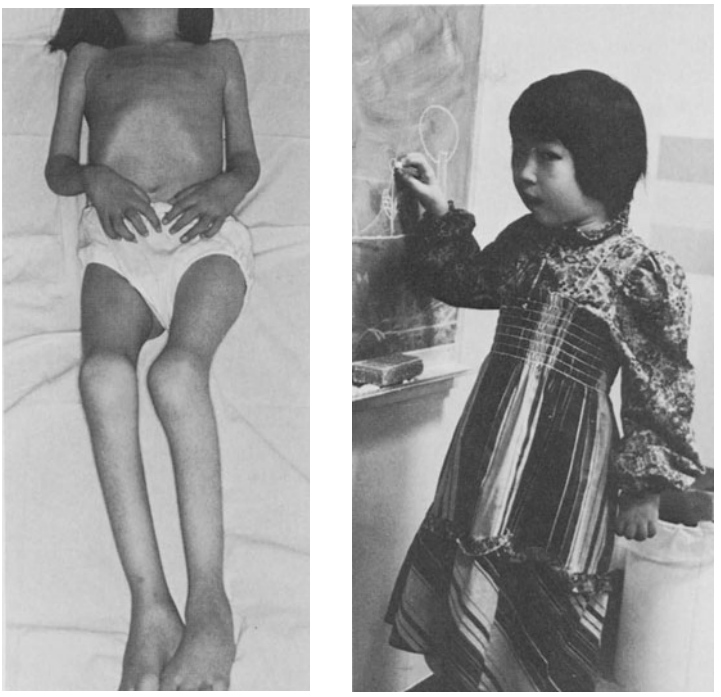


B

Figure 3.48. Hip radiographs in a 9-year-old Korean girl (Fig. 3.49) brought here for treatment of a systemic JRA. The child had been bedridden for 5 years. (**A**) Remineralization and filling-in of bony defects 2 years after patient began to fully bear weight on the joints. (**B**) Metallic objects are broken acupuncture needles. (From Jacobs et al., ref. 177A, with permission.)



A B

Figure 3.49. Patient at the time she was first seen (**A**) and 3 years later (**B**) following release of iliotibial bands and soft-tissue contractures about the hips and knees (at one operation) followed by 5 hours of physical therapy daily for several months. The mother was taught the regimen during the 3-week hospitalization and has continued therapy every since. Within 6 months, the child was able to attend a regular public school (despite the language barrier), and she now walks without any mechanical aid. The only medicine she has received during the past 5 years is aspirin.

sion) in the wrists and sometimes the knees. Splints must be adjusted and frequently modified; they meet with a fair amount of resistance from both child and family and are only useful when accepted by both as part of an ego-building program. If physical modes of therapy become a source of conflict between parent and child, either the conflict has to be resolved with a psychological approach, or the "therapy" will be unsuccessful or even countertherapeutic.

A heel lift on a short leg (usually the uninvolved leg in asymmetrical disease) will help correct or prevent a flexion contracture in the affected, more rapidly growing knee.

Swimming is an excellent exercise, and our families are encouraged to have pools if possible. The buoyant effect of the water allows large weight-bearing joints to be moved without force; most children enjoy swimming, and the pool attracts friends and is ego-rewarding for our patients. Other coordinated activities

such as ball playing or bicycle riding also provide muscle strengthening and ego-rewarding social opportunities. The disease may set limits on the child's performance, but we do not set any limits whatsoever. We also do not prescribe rest; these children naturally rest more than healthy children. Any limitation is inevitably countertherapeutic. Normal childhood is the best therapy. Supplementing normal activities with professionally delivered services can make a great contribution to the patient's welfare; substituting professionally delivered services for being busy with normal activities is relatively useless. Preventing children from doing things for themselves, developing motor skills, and thus achieving independence and autonomy leads to feelings of helplessness and anger that are countertherapeutic. No exercise program can equal the activities of daily living.

Surgery in JRA

Pediatric orthopedic surgery requires special understanding of children and growing bones. Juvenile rheumatoid arthritis creates additional special problems. Prolonged immobilization results in atrophy of bone and muscle. When a child has borderline function, immobilization associated with surgery or with treatment of traumatic fracture from a fall may be enough to make the child a bed-chair invalid. Months or years of effort may be required just to get the child back to where he started.

Thus, surgery is not to be lightly embarked upon and should only be performed by experienced operators in pediatric rheumatology centers. Most reports of surgery in JRA refer to adults who have had JRA since childhood, not to children. The subject of surgery in JRA has been thoroughly reviewed by Arden and Ansell, and the reader is referred to their excellent monograph.[134]

"Prophylactic" Surgery

Synovectomy as a means of preventing rather than relieving disability has been tried and abandoned twice in the history of rheumatology. Its value has not been demonstrated. Synovectomy of the knee often relieves pain but is rarely if ever required for that purpose in children.

Cosmetic Surgery

The small mandible caused by JRA troubles many teenagers and is relatively easily corrected with only a few days of hospitalization (Fig. 3.28). The particular surgical procedures must be individualized by experienced physicians. In very rare cases, temporomandibular joint surgery is needed in youngsters who cannot adequately open the mouth.

Some girls wish cosmetic correction of finger deformities. This can be successfully achieved with relative ease, but function does not improve or may even be somewhat reduced.

Surgery to Relieve Nerve Compression at the Wrist

In rare individuals, extensive tenosynovitis at the wrist may threaten nerve function; simple releases may be performed to prevent serious loss of function. We have not seen children who required wrist surgery to prevent tendon rupture or to relieve flexion contractures in dysfunctional positions, although others report experience with such procedures.

Corrective and Restorative Surgery

Soft-tissue release operations, débridement and therapeutic synovectomy are useful in selected instances in JRA (Fig. 3.49). In our experience, these procedures have only been necessary in children with flexion contractures of the hips and knees, accelerated by sitting in wheelchairs, who were bedridden when we first saw them. In these patients, multiple surgical procedures performed at one time may be an essential part of a massive program aimed at getting the child ambulatory again. This goal can then be achieved with a 7-day-per-week, 5-hour-per-day rehabilitation program (Fig. 3.50). However, success requires hard work by a well-coordinated, big-center, experienced pediatric rehabilitation team. Detailed surgical techniques and anesthetic precaution are reviewed elsewhere.[134]

Total Joint Replacement

Experience with hip replacement in young adults who have had destruction of the hips during childhood has been excellent both in our experience and in other centers. The roentgen appearance of the hips should not be used as the criterion for surgery since some patients function well despite an awful radiographic appearance (Figs. 3.51 and 3.52). Replacement of elbows, shoulders, and knees has not yet achieved success equal to hip implants. However, results improve each year.[209]

We urge our patients to wait as long as possible before having any joint replacement procedures. The advantage of waiting until the epiphyses close is obvious. In addition, we do not know how long these prosthetic joints are likely to last. Recent experience shows constant technical improvement in implant materials, design, and procedures. Our conservative approach is supported by increasing evidence of potential loss of seemingly fine early prosthetic repair.[210] Early acetabular loosening and radiolucencies predictive of early failure are now reported in 10% of hip replacements in young arthritic patients even in the most experienced clinics (Fig. 3.53).[211]

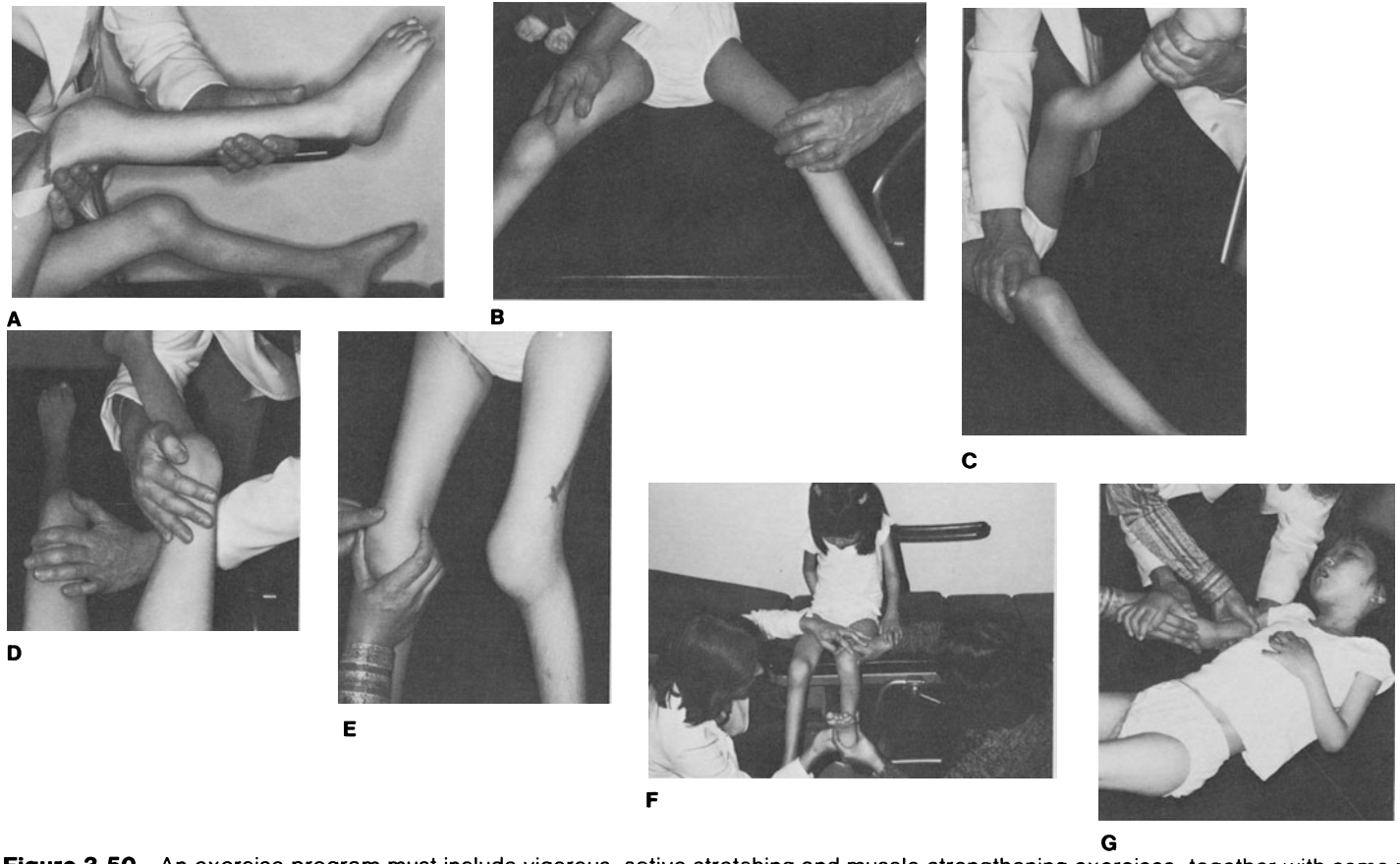


Figure 3.50. An exercise program must include vigorous, active stretching and muscle-strengthening exercises, together with some passive stretching. The parent must carry out the program with the child at home every day, 7 days a week. The therapist provides instruction and encouragement but doesn't actually do the daily exercises. A vigorous physical therapy program was successful in achieving full ambulation in a youngster who had been bedridden for 5 years. The therapy was begun immediately following surgery to release soft-

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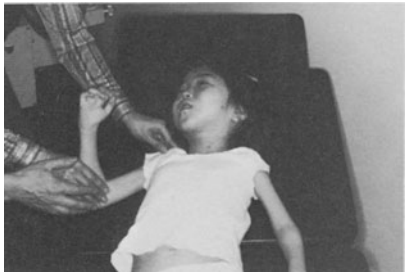

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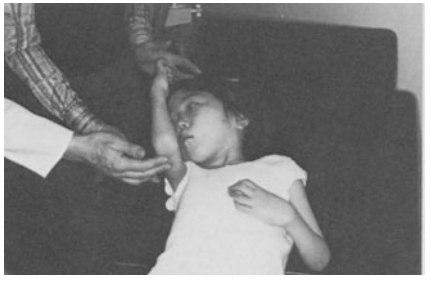

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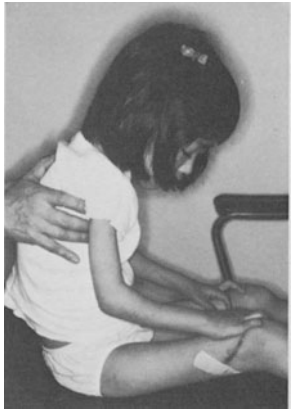

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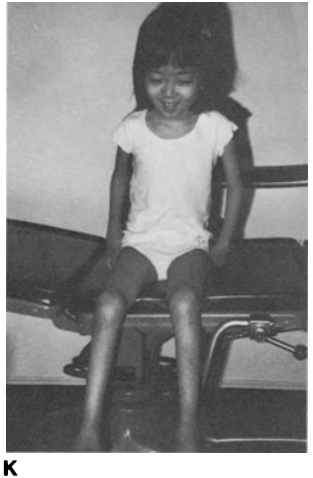

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tissue contractures in the iliotibial ligaments and around the hips and knees. In addition to other items, the exercise program included (**A**) active assisted knee extension, (**B**) stabilizing the right leg to abduct the left, (**C**) straight leg raising and hip flexion, (**D**) stabilizing the left leg to achieve maximum right hip flexion, (**E**) isometric quadriceps contraction (one hand stabilizes the knee while the other feels the contraction), (**F**) active assisted knee extension, (**G**) active assisted elbow extention, (**H**) assisted shoulder extension with shoulder stabilized, (**I**) assisted shoulder flexion, (**J**) trunk and hip flexion reaching forward toward the toes, and (**K**) active knee-extensor (quadriceps) strengthening exercise. (**L** and **M**) Grasp, shoulder, and elbow extension, and visual motor coordination are all involved in blowing bubbles and snapping beads. (**L** and **M**: Copyright by Elizabeth Wilcox)

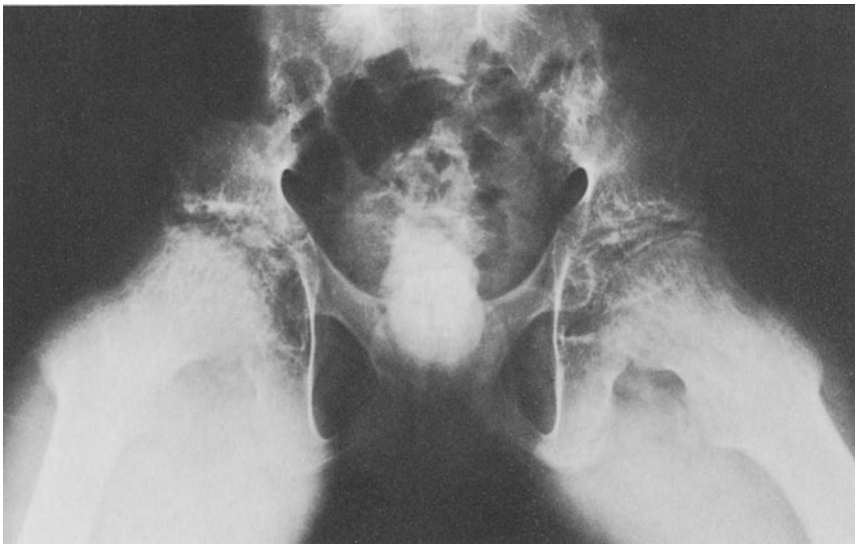

Figure 3.51. Radiograph of the hips in a boy with HLA-B27–associated spondyloarthritis.

Figure 3.52. Despite the severe radiographic changes (Fig. 3.51), this boy could unexpectedly play basketball and was on his neighborhood team. Although he will ultimately require hip replacement, it has not yet been necessary (5 years after this photograph was taken).

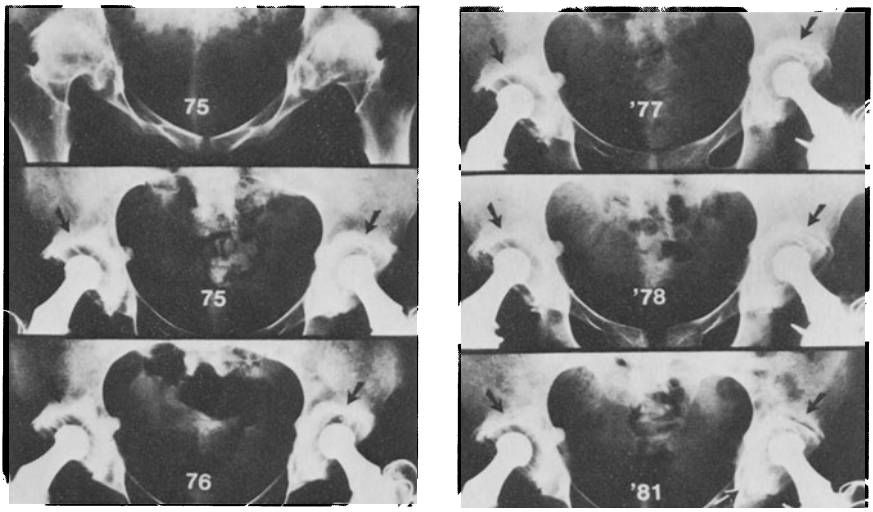

Figure 3.53. Pre- and postoperative radiograph of the hips *(1975)* in a college girl with long-standing JRA who had no hip abduction and desired hip replacement in order to be able to abduct the hips for normal sexual function. Bilateral total hip replacements were well tolerated (in two steps; one hospital admission), and the patient has no pain and is delighted with the result. However, from 1975–1981, as shown by the *arrows,* a progressively increasing "lucency" (interface) is seen in the films. This rapid demarcation occurs in 10% of young JRA patients following total hip replacement and may be a permanent obstacle to achieving a permanent fixation of the prosthesis to bone in young individuals. It is thought to be due to hyperelasticity of the bone in young patients.

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