The University of Texas Southwestern Medical Center at Dallas

ADULT-ONSET STILL'S DISEASE

A Circadian Cytokine Syndrome?

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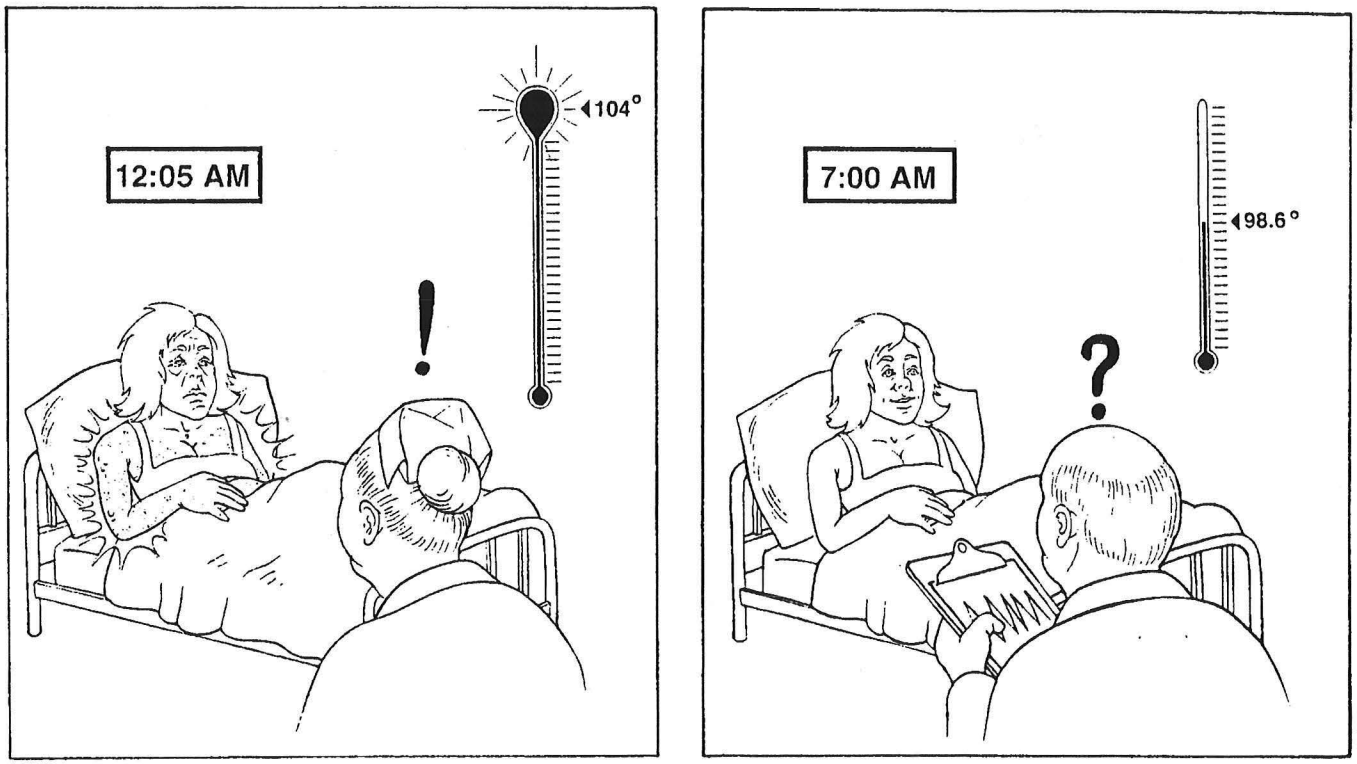

Internal Medicine Grand Rounds
5 January 1995

Introduction

Adult-onset Still's disease (AOSD) is a recently recognized systemic inflammatory disorder of unknown etiology and pathogenesis. Although this diagnosis was popularized by a 1971 report by Sir Eric Bywaters, similar cases have been sporadically reported thorough out this century. AOSD is likely to be the adult continuum of the better known systemic-onset juvenile arthritis (17,21,94). Characteristic manifestations include quotidian fever, evanescent rash, sore throat, arthritis, polyserositis, leukocytosis and seronegativity. Its clinical course is marked by systemic exacerbations and/or chronic arthritis.

There is no diagnostic test or pathognomonic histopathology and thus, the diagnosis of AOSD is often problematic. Early reports diagnosed AOSD in patients with long standing history of fever, arthritis and multiple systemic complaints. A large proportion of documented patients have suffered from extended delays in diagnosis due to protracted, expansive and often costly efforts to exclude occult infections or neoplasms. By contrast, AOSD is now considered after several week so in the evaluation of undiagnosed fever and rheumatic complaints. AOSD remains a painstakingly difficult clinical diagnosis, largely because of its rarity, protean manifestations and a lack of pathognomic features or diagnostic tests. This review will acquaint the clinician with this syndrome and provide an approach to these problems based on personal experience and information from the worlds literature.

Juvenile Arthritis (JA)

Juvenile arthritis (JA) is also known as Juvenile Rheumatoid Arthritis (JRA), Juvenile Chronic Polyarthritis or Still's Disease. Although the latter term is often broadly used in Europe to include all forms of JA, the term "Still's Disease" in refers to the systemic variant of JA that was described by George F. Still in 1897.

The growth of pediatric rheumatology as a subspecialty has enhanced our understanding of JA. Juvenile arthritis comprises several entities unified by the presence of a chronic inflammatory arthropathy with its onset before the age of 16 years (Ansell 1991, Fink 1983). These subsets are detailed below and are distinguished by the degree of articular involvement, onset age and other distinctive features (Table 1).

Pauciarticular-onset JA refers to involvement of 4 or fewer joints in the first 6 weeks, while polyarticular disease requires that 5 or more joints be involved at the onset and often continues throughout the disease. The pauciarticular group constitutes the vast majority of juvenile patients with arthritis and is subdivided into 2 types. *Type I Pauciarticular JA* comprises the largest percentage of JA patient and has a younger onset and a relatively good articular prognosis. A significant number of these children are at risk to develop iridocyclitis (uveitis) that may correlate with the presence of antinuclear antibodies (usually in low titer), but not autoantibodies to native DNA. A minority of pauciarticular-onset children will manifest *Type II Pauciarticular JA*. These children tend to be older-onset (> 9 years) males, who are often HLA-B27 positive and present with large joint monarticular disease, hip or spinal involvement. This subset has also been labeled juvenile spondylitis and includes children with early ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis (PsA), or inflammatory bowel disease (IBD) associated arthropathy. In the juvenile spondylitis population, arthritis usually precedes the onset of extra-articular disease (ie, enthesitis, uveitis, nail pitting, psoriatic plaques, diarrhea, etc.). Such patients may have a family history of AS, RS, IBD or psoriasis.

Polyarticular JA is seen in a minority of patients and often presents as a symmetric inflammatory polyarticular process with a propensity for chronicity and significant disability. Up to 10% of JA patients will be seropositive for IgM rheumatoid factor (RF) and are considered to be the juvenile continuum of adult rheumatoid arthritis and behave as such. The larger number of seronegative polyarticular JA patients are also at risk for aggressive joint disease, and should be monitored closely and treated aggressively.

Table 1. JUVENILE ARTHRITIS - Distinguishing features

Variant (Onset-type)	% JRA	Age	Sex	Clinical Features	ANA	RF	HLA	Prognosis
Pauciarticular - Type I	50%	1-8	F	Few joints	60%	0	DR5 DR6 DR8	Joints OK Uveitis 30-50%
Pauciarticular - Type II	10%	9-16	M	Few Joints, uveitis, Sxs of Reiter's, Psoriatic or IBD arthritis	0	0	B27	? Risk of spondylitis
Polyarticular RF+	5%	10-16	F	RA nodules weight loss	70%	100	DR4	Erosive arthritis >50%
Polyarticular RF-	15%	3-9	F	Symmetric polyarthritis	0	0		Erosive arthritis 15%
Systemic Onset	20%	5-16	M=F	Spiking fever, rash, serositis organomegaly anemia, WBC & ESR	0	0	Bw35 DR4	Erosive arthritis 20%

Systemic-onset JA is seen in roughly 20% of all JRA patients (Hafner 1986, Prieur 1984, Svantesson 1983). While this variant has been reported at all ages (up to age 16 years), the onset is most common between 5 and 15 years of age. Cardinal manifestations include high spiking, daily (quotidian) fevers, evanescent rash, arthritis, splenomegaly, lymphadenopathy, serositis, weight loss, neutrophilic leukocytosis, increased acute phase proteins and seronegative tests for ANA and RF. Up to 25% of these patients will develop a chronic symmetric polyarthritis that is indistinguishable from rheumatoid arthritis.

Similarity between systemic-onset JA and AOSD? Although frequently inferred, it is unknown if systemic-onset JA and AOSD are the same disease and share similar manifestations and clinical course. Neither systemic-onset JA nor AOSD have been ascribed an acceptable or unifying etiology to date. Nonetheless, despite the defined differences in onset age, both populations share a remarkable number of clinical features (Table 2). Few reports have attempted to compare these populations.

Table 2. Comparison of Systemic-Onset Juvenile Arthritis and Adult-Onset Still's disease

FEATURE	SYSTEMIC-ONSET JA*	AOSD
Sex	M = F	M = F
Quotidian Fever	99%	94%
Evanescent Rash	90%	87%
Arthritis	95%	93%
Prodromal Sore Throat	15%	70%
RES Involvement	40 - 70%	50 - 70%
Serositis	20 - 50%	20 - 40%
Serologic Tests	ANA(-), RF(-)	ANA(-), RF(-)
Carpal Ankylosis	28-50%	45-55%
Destructive Arthritis	30 (20-60)%	20-25%
HLA Associations	Bw35, DR2, DR4, DR5, Dw7	Bw35, DR4, Dw7

* based on reports of Fernandez-Vina, Lang, Cabane, Calabro, DelPaine, Tanaka, Talesnik

In Japan, Tanaka and colleagues have shown comparable clinical manifestations, treatment responses and prognosis for 26 systemic-onset JA and 19 AOSD patients (Tanaka 1991). The only disparate feature was the prodromal sore throat that was present in 68% of AOSD, but only 19% of systemic-onset JA patients. Cabane et al have shown that both juvenile and adult populations share a good prognosis with regard to systemic/extraarticular disease, but are at significant risk for chronic articular sequelae (Cabane 1990). Ultimately, 4/10 JA patients and 3/8 AOSD patients required total hip prosthesis because of advanced hip disease. The claim of problematic articular disease and sequelae has often been made for both juvenile (Cabane 1988, Mozziconacci 1983, Talesnik 1992) and adult populations (Cush 1985, Wouters 1986). Talesnik has also shown similar clinical courses when comparing 14 SOJA and 7 AOSD patients (Talesnik 1992). Nearly 50% of AOSD and systemic-onset JA patients both manifest chronic articular disease and that significant articular sequelae were only observed in these patients. Lastly, multiple investigators have demonstrated similar HLA associations (ie, HLA-Bw35 and DR4) for both populations (Miller, Wouters, Terkeltaub). Therefore, it appears that Still's disease is likely to be the same disorder in both children and adults. This notion is likely to prove valuable when considering data regarding etiology, pathogenesis, or therapeutic measures in Still's disease.

History

Juvenile arthritis was first described by George Frederick Still (1868-1941) who presented his thesis in an 1897 address entitled, "A special form of joint disease met with in children". This work was based on Still's clinical experience as a medical registrar and pathologist at The Hospital for Sick Children on Great Ormond Street in London. Still was the first to comprehensively describe the occurrence of a chronic arthritis in 22 children, 19 of whom he cared for. In fact, Still described three variants of arthritis found in children: rheumatoid arthritis, Jaccouds' arthropathy ("chronic fibrous rheumatism"), and the systemic-onset variant that still bears his name (Bywaters 1967). He described a chronic disorder of the joints that differed from adult rheumatoid arthritis and stressed the onset before the second

dentition, near equal female:male ratio, fever patterns, lymphadenopathy, splenomegaly, pericardial and pleural inflammation, anemia, lack of deformity and retardation of growth (Baum 1978, Birch 1973, Ansell 1991. Such a chronic arthropathy was also described in adults by Bannatyne and Chauffard (1896) who each reported patients with acute onset rheumatoid arthritis associated with fever, lymphadenopathy and/or splenomegaly.

The distinctive evanescent rash, termed a "rheumatoid rash" or "Still's rash" was not described by Still, but instead by Boldero who, in 1933, described the characteristic evanescent erythematous rash involving the extensor surfaces (Boldero 1933). Commentary offered by Professor F. Langmead suggested that pyrexial attacks were often associated with this rash. The characteristics of this distinctive exanthem were further described by Isdale and Bywaters who demonstrated a strong association between the "rheumatoid rash" and other characteristic features of Still's disease (eg. intermittent fever, lymphadenopathy, splenomegaly, leukocytosis, and an elevated erythrocyte sedimentation rate) (Isdale 1957). They also described the occurrence of this rash in 7 of 500 adults with rheumatoid arthritis. These 7 patients later comprised the basis for Bywaters 1971 report of Still's disease in the adult (Bywaters 1971).

Table 3. History of Still's Disease

1896 - Bannatyne and Chauffard

1897 - GF Still describes 22 JA pts.

1933 - Boldero: 1st described "rheumatoid rash"

1933 - Moltke: "Still's disease in adults"

1943 - Wissler & Fanconi: "subsepsis hyperallergica"

1971 - Bywaters: 14 females with AOSD

1973 - Bujak et al: 10 males with AOSD

1976 - Medsger et al: carpal ankylosis in AOSD

Sporadic descriptions of patients with manifestations similar to that described by Still are occasionally found and even predate Still's original description. Nonetheless, in 1933 Otto Moltke published a report entitled "Still's disease in adults". Moltke first questioned the arbitrary age limits ascribed to JA and Still's disease and suggested that this affliction may occur up to 35 years of age (Moltke 1933). He described 4 young males, ages 15-28, with an acute polyarthritis, fever, profuse perspiration, lymphadenopathy, sore throat, muscular atrophy, anemia and elevated erythrocyte sedimentation rates. Soon thereafter the 1940's French literature popularized the "Wissler-Fanconi syndrome" and "subsepsis hyperallergica" as terms to describe an analogous clinical picture of AOSD in young adults (95). Numerous descriptions have since appeared in the English literature describing similar clinical pictures without the label of AOSD. It wasn't until the early 1970's that Bywaters (1971) and Bujak et al 1973) revealed two large, independent clinical series establishing this juvenile entity as an adult affliction. Finally, in 1976 Medsger and Christy described the frequency of carpal ankylosis in AOSD. This distinctive pattern of arthritis along with the characteristic quotidian fevers and evanescent rashes constitutes the triad of features upon which the diagnosis of AOSD frequently rests.

Epidemiology

Reports of AOSD have appeared from many countries, involving many races and therefore seems unlikely that a significant racial geographic distribution. While all races have been affected, a majority of patients thus far reported have been Caucasian, although a substantial

number of Blacks, Orientals and Latinos have been described. Although the number of published reports has increased and enhanced the awareness of AOSD (Figure 1), it is a rarely encountered disorder. This review details over 400 patients reported in the English and foreign literature since 1971, with nearly half of these being individual case reports. The rarity of this syndrome is also suggested by the paucity (n = 13) of large series (ie, $\geq$ 10 patients) reported. The infrequency of AOSD has therefore contributed to the lack of reliable epidemiologic data regarding the incidence or prevalence in an adult population. The frequency of AOSD may therefore be inferred from rates observed in a juvenile population, and data drawn from large clinical series of AOSD and population based reports regarding fever of unknown origin (FUO).

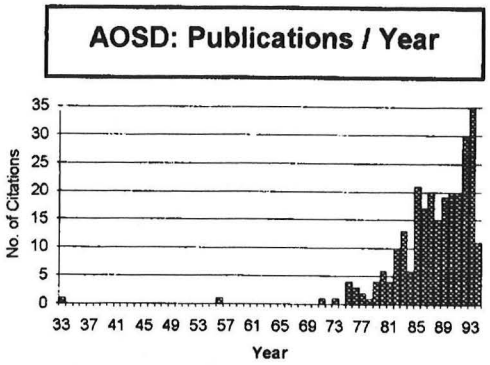

Figure 1. AOSD Publications

Several investigators have attempted to study the epidemiology of Juvenile Arthritis. Most have estimated the annual incidence rate of Juvenile Arthritis to be 10 cases/100,000 children (range 6 - 19.6 cases/100,000/year) (Cassidy 1988). Estimates of prevalence report that somewhere between 65 and 220 cases/100,000 children will be affected by JA. It is expected that 15-20% of JA cases will manifest the systemic-onset or Still's variant and thus, the annual incidence rate for systemic-onset JA will be 1-3 cases/100,000 children. Incidence rates of Still's disease in an adult population is likely to be considerably less. This notion is supported by the frequency in which AOSD is reported from rheumatologic centers and from large series of FUO patients.

Table 4. Frequency of AOSD

Author/Year	No. (%)	Time Period (yrs)	Patients Identified From
Bywaters 1971	14	20	Rheumatology unit survey
Goldman 1980	13	4	Rheumatology unit survey
Del Paine 1983	7	9	Rheumatology unit survey
Cush 1985	21	15	Rheumatology unit survey
Bujak 1973	10 (5%)	11	200 FUO patients
Aduan 1979	21 (6%)	15	347 FUO patients
Larson 1982	5 (5%)	10	109 FUO patients
Kazanjian 1992	5 (6%)	6	86 Community FUO patients
Knockaert 1993	4 (9%)	9	45 "Episodic FUO" patients

Studies from the University of Pittsburgh identified 21 AOSD patients seen at once center over a 15 year period (Cush 1986). Bywaters has reported a similar prevalence by reporting 14 patients from two hospitals over a twenty year period. Bujak et al identified 10 patients from 200 consecutive FUO patients under evaluation at the NIH. Additional data can be

Table 5. Clinical Manifestations of 382 AOSD Patients from World Literature

FEATURE	(+)/TOTAL	PERCENT
Male	173	
Female	189	
JRA Hx	39/258	15.1%
Quotidian T > 39F	301/320	94.1%
Fever T > 39F	346/349	99.1%
Still's Rash	311/358	86.9%
Rash	259/281	92.2%
Alopecia	20/136	14.7%
Arthralgia	295	99.7%
Arthritis	314/338	92.9%
Destr/Erosive Dz	55/253	21.7%
TMJ Pain	24/129	18.6%
Cervical Pain	24/52	46.2%
Myalgia	175/235	74.5%
Wt.Loss > 10%	83/127	65.4%
Sore Throat	190/268	70.9%
Lymphadenopathy	193/300	64.3%
Splenomegaly	139/327	42.5%
Hepatomegaly	91/228	39.9%
Hepatotoxicity	12/176	6.8%
Pleuritis	111/311	35.7%
Pericarditis	90/301	29.9%
Pneumonitis	50/229	21.8%
Abdominal Pain	46/153	30.1%
Pos. RF	17/341	5.0%
Pos. ANA	7/334	2.1%
Elevated ESR	288/291	99.0%
WBC >=10.0	282/305	92.5%
WBC >=15.0	173/244	70.9%
Thrombocytosis	44/97	45.4%
Hct < 35%	181/249	72.7%
Pos. Coombs	5/74	6.8%
Hemolysis	2/70	2.9%
Albumin <3.5gms	96/126	76.2%
Elevated LFT's	186/265	70.2%
Proteinuria	28/82	34.1%
Carpal Ankylosis	100/233	42.9%
Cervical Ankylosis	18/148	12.2%
Tarsal Ankylosis	16/84	19.0%
Sacroiliitis	10/110	9.1%

ascertain from the frequency of AOSD among patients with fever of unknown origin (FUO). In 1973 Bujak et al reported a 5% prevalence of AOSD among 200 FUO patients referred to the NIH. Larkin and Petersdorf (1982) also demonstrated a 4% prevalence of AOSD among 109 patients reviewed between 1970 and 1980. In most large series, AOSD has a 5-9% frequency and been noted to be the most common rheumatic cause of FUO (Aduan 1979, Larkin 1982, Kazanjian 1992). From these data and unofficial surveys of rheumatology units around the USA, a reasonable estimate would suggest an annual incidence rate of 1-3 new AOSD patients/year at most major medical referral centers.

Clinical Manifestations

AOSD is defined as a systemic inflammatory disorder of unknown etiology and pathogenesis that typically afflicts young adults. Characteristic manifestations include quotidian fevers, evanescent rash, pharyngitis, arthralgias, arthritis, hepatosplenomegaly, polyserositis, leukocytosis, and negative serological tests for antinuclear antibodies (ANA) and rheumatoid factor (RF) (Table 5). Its clinical course is marked by systemic exacerbations and/or chronic arthritis, frequently with disease-free intervals.

This multisystem inflammatory disease may manifest differently throughout the course of disease. Prominent systemic features are characteristic of AOSD early in the process, while articular manifestations may dominate the picture with chronicity. Nonetheless, all patients have a near textbook account of systemic-onset JA at the onset. Most patients will relate similar symptomatology with striking reproducibility from day to day. These symptoms evolve in a predictable daily fashion. This point is well illustrated by the wife of a 53 year old AOSD patients who kept a diary account of her husbands illness (Figure 2).

Figure 2. Letter from wife of patient DM:

Illness: Unknown crippling malady
Symptoms: Begins with an intense sore throat. Muscle weakness and soreness. Joints red and swollen with soreness. Itchy rash. Hearing loss. Can't eat. Alternatively feverish and shaking with cold. Practically immobile.
History: First had illness April 23rd and went to the hospital a week later. Chances of survival looked bad. Diagnosis was rheumatic fever. After the first week, it was decided that this was a wrong diagnosis. Tests of every sort were made and all proved negative. He was sent home May 19th, though he never felt good. His fever stayed up around 103°F. June was bad for him. By July he was working full time again.

Clearly is woman recorded several key features of this disease. This patient manifested with a characteristic rapid and severe onset of sore throat, cyclic fevers, rash and diffuse musculoskeletal manifestations. He looked gravely ill during the onset and underwent a lengthy and extensive search for an occult process. Response to antiinflammatory therapies sometimes takes weeks to months. This case also illustrates that the duration of disease and the potential for rapid recovery is unpredictable.

Sex and Age. Contrary to early disparate reports, males (48%) and females (52%) are equally affected. As this disease appears to be the adult counterpart of systemic-onset JA, the vast majority of AOSD patients are young adults with nearly 75% having their disease onset prior to age 35 (Figure 3). Although inclined to affect the young, AOSD has been reported in all age groups. Wouters et al (1986) noted that 26% of his 42 patients had a disease onset after the 35 years of ages. Less than 10% of patients will have their onset after age 50. Several patients have been reported with onset of AOSD in their 8th decade of life (Steffe 1983, Koga 1992, Uson 1993, Wouters 1986). This small subset of very late onset Adult Still's disease

are often difficult to diagnose, primarily because of age-related comorbid conditions, atypical cutaneous features and low grade fevers, rather than the spiking, characteristic fever of AOSD.

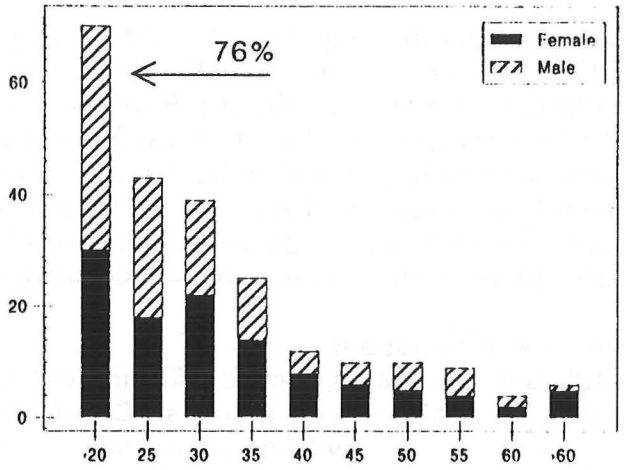

Figure 3. Age/Sex at Onset

Disease Onset. In the vast majority of patients, the onset of disease is heralded by a sore throat and other constitutional manifestations reminiscent of a viral syndrome. A prodromal sore throat is seen in over 70% of AOSD patients, seems to associate with onset or flare of disease activity. This nonexudative pharyngitis usually lasts days rather than weeks, is without microbacteriological evidence for infection and is unresponsive to antibiotics. It is unknown whether this represents mucosal infection or is a manifestation of AOSD related inflammation (Elkon 1982) is unknown. At the onset, constitutional features may be prominent and are often bothersome to the patient. These include severe myalgias or arthralgias, fatigue, anorexia, nausea and rapid weight loss. Weight loss is seen in 50-60% of patients and may be dramatic and rapid. Numerous patients have reported weight loss of 10-20 kg in the first month of disease activity. Overall, the constitutional manifestations will parallel the severity of systemic activity. Myalgias, fatigue, rash and serositis often show a diurnal rhythm and seem to worsen with the cyclical paroxysms of fever.

In most patients, the characteristic fevers and evanescent rash commence within 2-3 weeks of the sore throat. In a majority of individuals arthritis will manifest contemporaneously with fever and rash or shortly thereafter. However, few case reports have appeared in which an articular presentation antedates the fever and rash by up to 6 months. Del Paine and Leek (1983) point out that 5/7 patients had fever before arthritis and only 1/7 patients had arthritis before the onset of fever. There are no reliable parameters in onset period useful in predicting the severity of disease, clinical course or therapeutic response.

Quotidian Fever. Over 99% of patients with AOSD manifest with fever > 39°C at sometime during the course of their disease and greater than 94% will demonstrate the high spiking, quotidian pattern. Fever is highest during the onset of AOSD and in the younger age groups. Low grade fever and atypical fever patterns are sometimes encountered in older patients (>35 years) and sometimes late in the course of active disease, especially if articular manifestations dominate the clinical picture. The fever pattern in AOSD is characteristically quotidian (once/day) and sometimes double-qoutidian (twice daily) in pattern. A quotidian pattern produces daily febrile spike(s) and later returns to a normal baseline. A remittent pattern is characterized by spikes and an elevated baseline temperature. Bujak et al (1973) reported that 9/10 patients manifested a single quotidian pattern, 3/10 had a double quotidian pattern and 2/10 patients had a remittent pattern. With the initiation of antiinflammatory therapy or clinical improvement fever patterns may change (ie, a remittive fever may become quotidian or a double quotidian fever may become single quotidian). The highest recorded temperature to date was 107.6°F and nearly two-thirds of all patients will have peak temperatures of

greater than 40°C (Figure 4).

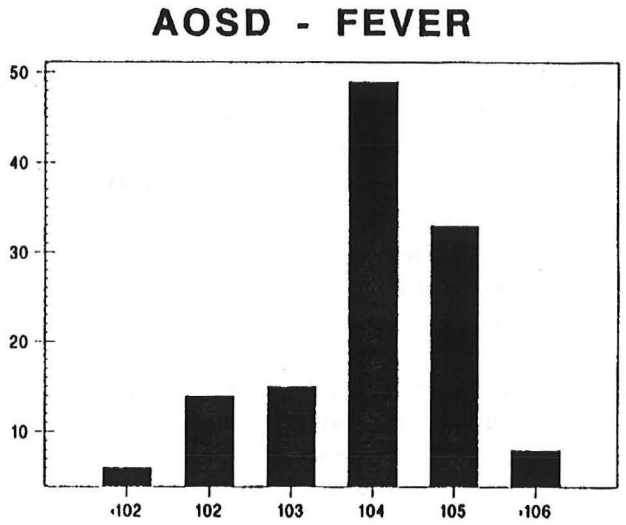

Figure 4. Tmax in AOSD

The febrile paroxysms are cyclic and tend to recur every 24, or sometimes every 12, hours. In 1897, Still noted the "pyrexial attacks show a curious regularity in their recurrence". Bywaters has noted that fever is "characteristically very high in the evening, returning to normal by morning.." (Bywaters 1967). The chronology of febrile paroxysms are quite similar from patient to patient. Paroxysms are heralded by shaking chills, followed by 2-4 hours of high fever (>104°F), and ending with defervescence and drenching sweats. A majority of AOSD patients will note the onset of fever usually late at night (between 10PM-2AM). It has also been described in the late morning (11-12 AM) or late afternoon (4-6 PM). More importantly, individual patients demonstrate a striking tendency to reproduce the fever at the same time of day, each day, until appropriate antiinflammatory therapy is begun. As such, AOSD patients often appear normal during early morning physician rounds and tend to "flare" late at night when rash and fever may go unnoticed or undocumented (Cover illustration). Febrile spikes are often accompanied by contemporaneous exacerbation of other systemic manifestations (ie, rash, myalgias, arthralgias, fatigue, serositis, headache or nausea). The degree and frequency of fever correlates best with constitutional manifestations, less so with other systemic complaints (serositis, RES, leukocytosis, ESR), and shows little relationship to articular manifestations.

Evanescent Rash. The classic, evanescent rash of Still's disease was first noted by Boldero in 1933 and is referred to as a "Still's rash" or "rheumatoid rash" despite the absence of an association with adult seropositive rheumatoid arthritis. While 92% of all patients demonstrate some cutaneous manifestation during their illness, the more specific Still's rash is seen in 86% of patients with AOSD. This rash displays a characteristic periodicity, appearance and location (Table 6) (Isdale 1956). Evanescent by definition, the rash frequently appears during febrile attacks and may last for several hours following defervescence. In general, the Still's rash lasts hours and changes daily, although in some patients, the duration of rash correlates well with the degree of systemic activity and may last for days without change. It is typically salmon-colored (infrequently erythematous), maculopapular and may be confluent or show areas of central clearing. It is usually found on the extremities (extensor surfaces), trunk, neck, and rarely manifests on the face. Two characteristic and common findings are Koebner phenomena and dermatographism. Koebnerization refers to the reproduction of characteristic isomorphic lesions at sites of earlier

Table 6. Rheumatoid or "Still's" Rash

- Characteristically evanescent (worse with fever)
- Salmon-pink, faint erythema
- Maculopapular on trunk, neck, & extremities
- Dermatographism
- Koebner phenomenon

- Uncommon in AOSD: pruritus, urticaria, dermal plaques, facial rash, alopecia, erythema nodosum, Raynauds

physical trauma. Dermatographism is an exaggerated cutaneous urticarial response to cutaneous stimuli (ie, the scratch test). While some claim this rash is typically nonpruritic, I have found that up to 35% of patients have complained of pruritis at sometime during their course and that urticaria is not uncommon. Seldom is pruritis a prominent manifestation and if so, should raise suspicions of alternative diagnoses, such as primary biliary cirrhosis or urticarial vasculitis. Kaur et al (1994) has recently described another cutaneous manifestation of AOSD, namely persistent dermal plaques which have the same distribution but, are usually erythematous. Cutaneous anergy is also common in the face of active disease.

Atypical cutaneous manifestations include alopecia, raynauds phenomenon, and petechial, malar, circumoral or erythema nodosum-like lesions. Cutaneous manifestations of AOSD are most prominent early in the disease and tend to decline with time, evanescent rashes are uncommon in those with more than 10 years of disease.

Pathological examination of lesional skin shows a nonspecific chronic inflammatory picture with a perivascular mononuclear, and seldom polymorphonuclear, infiltrate, vascular dilatation and dermal edema. Serial skin biopsies done by Ridgway (1982) showed episodic deposition of circulating immune complexes. In all instances skin biopsies and immunofluorescent studies have been nondiagnostic.

Articular Manifestations. The presence of arthritis completes the triad of AOSD, however its presence and extent is less evident at the onset than during the disease course. As stated earlier, it is rare that AOSD will present with arthritis prior to the onset of other systemic and extraarticular manifestations. Morning stiffness, myalgias and arthralgias dominate the early clinical picture. Tenosynovitis is also common early on and is often overlooked or mistaken for arthritis or arthralgias (Table 7).

Table 7. Musculoskeletal Features of AOSD

COMMON	UNCOMMON
Myalgias	Tenosynovitis
Arthralgias	Periostitis
Fleeting Arthritis	Tarsal ankylosis
Chronic Polyarthritis	Cervical ankylosis
Syn.Fluid WBC = 3-40K	Myositis
Carpal Ankylosis	Micrognathia
Erosive Hip Dz	Rhabdomyolysis
HLA-DR4(+)	DIP capsular calcification

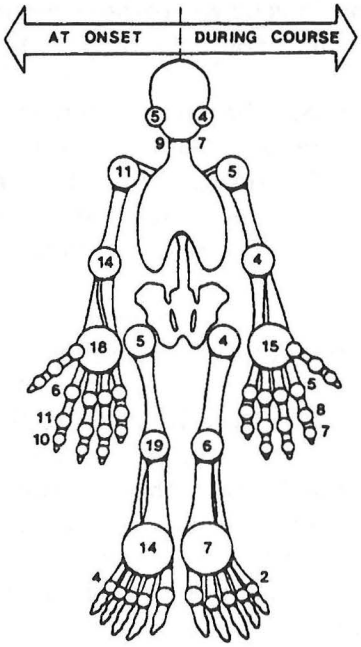

Figure 5. Arthritis in AOSD

During the first 6 mos. the onset of polyarthritis is expected in >90% of patients and may involve large and small articulations. Affected joints most commonly include (in decreasing frequency): the knees, wrists, ankle, elbow, shoulder, PIPs, DIPs, TMJ and cervical spine. Early on, synovitis may be fleeting, migratory or additive (Figure 5). However, with chronicity synovitis predominantly involves the wrist, with

a less commonly the tarsal, cervical, PIP and DIP joints. Neck pain is seen in nearly half of patients at sometime in their disease and is either due to cervical myalgia or arthritis. Several authors have noted the late development of Heberdens-like lesions at the PIP joints in patients (Cush 1985, Wouters 1986). Sacroiliac involvement is uncommon, but has been reported by Bywaters (1971) and Goldman et al (1980). Although both symmetric and asymmetric poly- or oligoarthritis is commonly observed, chronic monarthritis is decidedly rare and should suggest other diagnoses.

The association of AOSD with bony ankylosis of carpal and carpometacarpal articulations first noted by Medsger and Christy in 1976 has since been confirmed by others (Wouters, Pouchot, Zajaczek-Grabowaka). The incidence of carpal - carpometacarpal ankylosis approaches 50% for most clinical series and is also prevalent among systemic-onset JA patients (Talesnik). Bony ankylosis tends to be a symmetric process occurring as a consequence of active synovitis. Once ankylosis is complete, the wrist is a painless, irreversibly fused articulation. The incidence of bony ankylosis is somewhat greater if one examines the tarsus and cervical spine. Ankylosis at these sites is further radiographic evidence favoring a diagnosis of AOSD. Ankylosed articulations are rarely evident on initial evaluation or early in the disease, but evolve quickly (ie, 18-36 mos.) in the face of active articular disease. Whether the presence of ankylosis portends a graver articular course is debatable, however carpal ankylosis is more common among those with a chronic articular course (Cush 1985).

The risk for erosive and destructive polyarthritis is significant, especially in those with a chronic polyarticular course and in those with hip involvement (Wouters 1986, Cush 1985). In the Pittsburgh study, we found an 19% incidence of disability (ARA functional class III/IV disease) among our AOSD patients, with an even greater risk (40%) for those with a polyarticular onset and course (Cush 1985). Nearly 20-25% of all patients will progress to class III/IV disease because of early erosive and late secondary degenerative arthritis. Erosive disease has its greatest impact on weight bearing joints. The most common form of joint surgery is hip joint replacement.

Arthrocentesis frequently reveals type II inflammatory synovial fluid. Leukocyte counts usually range from 3.0-40.0 x 10^3 WBC/mm^3, often with a polymorphonuclear predominance. Several reports have noted a decrease in synovial fluid complement levels. Numerous synovial biopsies have consistently shown a chronic synovitis, with proliferation of synovial cells and infiltration of lymphocytes and plasma cells. Electron micrographs have demonstrated type B synovial cell hypertrophy.

Muscle Involvement. Generalized myalgias are seen in 75% of AOSD patients and is frequently a prominent complaint at the onset of disease. Occasionally, mild-moderate elevations of muscle enzyme have been reported, as have poorly documented cases of myopathy and abnormal electromyograms (Esdaile 1979, Bujak 1973). Nonetheless, overt myopathy or myositis has seldom been reported (Moreno-Alvarez 1993, Samuels 1989, Schwarzberg 1982). Similarly, myocardial involvement has been rarely noted in both children and adults with Still's disease (Bank 1985, Hosaka 1992, Sachs 1990, Ward 1988). One should not overlook the possibility of myositis or myocarditis if CPK elevations are present. The distinction between AOSD and dermatomyositis may be difficult (Moreno-Alvarez 1993), but is likely to be determined by the degree of muscle inflammation and the character of the

cutaneous lesions. Rare report of rhabdomyolysis (Samuels) and diaphragmatic weakness due to myositis (Braidy 1984) have appeared in the literature.

Reticuloendothelial Disease. Lymphadenopathy, hepatomegaly (with or without hepatic dysfunction), and/or splenomegaly is very common early in the disease and reflects tissue infiltration with inflammatory cells and heightened immunologic activity within the reticuloendothelial system (RES).

Palpable or radiographic demonstration of splenomegaly is seen in 42% of individuals and is most likely the result of hyposplenism and passive congestion. Hyposplenism and splenic sequestration of red blood cells may account for the rapid anemia and splenomegaly often seen in the acute stages of AOSD. Elkon et al (1982) utilized radiolabeled RBC's in 9 AOSD patients to gauge their splenic function. Both active patients and those in remission demonstrated impaired clearance of RBC's. Other investigators have used this method of testing splenic function and have shown an inverse relationship between the presence of circulating immune complexes and splenic clearance of RBC's. These authors postulated that hyposplenism may predispose AOSD or alternatively, splenic function may be impaired as a result of AOSD. Pathological analysis provided by splenectomy during exploratory laparotomies have shown sinus hyperplasia, histiocytosis and slight infiltration of leukocytes (Esdaile, Bujak, Medsger).

While nearly 40% of patients are found to have hepatomegaly, nearly 70% demonstrate abnormalities of hepatic enzymes at some time during their illness. Liver biopsies done in the face of active systemic disease have demonstrated periportal mononuclear infiltrates (lymphocytes, plasma cells) and Kupffer cell hyperplasia. Lobular inflammation, focal hepatocellular degeneration, and periportal fibrosis have also been infrequently noted by some authors. Tender hepatomegaly well with abnormalities of hepatic enzymes, which show equal percentage of hepatocellular and cholestatic inflammatory changes. Further evidence of hepatic dysfunction is provided by modest elevations in the prothrombin time and often impressive hypoalbuminemia. Hypoalbuminemia may be rapid and profound and is seen in 76% of AOSD patients. Elevation of the serum bilirubin is uncommon, but when present may suggest active hemolysis, salicylate-induced hepatotoxicity, or severe hepatocellular damage and risk of hepatic failure (Reginato 1987). Chronic liver disease has been reported in one individual, with the authors stressing the discordance between the hepatic dysfunction and other features of AOSD activity. This is in contrast to most individuals in whom elevations of hepatic enzymes often subsides with the initiation of anti-inflammatory therapy. These changes of inflammatory hepatitis are sequelae to systemic inflammation and heightened cytokine activity (ie, IL-6, IL-1).

A relationship between hepatic dysfunction and salicylate-induced hepatotoxicity in AOSD has been suggested, but is probably overstated. The incidence of salicylate hepatotoxicity in juveniles with Still's disease is far greater than that seen in this adult population and may reflect the functional immaturity of the liver in a juvenile population. The risk for hepatotoxicity in this population is associated with high doses of salicylates therapy (90-100 mg/kg) and the secondary rise in unbound, pharmacologically active ASA with the disease-related decline in serum albumin. Rich and Johnson reviewed ASA hepatotoxicity in the juvenile population and suggested that ASA hepatitis 1) was dose related and reversible; 2) manifested identical pathology and enzyme elevations, as AOSD hepatitis; and 3) that

eosinophilia preceded the rise of enzymes and the subsequent fall in eosinophil count coincided with maximal hepatic dysfunction (Rich 1973). Our review discloses 12 well-documented cases of salicylate hepatitis in AOSD. Esdaile et al (1979) demonstrated that 60% of salicylate treated patients improved their hepatic abnormalities and stated that "..in some patients ASA may be acting to unmask underlying disease related abnormalities". Acute liver failure and chronic liver disease have been sporadically reported (Tesser, Esdaile, Reginato).

Lymphadenopathy is seen in 65% of AOSD patients. Despite the frequency of this finding, lymphadenopathy is seldom the dominant presenting feature. Lymphadenopathy most frequently manifests as generalized mild to moderate nodal enlargement of nontender lymph nodes located in the cervical, axillary, epitrochlear, or inguinal regions. Mesenteric, para-aortic and hilar nodes may be discovered during diagnostic imaging. Tenderness or focal enlargement of a solitary node or chain should suggest either infectious or neoplastic etiologies rather than AOSD (Table 8). Lymphangiograms are of no value and lymph node biopsies yield nonspecific, reactive hyperplasia or lymphadenitis, sometimes accompanied by histiocytic infiltration.

Table 8. When to Consider Lymph Node Biopsy in AOSD

- Focal, tender, or rapidly changing adenopathy
- Adenopathy in AOSD patients > 50 yrs
- When clinical/lab features conflict with Dx of AOSD
- Peripheral smear - shows many myeloid precursors or atypical lymphocytes

On occasion, lymph nodes removed from patients with established or presumed AOSD show atypical changes that may question the diagnosis of AOSD. At least 5 cases of Kikuchi's syndrome or necrotizing lymphadenitis, have been described (Ohta 1988, Lyberatos 1990) in patients with established AOSD. Kikuchi's syndrome is a benign disorder, often associated with viral infection, and may manifest as fever, tender lymphadenopathy, hepatomegaly, leukopenia and elevated ESR (Ohta 1988). Because of similar features Ohta et al has suggested that it is plausible that many of the patients reported with Kikuchi's syndrome may have AOSD also. Alternatively, necrotizing lymphadenitis may be a milder more localized form of the more systemic RES involvement seen in AOSD (Ohta 1990). Histologically, Kikuchi's syndrome must be distinguished from malignant lymphoma, angioimmunoblastic lymphadenopathy, etc.

Valente et al (1989) reviewed 8 lymph node biopsies from 97 AOSD patients seen at the Mayo Clinic and found distinctive pathology in 7/8 AOSD patients. These biopsies demonstrated an intense, somewhat atypical, paracortical hyperplasia with nodal effacement and scattered atypical immunoblasts. Although the original pathologic interpretations included malignancy (3 cases), mixed lymphoma (1 case) and angioimmunoblastic lymphadenopathy (2 cases), prolonged follow-up confirmed the diagnosis of AOSD. Several other authors have questioned the lymphomatous appearance of AOSD lymph node biopsies (Quaini 1991, Reichert 1992), while others have documented the occurrence of lymphoma in patients with established AOSD (Trotta 1993, Kawasaki 1995). Trotta et al described a case of B cell lymphoma (associated with a trisomy 12 karyotype) arising 2 years after typical AOSD without lymphadenopathy (Trotta 1993). Biopsy was prompted by occurrence of persistent lymphadenopathy and the development of hypogammaglobulinemia, paraproteinemia and hyperferritinemia. In contrast, Reichert (1992) has reported a case of AOSD wherein the

lymph node histology was interpreted as "malignant T cell lymphoma". Nonetheless, the patient responded well to minimal antiinflammatory therapy only and showed no evidence of lymphoma after 3 years of therapy. These authors appropriately point out that the clinician should be aware that "lymph node histology in AOSD may mimic malignant lymphoma".

Serositis. Pleuritis (40%) and pericarditis (30%) are quite common when detected by pleuritic chest pain, auscultatory rub, or the demonstration of pleural or pericardial fluid by abnormal chest radiographs or echocardiogram. In some, the pain of serositis may be the presenting complaint, while in others it may be an asymptomatic finding. Pleural effusions are usually bilateral, seldom large enough to be symptomatic, and rarely produce pleural thickening. Thoracentesis often yields bloody, exudative effusions with white blood cell counts ranging from 3-20 x $10^3/mm^3$ with a polymorphonuclear predominance. Pleural biopsies have not yielded diagnostic information showing only acute and chronic inflammation.

Pericarditis is the more worrisome finding as some AOSD patients have presented as acute cardiac tamponade and have required emergency pericardiocentesis or pericardial stripping (Alukal, Jamieson, Strumpf, Drouot, Esdaile, Desablens). While pericardial tamponade is quite rare, pericarditis is seen in 30% of AOSD patients. Clinically, such patients present with acute sharp chest pains, with dyspnea and partial positional relief. Documented cases have responded well to drainage and high dose corticosteroids. Pericardial fluid is frequently bloody and usually exudative with with WBC counts ranging from 1.2-26,000 (PMN predominance). Myocarditis is rarely seen in AOSD, but tends to occur in patients with very active systemic disease and evidence of pericarditis and/or pleuritis.

Pneumonitis is found in over 20% of patients and often presents a diagnostic challenge. These individuals often appear septic with complaints of fever, dry cough, dyspnea and are found to have pulmonary infiltrates that are unresponsive to anti-infective therapy. Infiltrates tend to be bilateral more commonly than unilateral, alveolar or interstitial in pattern and responds well to antiinflammatory therapy with steroids. Several authors have noted restrictive changes on spirometry and few progress to chronic respiratory insufficiency as a result of aggressive parenchymal inflammation (Pedersen 1991, Corbett 1983, Cantor 1987, Vaan hoeyweghen 1993). Braidy (1984) has demonstrated that diaphragmatic weakness from myositis may contribute to the pulmonary pathology noted.

Abdominal pain is seen in 30% of patient, primarily during the onset phase. Abdominal pain is often diffuse and may be accompanied by nausea, vomiting and sometimes diarrhea, but seldom do these features dominate the clinical picture. Abdominal pain has been ascribed to serous peritonitis (Pollet 1990, Bujak 1973), mesenteric adenitis, hepatic or splenic distention, ileus or small bowel obstruction.

Miscellaneous Features and Uncommon Associations. Renal disease is uncommon, yet many patients will manifest minor and transient proteinuria (34%) during periods of febrile paroxysms. Chronic or substantial proteinuria is uncommon and likely to be secondary to amyloidosis. Amyloidosis has been reported in a handful of patients and should be suspected with persistent hematuria and proteinuria. While most cases have been reported from Europe (Wendling, Hory), several AOSD patients from the United States have been reported (Harrington 1981, Elkon 1982, Larson 1985, Medsger 1976, Terkeltaub 1981). CNS disease is also rare and may manifest as sensorineural hearing loss, mental status changes, aseptic

meningitis, meningoencephalitis, peripheral neuropathy, ulnar tunnel syndrome or orbital tenosynovitis (Browns syndrome) or inflammatory orbital pseudotumors. Other uncommon associations include leukopenia, mild eosinophilia, disseminated intravascular coagulation (DIC), Sjogrens syndrome, Raynauds, nodules, uveitis, episcleritis, retinal hemorrhages or exudates, psoriasis, autoimmune thyroid disease, glomerulonephritis, nephrolithiasis, hemophagocytic syndrome and Takayasu's arteritis.

Several authors have suggested an association between AOSD and pregnancy. However, the the lack of a consensus (despite the number of patients reported) and the high percentage of young women among AOSD patients suggests that this an association is coincidental rather than causal.

Laboratory and Radiographic Abnormalities

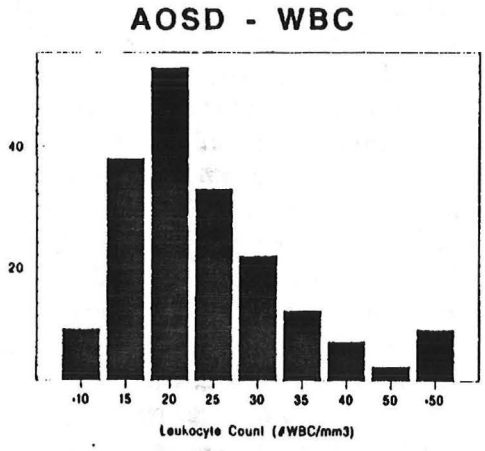

Figure 6. WBC counts in AOSD

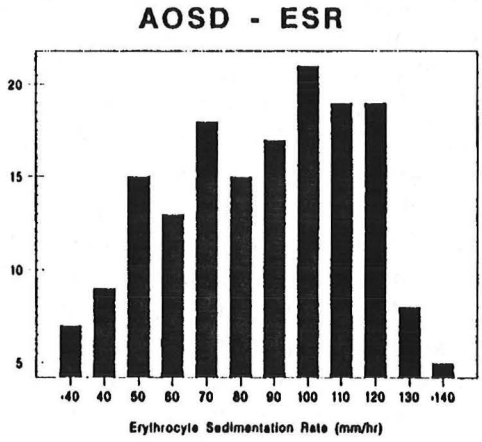

Figure 7. ESR in AOSD

In parallel with systemic inflammation, laboratory investigations are notable for the consisent absence of antinuclear antibodies and rheumatoid factor, but the impressive degree of neutrophilic leukocytosis (92%) and elevated sedimentation rates (Table 5, Figures 6 and 7). The simultaneous occurrence of both may prove to be a valuable feature in the diagnosis of AOSD (Cush 1984). Leukocyte counts generally range between 12,500-40,000 cells/mm^3, with the highest recorded to be 69,000. Nonetheless, nearly 20% of patients may demonstrate marginal WBC elevations (10-15K), in which case the identification of other characteristic features will be required to affirm the diagnosis of AOSD. Acute phase reactants are markedly elevated in AOSD, including the ESR, C-reactive protein (CRP), serum amyloid A (SAA), thrombocytosis and serum ferritin. Over 90% of AOSD patients have an ESR > 50 mm/hr and 50% have and ESR > 90 mm/hr. Extreme leukocytosis or leukopenia are rare in AOSD (Scopelitis) and should raise the possibility of an occult leukemia or lymphoma (Trotta 1993, Sugawara 1993).

During periods of active systemic disease red blood cell counts may drop precipitously and in parallel with the weight loss and/or serum albumin - all reflecting systemic inflammatory activity. Aplastic anemia has been reported, presumably as a consequence of therapy (Medsger 1976, Kahl 1988). Rare reports of hemolytic anemia and/or DIC should question

the diagnosis of AOSD or the possibility of an associated hemophagocytic syndrome (Coffernils 1992, McPeake 1993).

Elevations in the hepatic enzymes frequently occur (70%) as a manifestation of inflammatory hepatitis, rather than the rare ASA or NSAID-induced hepatotoxicity. Both cholestatic and hepatocellular patterns of enzyme elevations have been observed. Depressed serum albumin levels between 2.0 and 3.5 mg% is seen in over 75% of patients. Other reported laboratory abnormalities include: eosinophilia; hypergammaglobulinemia (50% of pts); IgA deficiency (5 cases); circulating immune complexes (20-50% of pts); and elevated ASO titers in one-third of patients. Serologic tests for complement, HLA-B27, cold agglutinins, serum immunoelectrophoresis, and thyroid studies are consistently normal.

Hyperferritinemia. It has been suggested that extreme elevations of the acute phase reactant, ferritin, may be of diagnostic value in assessing patients with AOSD. Hyperferritinemia with values between 4000 - 30,000 ng/ml have often been reported in association with the onset and/or flare of disease activity (Ohta 1987, Pelkonen 1986, van Reeth 1994). Levels as high as 250,000 ng/ml have been reported (Coffernils 1992). Ohta has reported on 38 Japanese patients with active systemic AOSD. Of these, only 7 patients had normal ferritin levels, 26 were greater than 1000 ng/ml and 20 were greater than 4000 ng/ml (Ohta 1989). In a survey of 20 systemic-onset JA patients, Pelknonen found elevated ferritin values in 19/20 JA patients at the onset of their disease. Values above 1000 ug/l were seen in 50% of patients, while only 3/20 patients had values > 4000 ug/l. In contrast, Coffernils et al (1992) has reported normal levels in 40% of active AOSD patients, 30% with levels between 300 - 1000 ng/ml and only 30% with levels above 1000 ng/ml. Ferritin is found in nearly all tissues, with the highest concentrations in the reticuloendothelial systems (liver, spleen, bone marrow) and heart. It has been suggested that highest levels are common among patients with abnormal hepatic enzymes (Ohta), although this has not been universally observed (van Reeth 1994, Pelkonen 1986, Schwarz-Eywill 1992). van Reeth et al (1994) has shown by isoelectric focusing that circulating ferritins were uniformly basic and almost completely desialylated and that this distinguished active AOSD from inactive AOSD or patients with other systemic rheumatic disease. The reason underlying the inadequate sialylation of ferritin in AOSD is unknown, but may contribute to its impaired clearance and accumulation in the circulation. van Reeths patients with active AOSD demonstrated exceptionally high mean ferritin values (4519 ng/ml) when compared with inactive AOSD patients (233 ng/ml) (Figure 8). Multiple reports have shown a close correlation between elevated ferritin and the high spiking fevers of Still's disease (Pelkonen 1986). Moreover, ferritin levels are rapidly responsive to effective antiinflammatory therapy (Pelkonen) (Figure 9).

Ferritin is known to increase in the face of infection, neoplasia and inflammatory states, and is thus an acute phase reactant. Ferritin synthesis and release is strongly influenced by cytokines (Rogers 1990, Tsuji 1991). Gonazalez-Hernandez et al (1989) has shown that of the 5,600 ferritin levels done at one center over an 8 month period, hyperferritinemia (>4000 ng/ml) was observed in 37 instances and these were due to polytransfusion states (14 pts), neoplasia (7), AOSD (4), chronic hepatitis (4), and 2 each with hemochromatosis, pancreatitis, sepsis and 2 patients were undiagnosed. Other common causes of raised ferritin levels include chronic leukemia, malignant lymphoma, melanoma, neuroblastoma, germ cell tumors, hepatic necrosis, and rarely rheumatoid arthritis or SLE. The predictive value of increased

Serum Ferritin in AOSD

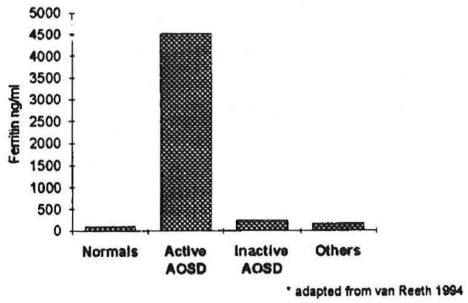

Figure 8. Hyperferritinemia in AOSD

ferritin levels is only likely to be helpful if greater than 4000 ng/ml. Otherwise, mild-moderate elevations would reflect a nonspecific acute phase response that might accompany a number of common inflammatory febrile disorders. Hyperferritinemia in AOSD is unrelated to iron metabolism and is more likely to be a consequence of cytokine induce augmented synthesis by the RES or hepatocyte damage resulting in increased release. Lastly, some reports have suggested that hyperferritinemia is associated with histiocyte hyperactivity that may lead to the seldom reported association of Still's disease and the hemophagocytic syndrome (Morris 1991).

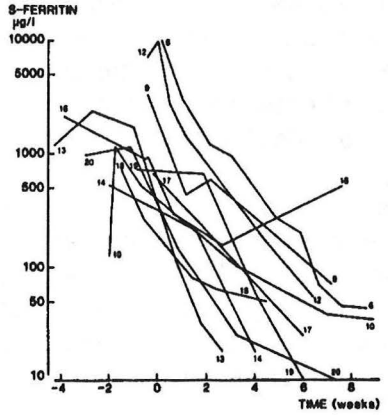

Fig 9. Ferritins response to Steroids in Still's Dz

The hemophagocytic syndrome has been reported to be either familial or associated with viral infections, neoplasms or immune mediated disorders (McKenna 1981). It is characterized by proliferation of mature nonneoplastic histiocytes with prominent hemophagocytic activity within the bone marrow, spleen or lymph nodes. Patients often present with impressive fever, lymphadenopathy, hepatosplenomegaly, and cytopenias. Still's patients have a similar presentation, but are hardly ever cytopenic. When reported in association with Still's disease, the hemophagocytosis syndrome has occurred following seroconversion to one of several viruses, including: EBV, hepatitis A, varicella and influenza A (Coffernils 1992, McPeake 1993, Morris 1985). Extremely high ferritin levels are often seen in viral associated hemophagocytosis syndrome and malignant histiocytosis (Coffernils 1992). The presence of this complication is associated with very high mortality rates. Disseminated intravascular coagulation, hemolytic anemia profound cytopenias are often present in those who are severely affected by this syndrome.

Carpal ankylosis is a distinctive feature of AOSD and should be sought for. Nearly half of patients will manifest ankylosis after several years of disease activity. While carpal ankylosis is common and distinctive in AOSD, it is uncommonly observed be seen in other familiar rheumatic disorders (ie, rheumatoid arthritis, psoriatic arthritis, chronic Reiter's syndrome), thus limiting its predictive diagnostic value. Nonetheless, the identification of early erosive disease and osteopenia, followed by late ankylosis in a pericapitate distribution (Figure 10) may have diagnostic and possibly therapeutic implications. Similarly, a striking tendency for intertarsal ankylosis and ankylosis of the zygoapophyseal joints of the cervical spine (Garcia-

Morteo 1988, Bywaters 1971, Healy) has been reported.

Differential Diagnosis

For those who manifest the AOSD triad of fever, rash and arthritis, diagnostic considerations must be tailored to the age and distinguishing features at presentation. Personal experience suggests that the most difficult cases involve the differentiation between AOSD and patients with acute systemic viral syndromes, Reiters' syndrome, dermatomyositis, or inflammatory bowel disease. Depending on the clinical picture, AOSD will need to be distinguished from: infectious etiologies, mycobacterial infection, subacute bacterial endocarditis, occult abscesses, leptospirosis, brucellosis, malaria, granulomatous hepatitis, sarcoid, Whipples' disease, acute rheumatic fever, Sweets syndrome, serum sickness, hypocomplementemic urticarial vasculitis, polyarteritis, lymphoma and leukemia.

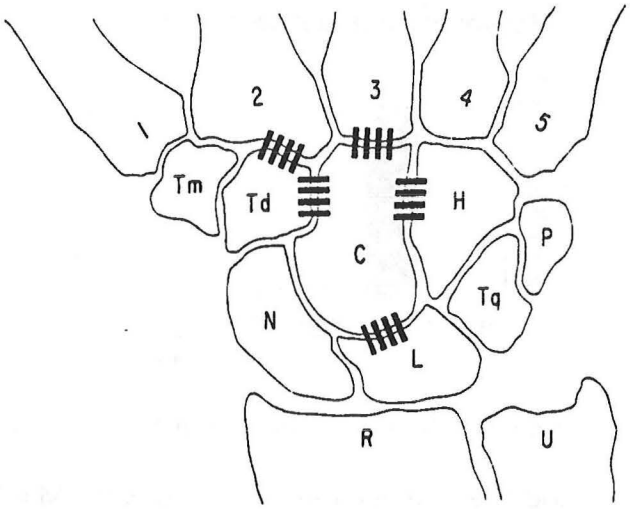

Figure 10. Pericapitate pattern of ankylosis in AOSD

Bywaters has suggested up to half of juvenile arthritis patients classified as "probable Still's disease" will go on to develop either psoriatic arthritis, ankylosing spondylitis, IBD arthritis, rheumatic fever, SLE, dermatomyositis, scleroderma, leukemia, reticulosarcoma, or neuroblastoma (Bywaters 1967). Other diagnoses that have commonly been misconstrued with AOSD include: EBV lymphadenitis, acute leukemia, psittacosis, myelodysplastic syndrome and lymphoma.

Diagnosis

In decades past, AOSD patients were subjected to numerous invasive and noninvasive investigations in search of an occult infective or neoplastic diagnosis. In due course it has become apparent that this syndrome lacks a diagnostic serologic test or histopathology and thus, today AOSD remains a clinical diagnosis of exclusion.

With greater awareness of this syndrome, AOSD is now being considered earlier in the course of evaluation patients with fever, dermatitis and arthritis. Whereas prior to 1980, knowledge of AOSD was the major obstacle to diagnosis, henceforth the primary challenge will rest with the ability to make an early and correct diagnosis. Requisite steps should include a comprehensive, noninvasive workup, documentation of fever pattern, and patient observation over a minimum of at least 6 weeks prior to the diagnosis of possible AOSD. A probable diagnosis will required an extended period (ie, 6 months) of follow-up and reassessment. Guidelines published for the evaluation of FUO are applicable to AOSD patients and will minimize the cost and invasiveness of diagnostic testing (Smith 1986, Kazanjian 1992).

Diagnostic criteria have been developed by various investigators (Table 9) and each have been tested for sensitivity and specificity in both AOSD patients and FUO controls (Yamaguchi

1992). Whereas the criteria of Cush and Yamaguchi both have specificities greater than 92%, the sensitivity of Yamaguchi is superior to Cush (96% vs. 80%, respectively). Nonetheless, these criteria may prove useful in the study of other AOSD patients or in the evaluation of individual patients with presumed AOSD.

Table 9. Proposed Diagnostic Criteria for Adult-Onset Still's Disease

Reginato et al 1987

Definite AOSD: all 4 major
Probable AOSD: Fever + arthritis + 1 major + 1 minor

Major Manifestations	Minor Manifestations
Persist/intermittent fever	Serositis
Evanescent rash	Sore throat
Poly- or oligoarthritis	Hepatic dysfunction
Neutrophilic leukocytosis	Lymphadenopathy
	Splenomegaly
	Organ involvment

Yamaguchi et al 1992

AOSD = Total of $\geq$ 5 criteria (including 2 major)

Major Criteria	Minor Criteria
Fever > 39°C	Sore throat
Arthralgia > 2 wks.	LN or splenomegaly
Still's rash	Liver dysfunction
Neutrophilic leukocytosis	Negative RF & ANA

Goldman et al 1980

* High spiking fever
* Polyarthritis
* Leukocytosis > 10,000/mm^3
* Negative serum RF
* One of the following:
  - lymphadenopathy
  - splenomegaly
  - serositis
  - evanescent rash
* No evidence for other causes

Cush 1984

Definite AOSD: $\geq$ 10 points + 6 months observation
Probable AOSD: $\geq$ 10 points + 6 weeks observation

Major Criteria (2 points)	Minor Criteria (1 point)
Quotidian fever > 39°C	Onset age $\leq$ 35 yrs.
Still's rash	Arthritis
↑ WBC + ↑ ESR	Prodromal sore throat
Negative RF & ANA	RES involved or ↑LFTs
Carpal ankylosis	Serositis
	Cervical/Tarsal ankylosis

Therapy of AOSD

Therapy is directed at controlling inflammatory symptoms and signs without exposing the patient to unacceptable toxicity. Historically, the juvenile literature tells us that high dose salicylate (ASA) is the drug of choice. Responses to ASA similar to that seen in acute rheumatic fever are likewise thought to be of diagnostic import. Nevertheless, the risk of Reyes syndrome and the incidence of ASA-induced hepatotoxicity limits the utility of ASA in the systemic-onset JA population. In adults, ASA is better tolerated but, is only marginally efficacious, with less than one third of AOSD patients responding during the acute phase of their illness. Nonsteroidal antiinflammatory drugs (NSAID) have been used for over 20 years and have been shown to be effective in up to 60% of AOSD patients (Table 10). Indomethacin (1-2 mg/kg/day) has been the most utilized NSAID, although all other NSAIDs may be equally effective when used at comparable antiinflammatory doses. The sustained release form of indomethacin is preferred by many patients because of once or twice daily dosing (ie, Indocin-SR 75 mg. bid). The practice of adding ASA to high dose NSAID therapy for a presumed additive or synergistic effect, should be discouraged because of the unacceptable toxicity without apparent benefit.

A majority of patients will require daily corticosteroids to control systemic features of AOSD. Unfortunately, low doses of prednisone (ie, <20 mg/day) and alternate day therapy have proven ineffective in most patients. Once the decision is made to start corticosteroids, prednisone should be started at 40-60 mg/day, in divided doses if necessary. Reliance on prednisone will be greatest early in the disease and should diminish over time. Therefore, if the patient is still steroid dependent after 3-6 months, the addition of a steroid sparing therapy with methotrexate (MTX), azathioprine (AZA) or hydroxychloroquine should be considered. Pulse steroids have been utilized and should be reserved for the morbidly ill. Systemic disease activity will require aggressive antiinflammatory therapy with NSAID, prednisone, MTX or hydroxychloroquine and will not respond to other conventional DMARDs (ie, gold or penicillamine) (Ansell 1991, Cush 1985). Multiple reports have documented the efficacy of low dose weekly MTX in the control of fever and other systemic features of AOSD. These data suggest that MTX may be used early, as a steroid sparing agent, to control systemic and articular disease and limit the toxicities associated with prolonged high dose corticosteroids therapy (Kraus 1991, Aydintug 1992, Hollingsworth 1989, Samuels 1989).

Chronic articular disease should be managed like rheumatoid arthritis and seems to respond in a similar manner to either gold salts, penicillamine, MTX, AZA, sulfasalazine, etc. Experimental therapies shown to be efficacious in a few patients include: IV gammaglobulins; pulse cyclophosphamide; cyclosporin A; and γ-interferon (IFNγ) (Silverman 1990, Shaikov 1992, Bjerkhoel 1988, Pernice 1989).

Table 10. Therapeutic Responses in 221 AOSD patients

	Acute Therapy		Maintenance Therapy	
Therapy employed (dose)	Responder	Nonresponder	Responder	Nonresponder
ASA only ($\geq$ 4 gr/d)	28	48	18	2
+ indomethacin	11	9	11	0
+ prednisone	28	0	-	-
Indomethacin (2 mg/kg/d)	33	17	17	2
+ prednisone	9	1	5	2
Prednisone only ($\geq$ 20mg/d)	71	13	32	3
+ ASA + indomethacin	9	0	5	2
Gold Salts (IM)			21	9
+ prednisone			12	8
Remittive Rx (PCM, AZA, Plaquenil, SSZ, CTX)			16	7
+ prednisone			15	12

Prognosis

Of 221 therapy patients surveyed above, 33 were in remission off all medications, 107 were still on medication and insufficient data exists for the remaining 81 patients. This is similar to the data gleaned from several large series that conclude that self-limiting disease is uncommon (ie, < 20%) and that intermittent systemic disease or chronic articular disease

requiring therapy is to be expected (Cush 1985, Wouters 1986, Pouchot 1991).

The majority of patients with systemic disease only will have self-limiting episodes of less than 1 year and will fair well once the disease abates. However the potential for recurrence and life threatening complications cannot be discounted. Such complications include pericardial tamponade, myocarditis, DIC, hepatic failure, inflammatory pulmonary disease and amyloidosis. For those patients developing chronic articular disease, the long term outcome is largely determined by the extent and duration of articular involvement. Thus, a polyarticular onset and course or the development of hip disease tends to correlate well with poor functional outcomes after prolonged followup. The presence of HLA DR4 may contribute to a poorer outcomes, while HLA-Bw35 may offer some protection, with a better joint prognosis and a propensity for self-limited disease (Terkeltaub 1981, Wouters 1986).

Etiology

No etiopathogenesis has been acceptably proposed or proven for AOSD. An infectious etiology or trigger has been inferred based upon the prodromal sore throat that heralds the onset or flare of disease. Most clinical manifestations are reminiscent of features seen during self-limited viral syndromes. Lastly AOSD is occasionally associated with other viral-related syndromes, such as the hemophagocytic syndrome and Kikuchi's syndrome. Although no etiologic factor has been identified, some have advocated that an infectious, and possibly viral, agent initiates a cascade of the immunological events resulting in the characteristic clinical syndrome of AOSD (Wouters 1988, DeVere-Tyndall 1984, Newkirk 1994). Multiple investigators have demonstrated that persistence of a viral antigens, especially rubella, in patients with JA and AOSD (Newkirk 1994, Chantler 1985). Whether such antigens remain immunogenic and contribute to the pathogenesis of systemic or articular disease is unknown. Reactivity to these ubiquitous microbes may therefore be dependent upon genetic, immunologic and other unidentified host factors. When sought for, microbiologic evidence of coexistent viral infections is found in nearly half of patients. Nonetheless, is unknown whether such identification constitutes causal proof. In many instances these findings are either coincidental or may reflect a nonspecific response to heightened immunologic activity.

Table 11. Implicated Organisms in AOSD

Rubella	Staphylococcus
Epstein Barr virus	Y. enterocolitica
Coxackie B4	Brucella abortus
Mumps	Mycoplasma
Adenovirus	Borrelia burgdorferi
Echovirus 7	
Cytomegalovirus	
Parainfluenza	
Parvovirus B19	

Chantler et al (1985) has demonstrated the persistence of Rubella in the mononuclear cells of nearly one-third of JA patients, including those with systemic-onset JA. Using semiquantitative PCR, Newkirk et al has shown that PBMC from AOSD patients more frequently contain viral genome for rubella than do normal controls (83% vs. 33%). In addition, AOSD patients carry a 4 fold greater amount of viral genome than do normal controls ($P=0.03$) and that the viral genome is primarily found in B cells and monocytes, but not T cells (Newkirk 1994). These data suggest that AOSD patients may be more susceptible to rubella infection and/or are unable to clear virus from their mononuclear cell population (monocytes and B lymphocytes). Impairment of RES function in AOSD has been suggested by Elkon et al (1982) who has documented hyposplenism and the impaired ability of the RES

to clear heat-damaged red blood cells. Lastly, the observation of clinical efficacy using subcutaneous γIFN in the treatment of refractory systemic JA questions whether the anti-viral effect of IFN lead to clinical improvement (Pernice 1989).

AOSD - A Circadian Cytokine Syndrome?

I would like to conclude with the suggestion that AOSD is a cytokine driven disorder and that the curious diurnal variations in fever and other systemic features suggest an underlying circadian rhythm. Predictable paroxysms of fever have also been noted in malaria wherein the periodicity of tertian or quartan fevers has been linked to the growth cycle of the parasites (Kwiatkowski 1989). Rupture of schizont has been associated with the release of TNFα and other cytokines capable of acting as endogenous pyrogens (Kwiatkowski 1993).

Endogenous pyrogens include a number of well known cytokines, such as interleukin-1 (IL-1), IL-6, TNFα, the interferons, and macrophage inflammatory protein (MIP1α). The in vivo effects IL-1, IL-6 and TNFα have been well characterized and many these correspond to the distinctive features of AOSD (Table 12). Both IL-1 and IL-6, but not TNFα, have been shown to be produced in a circadian fashion (Zabel 1990, Gudewill 1992, Arvidson 1994).

Table 12. Clinical Effects of IL-1, IL-6 and TNFα

Clinical Feature	IL-1	IL-6	TNFα
Fever >.39°C	+	+	+
Exanthem	+	0	+
Myalgias	+	+/-	+
Arthralgia/arthritis	+	+	+
Weight Loss	+	+	+ +
Leukocytosis	+	+ +	+
↑ Acute Phase Response	+	+ +	+

It therefore seems likely that IL-6 or IL-1 may act as effector molecules that give rise to many of the features that characterized AOSD. DeBenedetti et al has demonstrated markedly elevated levels of IL-6 in the serum and synovial fluid of patients with systemic-onset JA (SOJA) (DeBenedetti 1991, 1994). Moreover, these levels correlate with the level of thrombocytosis and synovitis. Sequential analysis of IL-6 production showed diurnal variation, with peak levels between 1800 and 2200 hours, with the lowest levels approximating the early morning rise in serum cortisol (Zabel 1990). David et al (1990) has also shown that serum IL-6 levels paralleled the febrile spikes in SOJA. Increases in TNFα followed the fever by 5 hours and IL-1 levels were low during the fever and rose once the fever dissipated.

These data suggest that in Still's disease, the diurnal alterations in fever and inflammatory symptomatology are paralleled by the increased production of IL-6 and possibly, other unidentified pyrogens or cytokines. Factors responsible for the circadian production of cytokines are unknown, but may relate to host susceptibility and immunologic reactivity to viral antigens (ie, rubella) sequestered within monocytes, macrophages and other immunocompetent cells.

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