Still's Disease in Adults* **

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In 1897, Dr. George F. Still described 22 children with a form of chronic joint disease which differed from rheumatic fever (1). Twelve of these children had a syndrome characterized by glandular and splenic enlargement which, with a characteristic fever pattern, rash, and arthritis, has become known as Still's disease (2). Subsequent investigators have described patients over age 16 presenting with similar signs and symptoms suggesting that this syndrome is not specific for children (3, 4, 5, 6). We recently studied a patient in whom the diagnosis of adult onset Still's disease was made.

Case. J. O. is a 44-year-old male who was referred to the Medical College of Virginia Hospitals (MCVH) on May 22, 1973 for evaluation of fever of 12 weeks duration. In addition to the fever, he had a 25 pound weight loss over a four month period, shaking chills, drenching night sweats, and progressive weakness and anorexia. Two months prior to admission, pain developed in his right knee and soon progressed to involve the right great toe, both wrists, and fingers of both hands. Aspirin at variable doses, prescribed by his private physician, was not helpful. He had been admitted to another hospital on May 7, 1973, where he underwent extensive laboratory and radiological evaluation, but the cause of his symptoms was not ascertained and he was transferred to MCVH for further diagnostic investigation.

Past medical history revealed that 12 years earlier, he had been seen in another hospital for arthritis involving his right wrist which quickly resolved. He acknowledged mild morning stiffness in his fingers for several years prior to his present illness but denied swelling, heat, redness, or decreased function in any joint. Adult onset diabetes mellitus had been diagnosed one year earlier and had been treated with tolbutamide, 500 mg daily.

Family history was noncontributory. The patient lives in a rural setting and is employed as a maintenance worker in a local seat belt factory. He denied the use of cigarettes or alcohol.

Physical examination on admission revealed a T 102°F (39°C), P 92/min., BP 110/58. He was in no distress. Pertinent findings included a congenital terminal nystagmus on lateral gaze and numerous nontender, firm, small, freely movable lymph nodes in the anterior cervical region, right axilla, left inguinal, and left epitrochlear areas. The lungs and heart were normal. The liver measured 10 cm and was palpable 2 cm below the right costal

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margin on deep inspiration. The spleen was not palpable. The right knee contained a moderate effusion but was neither warm nor tender. Both wrists were tender and evoked pain on passive range of motion. The remainder of the physical examination was normal.

Representative hematological values were: hemoglobin 10 gm%, WBC 12,000/mm^3 with 75% PMN's, 20% lymphocytes, 5% mononuclear cells, and an ESR 66 mm/hr. (Wintrobe). Representative chemistries included an albumin 3.2 gm%, total bilirubin 0.3 mg%, alkaline phosphatase 125 mU/ml, lactic dehydrogenase (LDH) 325 mU/ml (LDH-4 and 5 isozymes elevated), and serum glutamic oxaloacetic transaminase (SGOT) 70 mU/ml. The following tests were either normal or negative: urinalysis, blood cultures, latex flocculation, antinuclear antibody test (ANA), LE cell preparations, HBAg (by CEP), heterophil, T_3, T_4, sickle cell preparation, serologic test for syphilis (STS), blood urea nitrogen (BUN), creatinine, calcium, phosphorus, uric acid, amylase, antistreptolysin-O (ASO) titer, febrile agglutinins for typhoid, brucella, proteus, tularemia, and toxoplasmosis. Several blood sugar determinations were above the normal range, the highest being 180 mg%. Intermediate and second strength PPD's were negative and a mumps antigen elicited 15 mm of induration. Examination of the cerebrospinal fluid and bone marrow was not helpful. Routine and tuberculosis (Tbc) cultures from synovial fluid, urine, sputum, bone marrow, spinal fluid, and liver were negative. Upper gastrointestinal series (UGI), barium enema, IVP, hand, wrist, and chest x-ray studies were normal. Cervical spine films showed only mild degenerative arthritis. A liver scan was normal. Serum protein electrophoresis showed increased α-1 and α-2 globulins only. Analysis of synovial fluid from his right knee revealed a WBC 1,144/mm^3 with 30% polymorphonuclear leukocytes (PMN's), 31% lymphocytes, and 39% mononuclear cells.

A biopsy of subcutaneous tissue from the patient's left forearm showed a granulomatous reaction with moderate vasculitis and lipid-filled macrophages. He underwent an exploratory laparotomy with celiac lymph node and liver biopsies. Histopathological interpretation of the liver was reactive hepatitis compatible with a number of systemic diseases and the lymph node showed chronic lymphadenitis with lipoid granuloma. A congo red stain for amyloid was negative.

The patient was discharged June 25, 1973 on 3.6 grams of salicylates per day in divided doses. Because of his mild glucose intolerance, it had not been felt necessary to supplement his diabetic diet with any drug therapy. He was readmitted July 15, 1973 because of persistent quotidian fever, pain in his proximal interphalangeal joints, and morning stiffness. In addition, he now complained of pruritus over his entire body associated with temperature elevations, although no rash was present. He had gained five pounds since the first admission. At this time he was found to have pain over the medial aspect of his right ankle. X-rays of his hands and wrists now revealed patchy osteoporosis and cystic lucencies involving the radial styloid and proximal row of carpal bones (Fig. 1). He was discharged July 25, 1973 on salicylates and Benadryl® with a diagnosis of seronegative rheumatoid arthritis.

Outpatient visits over the next two months documented continued quotidian fever (Fig. 2) and progressive arthritis, and on September 27, 1973, he was readmitted to the hospital. A maculopapular rash, lasting hours, mostly on his arms, now accompanied the temperature elevations. A synovial biopsy of the right knee was performed showing nonspecific chronic synovitis (Fig. 3). Serologic testing continued to be negative. A diagnosis of adult onset Still's disease was made and, in addition to salicylates, gold therapy was instituted.

Over the ensuing months, the patient has felt better, has gained 17 pounds, and has experienced general improvement of his joint symptoms. The general malaise, anorexia, night sweats, chills, and persistent quotidian fever have abated. He still, however, has an occasional temperature elevation with an associated fleeting rash.

Discussion. Despite the increasing sophistication of the practice of medicine and its effect on our diagnostic capabilities, certain patients continue to baffle the most astute clinicians with fever of undetermined origin (FUO). Many of these patients turn out to have neither infectious nor neoplastic disorders but, rather, connective tissue diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or even acute rheumatic fever (ARF) (7, 8). Still's disease, which is commonly included among the causes of FUO's in children, has been shown to persist or recur in adulthood

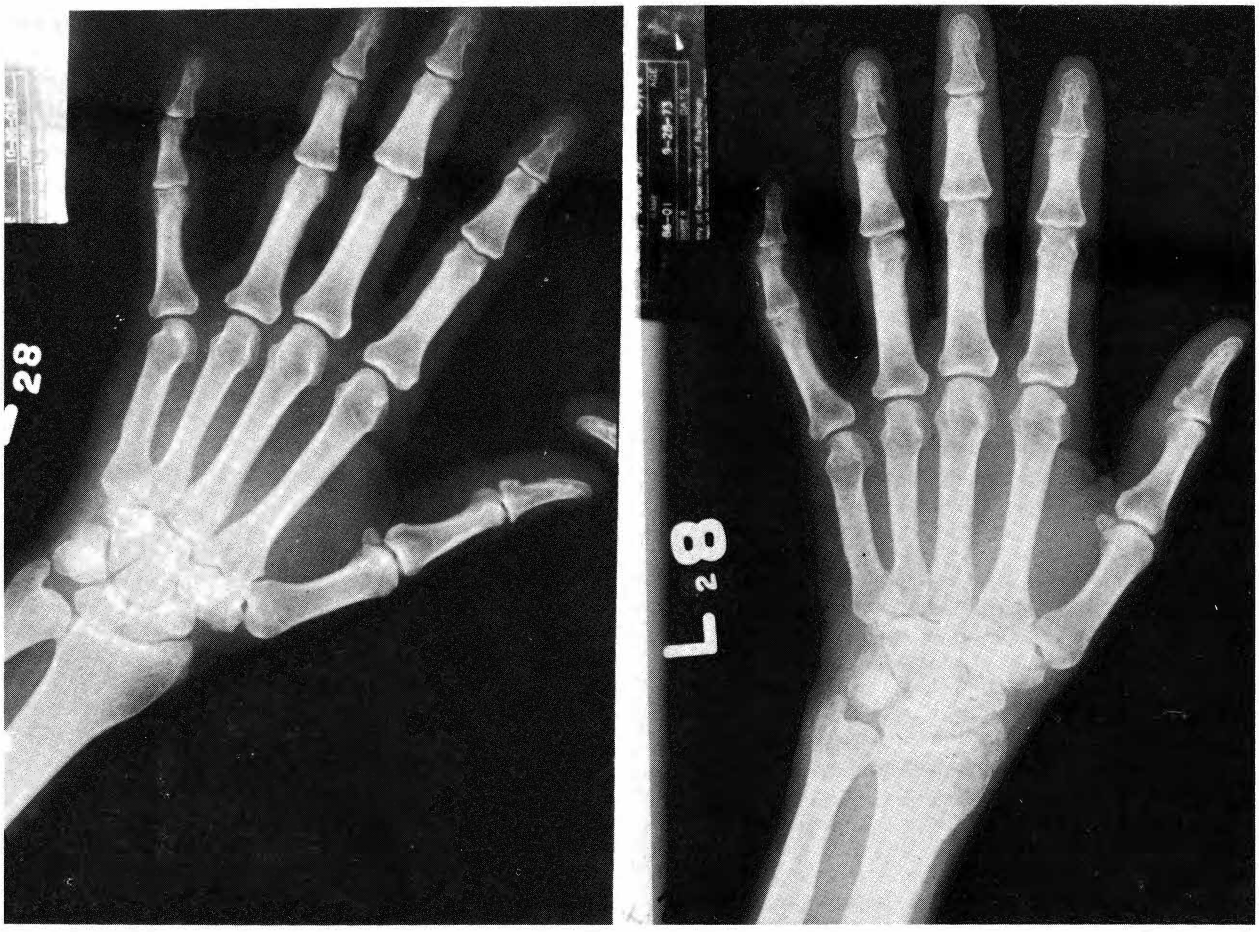

Fig. 1—The hand and wrist on the left are normal in May 1973. A subsequent x-ray of the same joints in September 1973, illustrates the cystic lucencies and osteoporosis.

(5, 9). In recent years, however, attention has focused on a syndrome indistinguishable from childhood Still's disease occurring *de novo* in adults (3, 4, 5, 6).

Although there is no pathognomonic finding in adult onset Still's disease, certain features may be diagnostically useful. A quotidian fever pattern is the rule rather than the exception. This quotidian pattern may, however, be preceded or succeeded by a remittent or even double quotidian pattern. It has been pointed out, also, that the fever may be present for weeks or for months before arthritis develops (2, 5). Often, in association with the temperature elevations, a macular or maculopapular rash is noted particularly in areas of pressure or friction. This migratory, evanescent eruption may recur for months in adult onset Still's disease in contrast to that of acute rheumatic fever which rarely persists longer than two weeks (2, 3, 5). Of historical interest concerning the rash of RA and juvenile rheumatoid arthritis (JRA), in 1956 Isdale and Bywaters (10) reported four adults who developed a rash in association with other systemic manifestations indistinguishable from Still's disease. It was not until 1971, however, that these same women, along with ten others, were the clinical material for Bywaters' original description of adult onset Still's disease (3). Many biopsies of the rash in adult onset Still's disease have been described, yet they all show nonspecific histology, that being a mild subepithelial and perivascular polymorphonuclear leukocyte infiltrate (3, 4, 5, 10).

Lymphadenopathy and splenomegaly correspond significantly with the high fever, rash, and leukocytosis in childhood Still's disease (11). While no mention was made of lymphadenopathy, By-

waters (3) did note splenomegaly in two of his patients with adult onset Still's disease, whereas six out of ten of those cases reported from the National Institutes of Health (NIH) had splenomegaly and seven had lymphadenopathy. As in our patient, the liver may be involved with an inflammatory infiltrate which may recur with relapses of the disease and return to normal after recovery (5).

It has been said that chronic erosive arthritis involving cervical spine, sacroiliac, temporomandibular, or peripheral joints may occur in a third or more of children with acute onset JRA (11, 12, 13). Radiographic studies of these areas have not been helpful in the adult form of JRA. Although erosive arthritis including cervical spine involvement has been documented in seven of 26 cases, it is usually not severe or widespread (3, 4, 5). On the other hand, arthralgias or nonerosive arthritis may be very common but transient (3, 4, 5). The histology of the synovium may vary in severity from a very mild inflammatory reaction as reported by Bywaters (3) to a very intense inflammatory response as reported by Fabricant *et al.* (4).

In addition to the more characteristic features of adult onset Still's disease, namely fever, rash, lymphadenopathy, and arthralgias or nonerosive arthritis, one may encounter less specific symptoms. Myalgias, particularly of the lumbar, cervical, or thigh regions, sore throat, alopecia, pericarditis pneumonitis, and pleurisy, with or without a pleural effusion, have been described. Abdominal pain may occur which possibly reflects mesenteric lymphadenitis (5). In contrast to JRA, especially the oligo-

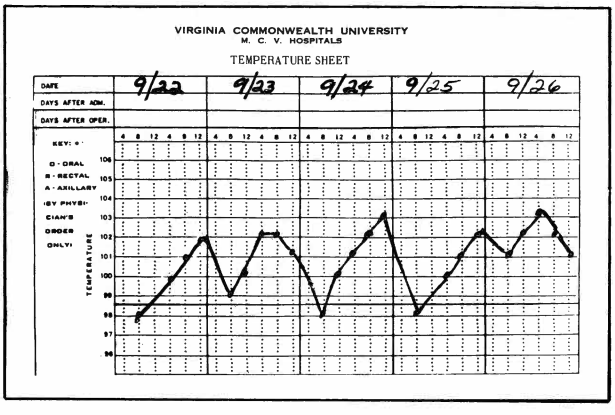

Fig. 2—Oral temperatures recorded by the patient show the characteristic quotidian fever pattern of adult onset Still's disease.

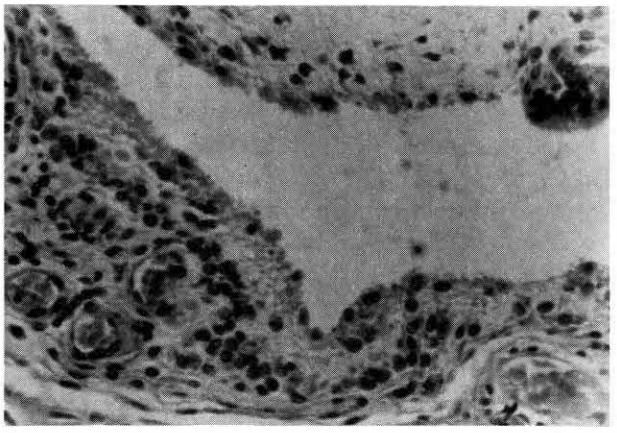

Fig. 3—Light microscopy of synovium obtained by needle biopsy shows synovial lining cell proliferation and round cell infiltration with edema and endothelial proliferation of the sublining tissue.

articular form, iridocyclitis is notably absent in adult onset Still's disease. Likewise, rheumatoid nodules are not found.

As in many other connective tissue disorders, laboratory confirmation of adult onset Still's disease is not possible. Characteristically, rheumatoid factor is not found in the sera of these patients. Probably the most helpful finding is a neutrophilic leukocytosis. Of 12 patients with adult onset Still's disease, ten had WBC's greater than 18,000/mm^3 with over 70% neutrophils. Similarly, the ESR is elevated and often parallels disease activity (3, 4, 5). In only two patients with adult onset Still's disease has synovianalysis been reported, one showing a white opaque fluid with 69,000 WBC/mm^3 and the other, a yellow turbid fluid with 14,000 WBC/mm^3. In both aspirates, over 90% of the cells were polymorphonuclear leukocytes (4).

Because of the therapeutic and prognostic implications, physicians should be especially aware of a syndrome occurring in an adult, which is indistinguishable from Still's disease. Salicylates in doses which maintain a serum level of 25–30 mg% may induce symptomatic relief in many patients with adult onset Still's disease. Others do not respond as favorably and may require additional therapy. Of the ten patients with adult onset Still's disease comprising the NIH study, four responded to high-dose aspirin or indomethacin therapy (5). Chloroquine, used in conjunction with aspirin, reportedly maintained a normal ESR and good func-

tional state in one of Bywaters' patients, although erosive carpal bones and ankylosis of C 2–3 were present (3). Ultimately, however, the majority of patients with adult onset Still's disease have been treated with prednisone. Alternate-day therapy is preferred if one must resort to steroids; however, it has been noted by Bujak *et al.* (5) that symptoms recur on the off day unless the steroids are accompanied by very high salicylate doses. Even steroid therapy may not fully suppress the activity of adult onset Still's disease. One patient who subsequently had a remission on gold therapy was reported by Fabricant *et al.* (4) to have experienced active symptoms despite 30 mg of prednisone daily. The only other mention of gold therapy in adult onset Still's disease has been by Bywaters in his original series, where he commented on two patients who improved while taking gold. In one patient, the gold therapy was instituted while steroids were being withdrawn and in the other patient, it was given in addition to aspirin and prednisone (3). Thus, our patient represents the only report to date of a patient with adult onset Still's disease responding to gold therapy without previous or concomitant corticosteroid therapy.

Conclusion. A patient with adult onset Still's disease and a review of the literature pertinent to this syndrome is presented. Several features should be emphasized: 1) Adult onset Still's disease should be considered in those patients with FUO who have an evanescent rash, leukocytosis, arthritis, or arthralgias and lymphadenopathy. 2) The prognosis of adult onset Still's disease is good with few patients, so far reported, developing chronic erosive arthritis. 3) The majority of patients with adult onset Still's disease will respond to salicylates, although some will require corticosteroids or gold therapy.

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