EARLY RECOGNITION OF RHEUMATOID DISEASE WITH COMMENTS ON TREATMENT

By Robert D. Gauchat, M.D., and Charles D. May, M.D.

Department of Pediatrics, College of Medicine, State University of Iowa

Within the past 10 years, increasing attention has been focused on children with chronic deforming arthritis. With few exceptions, such children have claimed interest of those concerned primarily with rheumatoid arthritis in adults, orthopedic surgeons and workers in the field of physical medicine, to whom these patients have presumably been referred for care by pediatricians and general practitioners. Lack of general pediatric interest in this disease is suggested by the small number of pertinent papers in the pediatric literature. Furthermore, the relative lack of importance of these children in the general thinking of students of arthritis is suggested by the fact that a current statistical study of the incidence and prevalence of rheumatoid arthritis in a large American metropolitan area has been arbitrarily limited to patients 15 years of age or older.1

Is rheumatoid arthritis sufficiently common within the pediatric group to deserve pediatric attention? Although there have been only a few statistical studies, the available evidence suggests that the incidence of new cases in the general population, under 15 years of age, is roughly the same for rheumatoid arthritis,2 diabetes mellitus3 and nephrosis,4 approximately 3 new cases per 100,000 persons under 15 years of age each year. In round numbers, 1200 new cases of rheumatoid arthritis, of diabetes and of nephrosis occur annually within the childhood population of this country. Parallel comparison of the amounts of attention paid to these three groups of patients by pediatricians would belabor the point. These juvenile victims of rheumatoid arthritis certainly deserve increasing pediatric attention, and we suggest that they also present many stimulating challenges.

The purposes of this paper are: to depict the classic features of juvenile rheumatoid arthritis; to emphasize the feasibility and importance of early diagnosis; to comment briefly on therapy; and to arouse interest in the etiologic, pathogenetic, diagnostic, and therapeutic problems which the disease still presents. For this occasion, it seems preferable to present the broad outlines of the subject as gradually discerned from our experience and the literature rather than an extensive documentation of the various details.

During the first third of the Twentieth Century, following the publication of Still's classic paper in 1897,5 physicians were distracted from comprehensive consideration of the clinical manifestations of juvenile rheumatoid arthritis. Instead, discussion centered on whether or not Still's disease and rheumatoid arthritis were manifestations of the same pathologic process. More recently both of these terms have come to be regarded as misleading. Descriptively more appropriate is the term "rheumatoid disease," proposed by Ellman and Ball in 1948,6 because it emphasizes the generalized systemic nature of the disease process, of which arthritis is but one component, regardless of the age at onset.

The etiology of rheumatoid arthritis remains unsolved. Because of the well-known tendency of children to manifest more vivid systemic reactions to many diseases than do adults, it seems possible that advances in our understanding of the pathogenesis of this disease may come from more careful study of the early stages of acute rheumatoid disease as seen in children.

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ADDRESS: (R.D.G.) University Hospital, Iowa City, Iowa.

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CLINICAL MANIFESTATIONS

Onset

The disease may have its onset at any age in childhood, even during the early months of life. Most commonly it begins during the second, third, and fourth years, but there is a second peak of incidence, for girls but not for boys, during the adolescent years. The mode of onset seems to bear no relation to age of onset, and is widely variable—from an acute and violent systemic illness preceding the appearance of joint manifestations to a slow, smouldering development of swollen joints and muscular debilitation with few gross systemic manifestations. As this latter type of onset and course offers no real diagnostic difficulties, it will be disregarded in the subsequent description.

Fever

A troublesome and challenging problem in differential diagnosis is presented by the child, usually under 6 years of age, who has an abrupt onset of high spiking fever usually from 40 to 41.2°C, often accompanied by profuse sweating and abdominal pain, and associated with voluntary reduction in physical activity, emotional depression, anorexia and a general appearance of profound acute illness. This fever is only slightly affected by therapy with salicylates, and does not respond to antibiotics. Bouts of fever may persist for days, weeks or months; spontaneous remissions and exacerbations extending over years are typical. Figure 1 depicts a portion of such a febrile episode which failed to respond to the therapeutic use of salicylates and antibiotics.

Rash

At the early stage of the disease, a highly significant clue as to the true nature of the patient's illness may often be obtained by

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**Fig. 1.** Febrile course characteristic of acute rheumatoid disease. The patient, S.G., a 12-year-old white girl, had severe arthralgia involving the knees, hips and wrists. Numerous cultures of blood and urine yielded no bacteria. Salicylates and antibiotics did not modify the fever.
careful and persistent observation of the skin. There is a rash which is a dependable diagnostic sign of acute rheumatoid arthritis. If carefully watched for, it can be observed in 75 to 80% of cases during febrile periods. It appears to be an index of activity of the disease process. This characteristic skin eruption is a recurrent, fleeting, salmon-pink, discrete, maculopapular, nonurticarial rash, fairly widespread in a scattered distribution over the extremities, trunk and frequently the face. As may be seen in Figure 2, there is a tendency for the lesions to appear circular or to be arranged in circinate fashion. There is usually an area of pallor immediately surrounding the lesion and occupying the center of circinate lesions. Dermatologic terminology would probably assign this rash to the general group termed erythema multiforme. Because this particular rash is so characteristic of the disease under discussion, perhaps it is proper to propose erythema multiforme rheumatoides as a specific designation. Typical lesions may appear during examination of the patient, and be gone again within a few minutes or hours. It tends to appear during febrile peaks, and to disappear when the temperature returns to normal. Observation of the rash, or description of its occurrence elicited from reliable parents, is of great assistance in arriving at the correct diagnosis, and should serve to reduce the number of laboratory studies to which patients suffering from this dramatically febrile illness are so frequently subjected.

**Arthralgia**

Arthralgia is another revealing early manifestation. This may be just as transitory as the rash, migratory, and not accompanied by redness, swelling, heat, or tenderness over the painful joint. Not infrequently the pain is localized in a knee or ankle, and is most noticeable during walking, or the patient refuses to walk for a few days until the arthralgia subsides.

![Fig. 2. The rash of acute rheumatoid disease, herein termed erythema multiforme rheumatoides. (a) depicts the more subtle blotchy macular lesions in several stages of development and regression. (b) shows the circinate pattern which the lesions may have, and suggests the central and marginal pallor which serves to accentuate the erythematous rings.](image-url)
Cardiac Manifestations

Involvement of the heart occurs more frequently in rheumatoid disease than is generally realized. Indeed, carditis may even be the initial manifestation. Physical findings may suggest involvement of the pericardium, myocardium, or endocardium, singly or in any combination. The diagnosis of acute rheumatic fever is apt to be strongly entertained. In such cases the electrocardiogram is of definitive diagnostic assistance. There is no prolongation of the P-R interval in the carditis of this rheumatoid disease. Figure 3 illustrates such an electrocardiogram. It may be observed that the heart rate is rapid, and that there are changes in the S-T segment and T-wave suggestive of myocarditis, but the P-R interval is within normal limits. Acute carditis in this rheumatoid disease may be fatal,* indeed, it accounts for a high proportion of deaths from this disease. The ultimate prognosis for the heart in patients who survive such an episode is good. The cardiac changes tend to disappear gradually and completely; clinically detectable permanent cardiac damage rarely occurs. Therapy with digitalis does not seem to influence this acute carditis. Figure 4 presents a roentgenogram of the heart of a 10-year-old girl. The heart is seen to be grossly dilated, with a configuration suggesting pericarditis. At the time, she was acutely febrile and there was a loud systolic murmur in the heart and a pericardial friction rub. Cardiac failure seemed imminent. Four months later, fever had disappeared and no cardiac abnormalities were detectable by physical examination. One year later, she developed arthralgia for the first time, with fever but without carditis. Her subsequent course was characterized by progressive arthritis, but the heart remained entirely normal by the usual clinical means of evaluation.
sudden in onset and suggesting acute appendicitis or peritonitis. Mesenteric adenitis may be suggested as the cause of such abdominal pain. Because of the generalized systemic nature of this disease, one should refrain from exploring the abdomen surgically unless signs of local disease are very compelling.

Other Manifestations

There may also be troublesome encephalitic manifestations\(^7\) and even choreiform symptoms. Ophthalmologic complications, including iridocyclitis and band-shaped keratitis, occur fairly frequently.\(^2\)\(^,\)\(^11\) It should also be noted that subcutaneous nodules are rarely present during this early stage of the disease in children,\(^12\) and that hemorrhagic manifestations, either in the skin or in the genitourinary system, are distinctly not characteristic.

DIFFERENTIAL DIAGNOSIS

Recognition of these severe systemic components as being characteristic of acute rheumatoid disease in children will permit the physician to reach the proper diagnosis by a direct approach, rather than by clumsy exclusion of other disorders. Many unrelated disease processes mimic this picture from one aspect or another, but when the entire panorama of clinical manifestations is kept in mind and the points of difference as well as similarity are carefully noted, most of the more virulent bacterial, viral, allergic and neoplastic diseases which may be suggested initially can be easily eliminated from the differential diagnosis. One may then approach the patient and his family with confidence, and direct all efforts to the alleviation of discomfort and the prevention of the deforming and immobilizing complications of the disease.

DIAGNOSTIC TESTS

Sorely needed is a specific diagnostic test to confirm clinical suspicion. Unfortunately none is yet available.\(^13\)\(^,\)\(^14\) Anemia, leucocytosis, moderate eosinophilia, and a markedly elevated erythrocyte sedimentation rate

Pulmonary Manifestations

Pleuritis and pneumonitis are often associated with episodes of carditis in these patients, and may also occur without carditis. Intense pleuritic pain, with nonproductive cough, may appear suddenly along with the previously described spiking fever. Physical findings suggesting pleuritis and pneumonitis are usually conspicuous and tend to be localized over the lower lobes. One may be surprised to find that roentgenograms taken at such times fail to match the extent of the physical findings, revealing only small areas of consolidation or widespread reticulated or mottled infiltrations. The pulmonary and pleural lesions tend to persist for months before slowly resolving. Pathologic examination of such lungs has demonstrated well-marked fibrinoid necrosis between the pulmonary alveoli, somewhat resembling anaphylactoid lesions in experimental animals.\(^9\)

Abdominal Pain

Another acute manifestation of rheumatoid disease which causes serious diagnostic concern is severe abdominal pain, often

Fig. 4. Roentgenogram of a 10-year-old girl with acute rheumatoid carditis, pericarditis and pneumonitis. Diffuse cardiac enlargement and straightening of the left cardiac border are seen. The Danzer ratio is 0.60. There is also a poorly defined pneumonitis in the bases of both lungs.
(often above 100 mm/hr) are characteristic but not pathognomonic. The anemia may become quite severe, but these patients should not be transfused unless the indications are imperative, because they are unusually prone to have severe transfusion reactions. Roentgenographic changes appear late in the disease. Recent efforts to provide a specific serologic test have not been entirely successful. The currently popular sheep cell agglutination test is positive in less than half of all cases of juvenile rheumatoid arthritis, and in these it rarely becomes positive during the first year of the disease. Similar agglutination tests using certain fractions of human serum globulin have also been shown to be unreliable in juvenile cases. Recently, Ralph Wedgwood, of Cleveland, has reported that the serum complement titer is elevated in juvenile patients with rheumatoid arthritis and dermatomyositis during the active phase, whereas children with disseminated lupus erythematosus have serum complement titres considerably below normal. Further serologic studies will be awaited with interest.

**THERAPY**

Certainly our basic therapeutic objectives should be to preserve good nutrition, promote normal skeletal, intellectual, and emotional growth, and prevent or lessen the occurrence of permanent deformities in the joints. A simple balanced nutritious diet is most satisfactory. Maximal tolerated activity should be encouraged, in association with other children of similar age if possible. Orthopedic attention and physiotherapy have an important role in the total program. Workers in the fields of psychology and rehabilitation may also make important contributions to the general care. Because spontaneous remissions are characteristic of the disease, one may hope that such supportive procedures are all that will be needed.

Although a vast array of agents has been tried, specific therapy for this disease remains unsatisfactory. Ethan Allen Brown has pointed out that the problem is complicated by the fact that rheumatoid arthritis is chronic but rarely fatal, and the drugs prescribed provide only symptomatic relief. In this context, the most meticulous evaluation of toxicity is needed to guide the clinician. All the drugs currently used may produce serious toxic manifestations. Thus, therapy must be conservatively prescribed and continuously subjected to re-evaluation.

Table 1 lists the drugs which our clinical experience, and a review of the pertinent literature, suggest are most useful. Salicylates may relieve discomfort and cause slight reduction of fever, but will not completely obliterate either the fever or the arthralgia, in contrast to the effect in acute rheumatic fever. Despite these shortcomings, salicylates in a dosage not to exceed 100 mg/kg/day, often provide adequate subjective relief.

Adrenal cortical steroids and their analogues have yet to achieve a final role in the therapeutic program. It seems preferable to reserve the use of these hormones for acutely and severely ill patients with major arthritic symptoms, in whom preservation of joint mobility and prevention of contractures are of primary importance. The daily dosage of cortisone which will effectively suppress arthritic symptoms ranges from 25 to 100 mg, depending on the size of the patient and the severity of the disease. If hydrocortisone is to be employed, a somewhat smaller daily dose may be tried, in the range of 25 to 75 mg/day. Prednisone may offer therapeutic advantages because it has less salt-retaining activity and greater antirheumatic potency than either cortisone or hydrocortisone. Ten to twenty-five milligrams per day will usually be effective.

### Table I

**Recommended Daily Dosages of Anti-rheumatic Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Dosage Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic Acid</td>
<td>100 mg/kg</td>
<td>in 4 to 6 doses</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25 to 100 mg</td>
<td>in divided doses</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>25 to 75 mg</td>
<td>in divided doses</td>
</tr>
<tr>
<td>Prednisone</td>
<td>10 to 25 mg</td>
<td>in divided doses</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>200 to 400 mg</td>
<td>in 3 to 4 doses</td>
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</table>
Phenylbutazone has been effective in many, but not all, cases of juvenile rheumatoid arthritis where it has been tried. A total daily dose of 200 to 400 mg, divided into three or four equal portions, will usually be sufficient to produce symptomatic improvement if the drug is to be effective at all in the particular patient. Because it does not possess adrenocortical activity, and does not influence spontaneous adrenal secretion, the usual precautions should be observed for avoidance of adrenal insufficiency, if therapy of a patient is to be changed from cortisone to phenylbutazone.

For each drug, the dosage given is a suggested dose for initiating anti-arthritic therapy. As soon as symptomatic control has been achieved, daily dosage should be gradually reduced to the point where distressing symptoms first reappear, and a minimal effective dose should then be continued. To completely suppress all symptoms may prove undesirable from the long-range viewpoint, because ultimate development of resistance to any or all of these drugs can be accompanied by severe disappointment of the patient. Because spontaneous remissions are characteristic of this disease, frequent trials of withdrawal of therapy should be planned, aiming toward discontinuation of drug therapy as quickly as possible.

PROGNOSIS

A word must be said concerning prognosis. Patients do not succumb to the arthritic component of the disease. However, death may occur at any stage of the disease from carditis, pneumonitis, or encephalitis. Some are of the opinion that juvenile rheumatoid arthritis usually remains active for 5 years or less, eventually "burns itself out," and leaves the patient with whatever residual skeletal deformities may be present. As a matter of fact, the disease may continue in an active phase for 20 years or longer, and may undergo exacerbation after a remission lasting as long as 30 years. Therefore, one should hesitate to consider any child who has apparently recovered from active rheumatoid arthritis as cured.

The principal message meant to be conveyed by this paper is the importance and feasibility of early diagnosis. Clear recognition of the typical clinical manifestations of acute systemic rheumatoid disease in children will avoid long periods of indecision and confusion that frequently characterize the approach to diagnosis of this disease. The bulk and devious content of the hospital records of many of these patients attest the need for improvement in such recognition.

REFERENCES


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