

# Chronic Salicylate Administration in Juvenile Rheumatoid Arthritis: Aspirin "Hepatitis" and Its Clinical Significance

Jane G. Schaller, M.D.

From the Department of Pediatrics, University of Washington, Seattle

**ABSTRACT.** Salicylates provide the backbone of therapy in juvenile rheumatoid arthritis. They are effective in controlling the disease approximately 75% of the time if they are properly used. Salicylate administration is relatively safe if carefully done. Serum salicylate levels should not exceed 30 mg/dl routinely. Patients, physicians, and parents should be alert to early clinical signs of toxicity. Chief hazards of chronic salicylate administration other than salicylism (which should be uniformly preventable) include gastric irritation with questionable relationship to peptic ulcer disease, and rare serious hepatotoxicity, bleeding diatheses, or hypersensitivity reactions. *Pediatrics* 62(suppl):916-925, 1978, salicylate, aspirin, juvenile rheumatoid arthritis.

Salicylates have provided the pharmacologic mainstay for therapy of rheumatic diseases for many years. Although various bark preparations were recognized for their analgesic properties by the ancients<sup>2-4</sup> (for example, Hippocrates recommended willow leaves to ease the pain of childbirth), their use in modern medicine probably dates back to 1763, when the Reverend Mr. Edward Stone of Chipping-Norton in Oxfordshire described in a communication to the Royal College of Physicians his observations concerning the use of willow bark in the treatment of "ague and intermitting disorders"<sup>1</sup> (Fig. 1).

In stumbling on this remedy, Stone invoked the doctrine of signatures, which suggests that within the cause may lie the cure. The "ague and intermitting disorders" that responded to willow bark in his time probably chiefly represented malaria, and it might be noted that although the bitter English willow bark worked as an antipyretic and analgesic in malaria, it was not truly curative of the disease since it contained none of the quinine of Peruvian bark. Other early promoters of English willow bark included William White, an apothecary of Bath,<sup>5</sup> and G. Wilkenson of Sunderland<sup>6</sup>; both noted its economy and

availability as compared to the Peruvian bark. The willow (Latin, *salix*) hence lent its name to the drug derived from its bark (salicylate).

The recorded use of salicylates in rheumatology began in the later 1800s with simultaneous reports from England and Germany of the efficacy of salicin<sup>7</sup> and salicylic acid<sup>8</sup> in the suppression of attacks of acute rheumatism (actually acute rheumatic fever). MacLagan,<sup>7</sup> a Scottish doctor, also invoked the doctrine of signatures in his investigations; he was a scrupulous investigator in conducting a safety control of his new drug before administration to his first patient:

It seemed to me that a remedy for that disease would most hopefully be looked for among those plants and trees whose favorite habitat presented conditions analogous to those under which the rheumatic miasm seemed most to prevail. A low-lying, damp locality, with a cold rather than warm climate, gives the conditions under which rheumatic fever is most readily produced. On reflection, it seemed to me that the plants whose haunts best corresponded to such a description were those belonging to the natural orders Salicaceae, the various forms of willow. Among the Salicaceae, therefore, I determined to search for a remedy for acute rheumatism. The bark of many species of willow contains a bitter principle called salicin. This principle was exactly what I wanted. . . . It will thus be seen that the employment of salicin in the treatment of acute rheumatism was no haphazard experiment, but had a fair foundation in reason and analogy. . . . I had at the time under my care a well-marked case of the disease [actually a patient, William R., 48 years old, five days into his second attack of rheumatic fever] which was being treated by alkalis but was not improving. I determined to give salicin; but before doing so, took myself first five, then ten, and then thirty grains without experiencing the least inconvenience or discomfort. Satisfied as to the safety of its administration, I gave to the patient referred to twelve grains every three hours. The result exceeded my most sanguine expectations.

Read before the Aspirin and Acetaminophen Symposium, New York, November 4-5, 1977.

ADDRESS FOR REPRINTS: (J.G.S.) Department of Pediatrics, RD20, University of Washington, Seattle, WA 98195.

XXXII. *An Account of the Success of the Bark of the Willow in the Cure of Ague. In a Letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edmund Stone, of Chipping-Norton in Oxfordshire.*

My Lord,

Among the many useful discoveries, which this age hath made, there are very few which, better deserve the attention of the public than what I am going to lay before your Lordship.

There is a bark of an English tree, which I have found by experience to be a powerful stringer, and very efficacious in curing ague and intermitting disorders.

About six years ago, I accidentally tasted it, and was surpris'd at its extraordinary bitterness; which immediately rais'd in me a suspicion of its having the properties of the Peruvian bark. As this tree delights in a moist or wet soil, where agues chiefly abound, the general opinion, that many natural maladies carry their cure along with them, or that disorders arise not far from their cause, was in very opposite to this particular case, that I could not help applying it;

cinnamon, or tartarous colic, which I believe is the case with the Peruvian bark and powder.

I have no other reason for publishing this salutary specific, than that it may have a fair and full trial in all its variety of circumstances and situations, and that the world may reap the benefits accruing from it.

For these purposes I have given this long and minute account of it, and which I would not have troubled your Lordship with, was I not fully perswad'd of the wonderful efficacy of this Cortex Salicinae in ague and intermitting cases, and did I not think, that this perfumation was sufficiently supported by the manifold experience, which I have had of it.

I am, my Lord,

with the profoundest admiration and respect,

Chipping-Norton, your Lordship's most obedient  
Gentleman,  
April 25, 1719.

Edmund Stone.

FIG. 1. Stone's original report of the use of willow bark in "ague and intermitting disorders."

William R. became afebrile within one day, and free of joint pain within three days of beginning treatment with salicin.

Aspirin (acetylsalicylic acid) was first synthesized in 1853,<sup>9</sup> but did not come into common use until the turn of the century, when Felix Hofmann, a Bayer Company chemist, devised a practical commercial method for its preparation. Hofmann was spurred by the observation that aspirin was a more palatable form of therapy than sodium salicylate for his own father who suffered from rheumatoid arthritis; the senior Hofmann was perhaps the first of many rheumatoid patients to be successfully treated with aspirin.<sup>10</sup>

#### Therapy of Childhood Arthritis

Juvenile rheumatoid arthritis (JRA) is the prototype of a chronic inflammatory disorder of children and, aside from acute rheumatic fever, the only childhood disease in which there is extensive experience with chronic salicylate administration. Salicylates and other anti-inflammatory agents have several distinct properties (Table I): analgesic, antipyretic, and anti-inflammatory. Of these, anti-inflammatory properties are the most crucial in rheumatic disease therapy, but are also unfortunately the most difficult to document, objective evidence resting largely on artificial animal models of inflammation.<sup>11</sup> Pain, fever, and inflammation are, of course, all prominent components of JRA. Simple analgesics and antipyretics, however, play little role in therapy. Of the available anti-inflammatory or antirheumatic agents, salicylates have been used more widely and for longer periods of time than any other agents in the treatment of chronic arthritis in both adults and children. Although there are only a few definitive studies,<sup>12</sup> there is general agreement among rheumatologists that salicylates are effective in suppressing the inflammation of

TABLE I

#### ANTI-INFLAMMATORY AGENTS IN CHILDREN

Antipyretics (suppress fever)
Salicylates
Acetaminophen
Nonsteroidal anti-inflammatory agents*
Corticosteroids
Analgesics (suppress pain)
Salicylates
Acetaminophen
Nonsteroidal anti-inflammatory agents*
Codeine
Narcotics
Anti-inflammatory agents (suppress inflammation)
Salicylates
Nonsteroidal anti-inflammatory agents*
Antirheumatic agents: gold, antimalarials
Corticosteroids

\*Nonsteroidal anti-inflammatory agents include indomethacin, phenylbutazone, ibuprofen, tolmetin, fenoprofen, and naproxen. Of these drugs, only tolmetin is currently available for use in children in the United States. The relative antipyretic, analgesic, and anti-inflammatory properties of these various agents have not been well documented.

rheumatoid arthritis. Mechanisms for anti-inflammatory actions of aspirin remain unknown, as does the comparative efficacy of aspirin as compared to other salicylate preparations such as sodium salicylate or choline salicylate. Possible mechanisms of anti-inflammatory action include inhibition of prostaglandin synthesis, stabilization of lysosomal membranes, and effects on immune responses.<sup>11</sup>

There are several distinct subgroups of JRA or childhood arthritis that vary in clinical manifestations, disease course, ultimate morbidity, and prognosis<sup>13</sup> (Table II). These disease subgroups and the particular manifestations of disease requiring therapy need to be considered in designing and evaluating therapy. Also essential to evaluation is the realization that therapy with anti-inflammatory drugs is only one aspect of appropriate therapy for a patient with JRA; other important aspects include physical therapy, occupational therapy, orthopedic therapy, education of the patient and family, careful follow-up, and attention to the psychosocial aspects of the whole child. Only if all of these receive consistent attention can drug therapy truly be evaluated.

#### Salicylate Therapy in Childhood Arthritis

Salicylates provide the mainstay of therapy for JRA. Aspirin is the most commonly used preparation<sup>14-17</sup>; other preparations occasionally used include sodium salicylate and choline salicylate.

TABLE II  
SUBGROUPS OF JUVENILE RHEUMATOID ARTHRITIS

Subgroup	% of Patients	Outcome
Systemic onset disease	20	Severe arthritis in 25%; systemic disease generally self-limited; severe heart involvement or anemia in <5%
Seronegative polyarthritis	30	Severe arthritis in 10%
Seropositive polyarthritis	10	Severe arthritis in >50%
Pauciarticular disease type I	25	Severe arthritis rare; chronic iridocyclitis in 50%; ocular damage common
Pauciarticular disease type II	15	Some will have disability of ankylosing spondylitis or other spondyloarthropathies

Appropriate doses of salicylates for children weighing 25 kg or less are 100 mg/kg of body weight. For children weighing more than 25 kg, total daily doses of 2.4 to 3.6 gm of aspirin are usually sufficient. It is important to realize that if salicylate dosages are calculated at 100 mg/kg of body weight for children weighing more than 25 kg, serious salicylate intoxication can result.<sup>18</sup> One study amply illustrated this: in a group of JRA patients receiving 100 mg/kg of salicylates, the only patients who became toxic were older, heavier children.<sup>19</sup> It is generally thought that serum salicylate levels between 20 and 30 mg/dl are adequate for maximum antirheumatic activity; such blood levels are usually achieved with the doses described above. There is little benefit and great potential hazard in pushing salicylates to serious toxicity. Salicylate doses may be monitored by blood levels; however, to avoid too-frequent procedures in children with a chronic illness like JRA, it is our policy to check salicylate levels in only two circumstances: (1) to determine

whether the salicylate level is too low if the patient is doing poorly on therapy, or (2) to determine whether the salicylate level is too high if the patient is possibly toxic. As Levy reports in another Symposium article (p 867), salicylate levels plateau about one week after salicylate therapy is started; checking salicylate levels before this time is probably needless. Salicylates may be given in four to six divided daily doses; according to Levy, four daily doses are probably adequate to maintain levels with chronic administration. Our policy has been to administer salicylates with meals and at bedtime with a snack, hopefully thus lessening gastric irritation and providing a convenient dosage schedule. The time required for maximum response to salicylates is often weeks or months; both the patient and the physician must be patient. The duration of salicylate therapy should extend for 6 to 12 months after the disease has reached full clinical remission. An interesting question pertinent to therapy with salicylates (as well as with other drugs) is why some patients respond and others do not; it may be that as yet unknown host genetic or metabolic factors exist to explain such differences in drug responsiveness.

TABLE III  
EFFICACY OF ASPIRIN IN CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS

	% of Patients
Adequate suppression of synovial inflammation	
Systemic-onset, chronic arthritis	50
Seronegative polyarthritis	70
Seropositive polyarthritis	25
Pauciarticular disease type I	95
Pauciarticular disease type II	75
Control of systemic manifestations of systemic-onset disease	75
Control of iridocyclitis	0

#### Efficacy of Salicylate Therapy in JRA

In our experience, salicylates are effective in controlling manifestations of JRA in approximately 75% of patients (Table III). Active arthritis can be satisfactorily suppressed in the majority of patients, especially in patients with pauciarticular disease and seronegative polyarthritis. Salicylate therapy is not curative of arthritis, nor does it always prevent ultimate joint destruction. However, salicylates are usually effective in suppressing inflammation and allowing retention of adequate joint and musculoskeletal function, so

that when arthritis remits, as it usually ultimately does in childhood-onset disease, patients are left in good functional shape. Much of the ultimate morbidity of JRA results from joint contractures and deformities rather than from actual joint destruction.<sup>13,18,20</sup> In the two subgroups of JRA in which joint destruction is a frequent part of the natural disease history (rheumatoid factor-positive arthritis and the chronic arthritis of systemic-onset JRA), salicylates may be less effective in controlling arthritis.

Salicylates are effective in suppressing the high fevers and attendant systemic manifestations of systemic-onset JRA in approximately 75% of patients; patients often need to be hospitalized and carefully watched while this systemic disease is brought under control. Salicylate therapy is not thought to be effective in chronic iridocyclitis.

#### Hazards of Chronic Salicylate Therapy in Childhood Arthritis

The major hazard of chronic use of salicylates is salicylism resulting from excessive blood levels of salicylate (more than 30 mg/dl). Salicylism is uniformly avoidable with careful attention to dosage and careful follow-up of patients. As noted previously, it is important not to use 100-mg/kg doses for children who weigh more than 25 kg. During times of intercurrent illness when fever or gastroenteritis results in fluid depletion, salicylate doses should be decreased accordingly. Parents and physicians should be constantly alert for signs of salicylate toxicity. Tinnitus and hearing loss, which occur with serum salicylate levels between 20 and 30 mg/dl, are rarely noted by children and are thus generally lost as early signs of salicylism. The most frequent signs of chronic salicylism in children are hyperventilation or central nervous system changes such as giddiness, drowsiness, or changes in behavior. These changes occur when salicylate levels exceed 30 mg/dl and are a sign for stopping aspirin administration, checking the serum salicylate level, and revising the dose appropriately. The central nervous system manifestations of chronic salicylism have been well described in adults<sup>21</sup> but less appreciated in children. Such effects are, however, well known to at least some physicians using chronic salicylates in children. Bywaters<sup>22</sup> once commented about a patient who, under the influence of salicylates, attacked him with a knife.

The following case report describes a similar episode:

A 6-year-old boy had been given aspirin by his family physician for transient arthritis of uncertain etiology; he received 100 mg/kg/day for four months. When the patient

was first referred to an arthritis clinic, he was experiencing episodes of what seemed to be myoclonic seizures and loss of consciousness, and appeared to be quite dull. There was no evidence of chronic arthritis, but he was hyperventilating mildly. Salicylate level was 34 mg/dl. After discontinuance of salicylates, the patient's central nervous system status returned to normal, and he remained well. An electroencephalogram was normal, with no evidence of seizure disorder; serum electrolyte, creatinine, and blood glucose values were normal.

This child received injudicious salicylate therapy for a transient illness that probably never warranted chronic drug administration. A dose of 100 mg/kg/day of aspirin was excessive. The chronic salicylism induced symptoms suggestive of a progressive central nervous system disorder that was, fortunately, rapidly reversible on discontinuance of the aspirin.

#### Hepatotoxicity

There are many fascinating ties between the liver and arthritis.<sup>23-25</sup> The liver may be affected in JRA and even in adult-onset disease<sup>23,24</sup>; patients with systemic-onset JRA may in fact have apparent primary liver disease.<sup>23</sup> The hepatic histology in systemic JRA is nonspecific with relatively normal hepatic architecture and modest collections of inflammatory cells in the portal areas.<sup>23</sup> Still<sup>20</sup> and Kornreich and associates<sup>25</sup> noted that, on the other hand, intercurrent liver disease can actually result in remissions of JRA. The effects of drugs on the liver add another dimension to relationships between rheumatoid arthritis and hepatic disease.

Effects of salicylates on the liver (Table IV) were first noted in 1955 by Nydick and associates<sup>26</sup> from Irvington House; they observed that 18 of 64 patients with rheumatic fever had elevated serum transaminase levels. They related these elevations to active carditis with myocardial damage. In 1956, Manso and associates,<sup>27</sup> from the same group, restudied the issue and concluded that 50% of children with acute rheumatic fever receiving salicylates had elevated transaminase levels that were, in fact, related to the salicylate therapy; serum salicylate levels in these patients ranged between 5 and 40 mg/dl. This observation lay fallow until 1971, when Russell and co-workers<sup>28</sup> reported that eight of 32 children with juvenile chronic polyarthritis (called JRA in the United States) had elevated transaminase levels. Seven of eight children with elevated transaminase levels had serum salicylate levels greater than 35 mg/dl. There was no related serious liver disease, and the transaminase levels reverted to normal when serum salicylate levels were lowered. Rich and Johnson<sup>29</sup> in 1973 reported six

TABLE IV  
SALICYLATES AND THE LIVER: REPORTED SERIES WITH FIVE OR MORE PATIENTS\*

Series	Disease	No. of Patients	No. With Elevated SGOT Level	Associated Salicylate Levels (mg/dl)	Severe Hepatic Changes
Nydick et al, <sup>26</sup> 1955	Rheumatic fever	64	18	Not reported	0
Manso et al, <sup>27</sup> 1956	Rheumatic fever	23	13	5-40	0
Russell et al, <sup>28</sup> 1961	JRA	32	8	>35 (7/8)	0
Rich & Johnson, <sup>29</sup> 1963	JRA	6	6	>25	0
Athreya et al, <sup>30</sup> 1975	JRA	34	22	7-43	3/22
Miller & Weissman, <sup>32</sup> 1976	JRA	88	52	0-53 (mean, 21 ± 11)	0
Rachelefsky et al, <sup>33</sup> 1976	JRA	37	8/11, no salicylate 5/6, some salicylate 13/20, regular salicylate	0-44	0
Bernstein et al, <sup>34</sup> 1977	JRA	102	60/102 sporadic determinations 42/46 with serial determinations	Mean, 16.5 for patients with normal SGOT levels Mean, 19.9 for patients with elevated SGOT levels	3/102
JRA Collaborative Study Group, <sup>43</sup> 1977	JRA	107	13/54, salicylate 1/53, no salicylate	Not done	0

\*Other reports: Seaman et al,<sup>35</sup> 1974, three adults: SLE; Zuker et al,<sup>36</sup> 1975, two children: SLE, arthritis; Gitlin et al,<sup>37</sup> 1974, one child: rheumatic fever; Wolfe et al,<sup>38</sup> 1974, one adult: SLE; Iancu & Elian,<sup>39</sup> 1976, one child: rheumatic fever; Sbarbaro & Bennett,<sup>41</sup> 1977, one teenager: JRA; O'Gorman & Koff,<sup>42</sup> 1977, two adults: rheumatoid arthritis, SLE.

patients with childhood-onset arthritis (three were adults) who had elevated serum transaminase levels associated with salicylate levels greater than 25 mg/dl. Four of these six patients also had elevated levels of lactic dehydrogenase and alkaline phosphatase; only one of six had hepatomegaly, elevated serum bilirubin level, or sulfobromophthalein retention. Abnormal tests were reversible with lowering of salicylate doses. Two patients had liver biopsy specimens showing mild periportal inflammation. In 1975, Athreya and associates<sup>30,31</sup> reported that 22 of 34 children with JRA had elevated transaminase levels associated with serum salicylate levels of 7 to 38 mg/dl. Nineteen of these patients had only mild changes; some continued to receive salicylates and none encountered serious problems. Three patients, however, had marked enzyme elevations and associated lowered serum prothrombin levels with serum salicylate levels of 18 to 43 mg/dl; salicylate therapy was discontinued in these children. Eight children without JRA, also given salicylates, showed no rises in serum transaminase values with salicylate levels of about 15 mg/dl. Athreya suggested that girls were more likely to

show elevations of transaminase levels than were boys, and that such elevations were associated with pauciarticular or mild JRA as well as with systemic-onset disease. In 1976, Miller and Weissmann<sup>32</sup> reported 88 children with JRA; 59% had elevated SGOT levels and 41% had elevated SGPT levels associated with salicylate therapy. They found no sex difference in transaminase level elevations, few or no associated symptoms, and a poor correlation of enzyme level elevations with serum salicylate levels. Changes occurred in patients with mild JRA as well as in those with severe JRA. A liver biopsy specimen from one patient showed spotty and mild cellular necrosis. In 1976, Rachelefsky and colleagues<sup>33</sup> studied 37 children with JRA; 20 were being treated with therapeutic salicylates, six were receiving salicylates only sporadically, and 11 were receiving no salicylates. Elevated transaminase levels occurred in all of these groups, and were considered to be related to the basic disease rather than to the salicylate therapy per se. Some individuals also had elevated levels of creatine phosphokinase. The authors concluded that the disease rather than the therapy played a major role in transam-

inase level elevations. Bernstein and associates<sup>34</sup> reported 102 patients with JRA who were receiving salicylate therapy; 59% had raises in serum transaminase levels at one time or another. Also, of 46 patients studied with four or more serial transaminase levels, 91% had elevated levels at one or more times. Although enzyme level elevations could be correlated with high serum salicylate levels, they also occurred in some patients with salicylate levels lower than 25 mg/dl. Enzyme levels exceeded 500 transaminase units in only three patients; biopsy specimens from these patients showed periportal inflammation of mild degree.

Seaman and associates<sup>35</sup> reported similar observations of elevated transaminase levels in three patients with systemic lupus erythematosus (SLE) receiving salicylates; two of three patients had liver biopsy specimens that showed more extensive hepatocellular changes than those described in the JRA patients. Additional reports concerning salicylates and the liver include those of Zucker and colleagues<sup>36</sup> (one child with SLE and one with sickle cell disease and arthritis), Gitlin and associates<sup>37</sup> (one child with acute rheumatic fever), Wolfe and co-workers<sup>38</sup> (one child with SLE), Levy and Yaffee<sup>39</sup> (a commentary concerning salicylates and the liver), Iancu and Elian<sup>40</sup> (one child with acute rheumatic fever), Sbarbaro and Bennett<sup>41</sup> (a teenager with JRA), and O'Gorman and Koff<sup>42</sup> (two adults, one with rheumatoid arthritis and one with SLE). In a recent double-blind study comparing tolmetin and aspirin,<sup>43</sup> transaminase level elevations occurred in 13 of 54 JRA patients receiving aspirin, but in only one of 53 JRA patients receiving tolmetin; these study groups were similarly matched for types and severity of disease, and serial enzyme levels were obtained over a six-month period. A clinical pathologic conference in the *New England Journal of Medicine* in 1977 described the death of a teenager due to acute hepatic disease; she had had fever and arthritis of uncertain etiology and had received both salicylates and acetaminophen.<sup>44</sup>

Several conclusions might be drawn concerning salicylates and the liver. Juvenile rheumatoid arthritis patients may have mild liver disease unrelated to drug therapy; this appears to be particularly true in children with systemic-onset JRA. Approximately 50% of JRA patients receiving therapeutic doses of salicylates will have elevated levels of SGOT and less frequently SGPT. These elevated enzyme levels are rarely associated with symptoms of liver disease, hepa-

tomegaly, bilirubinemia, alterations in prothrombin time, or evidence of severe hepatic dysfunction. Although such enzyme elevations may occur more frequently with serum salicylate levels higher than 25 mg/dl, they occur also with lower salicylate levels. Chronic or severe liver disease is not associated; indeed, enzyme level elevations may be transient and may revert to normal with continuing salicylate administration. Such changes do not appear to be a reason for cessation of salicylate therapy, although if the salicylate levels are higher than 25 mg/dl, the aspirin doses should be accordingly lowered.

There are, however, a few patients with rheumatic disorders who appear to have serious episodes of liver disease coincident with salicylate administration; such individuals have marked elevations of transaminase level and may have associated lowered prothrombin levels, bilirubinemia, and symptoms of liver disease. It is not known whether such severe changes are entirely related to salicylate therapy or are also determined by other events. Whatever the cause, children with severe enzyme level elevations or symptoms of liver disease should not continue to receive salicylates during the acute episode, and should be given salicylates only with caution in the future. Liver biopsy specimens have shown periportal inflammation similar to that described in systemic-onset JRA in the absence of salicylate therapy.<sup>23</sup> It may be that children with JRA have a hepatic state that predisposes them to hepatic injury due to drugs. One recent series of JRA patients<sup>45</sup> noted three deaths due to liver disease; the causes of this liver disease and possible relationships to drug therapy were not stated. Deaths from liver disease have been reported in children receiving indomethacin,<sup>46</sup> and intercurrent liver disease has been noted in children with JRA who have received gold injections (Kornreich et al.<sup>23</sup> and J.G. Schaller, unpublished data).

Similar changes in serum enzyme levels with salicylates have been noted in patients with SLE and with rheumatic fever. From available information, it appears that transaminase level elevations rarely occur in nonrheumatic individuals who are receiving salicylates, although perhaps such control studies have not been adequate. The elevation of serum hepatic enzymes is not a function of the particular ester of salicylic acid; this effect has been reported with aspirin, sodium salicylate, and choline salicylate. In practice, it would seem wise to determine SGOT levels prior to treatment of any rheumatic disease patient

TABLE V  
SALICYLATE HEPATOTOXICITY IN CHILD WITH  
PAUCIARTICULAR JUVENILE RHEUMATOID ARTHRITIS\*

Date	SGOT Level (Units)	Salicylate Level (mg/dl)
11/75	120	24
2/76	54	17
3/76	241	28
4/76	135†	24
8/77	186	22
8/77	52	11
10/77	23	0

\*Onset in September 1975, at age 2 years.

†Liver biopsy specimen showed minimal inflammatory infiltrates.

with salicylates, and to remain alert for possible symptoms of liver disease in rheumatic disease patients being treated with salicylates (and with other drugs as well).

### CASE REPORTS

#### Case 1

A 4-year-old girl with severe systemic-onset JRA was treated with salicylates. No liver function studies were done prior to salicylate therapy although the child had hepatosplenomegaly. Two weeks after initiation of therapy, she remained ill and was vomiting. Serum salicylate level was 25 mg/dl; SGOT level, 1,500 units; and serum bilirubin level, 1.2 mg/dl. Salicylate therapy was discontinued. One month later, she continued to have active systemic-onset JRA, but was receiving no drug therapy. SGOT level was 149 units; bilirubin level, 0.6 mg/dl. Three months after onset, SGOT level was 162 units, bilirubin level was 0.7 mg/dl, and the systemic disease remained active on no therapy. After six months of active systemic febrile disease, there was a partial remission. Nine months after onset, SGOT level remained slightly elevated at 74 units, serum bilirubin level was 0.8 mg/dl, and the child was afebrile although she continued to have chronic arthritis. She was still receiving no medications.

This child had severe systemic-onset disease with dramatic elevations of transaminase levels coincident with appropriate therapy with salicylates. She had had hepatosplenomegaly prior to salicylate therapy although no liver function tests had been done. After cessation of salicylate therapy, she continued to have mildly elevated transaminase levels that may have reflected hepatic disease of systemic JRA, but there was no evidence of severe liver disease.

#### Case 2

A 4-year-old girl with systemic-onset JRA was treated with salicylates. One year after onset, gold injections were started because of active arthritis. She had had no liver function studies. After the second gold injection, she was admitted to the hospital because of severe systemic disease and arthritis. She was found to have an SGOT level of of 244 units, a serum

bilirubin level of 2.2 mg/dl, and hepatomegaly. Two days later, she had a recognized episode of disseminated intravascular coagulation (DIC); serum salicylate level was 20 mg/dl; SGOT level, 348 mg/dl; bilirubin level, 4.3 mg/dl. Salicylate therapy was discontinued and prednisone treatment begun, with rapid resolution of both the DIC and the systemic JRA. Seven days after the prednisone therapy was started, the SGOT level had fallen to 25 units and the bilirubin level to 1.2 mg/dl. When she was first referred to an arthritis clinic seven days later, the SGOT level was 10 units, bilirubin level was 0.8 mg/dl, and she remained well aside from an exfoliative pruritic rash thought to be consistent with gold sensitivity. Viral and bacterial cultures taken during her acute illness showed no pathogens.

This child had systemic-onset JRA with unknown hepatic status at onset. Elevated transaminase levels were recognized shortly after the initiation of gold therapy. An episode of DIC followed. This has been previously reported in connection with salicylates and elevated serum enzyme levels.<sup>41</sup> All manifestations of JRA, DIC, and her liver problem resolved promptly with corticosteroid therapy. The possible roles of systemic JRA, gold, aspirin, and possible intercurrent viral infection in her illness are not clear.

#### Case 3

A 2-year-old girl with pauciarticular disease was treated with salicylates. Two months after onset of salicylate therapy, it was recognized that her serum transaminase levels were elevated. Serial levels are shown in Table V. She had no manifestations of liver disease other than occasional nausea, and no hepatomegaly. Coincident with cessation of salicylate therapy, transaminase levels fell to normal. A liver biopsy specimen obtained by the referring physician showed minimal periportal inflammatory infiltration with no evidence of hepatocellular necrosis or chronic liver disease.

This child had mildly elevated serum transaminase levels with salicylate levels in the therapeutic range. Her transaminase levels returned to normal when salicylate therapy was stopped. There was no evidence of serious liver disease.

### Gastrointestinal Toxicity

The gastrointestinal toxicity of salicylates is discussed by Fromm in another Symposium article (p 938). Little experimental work has been done to determine how the gastric irritation of salicylates can, in fact, be lessened. It has been our policy to give salicylates with food, to substitute buffered aspirin or choline salicylate if dyspepsia occurs, and to use antacids for the treatment of dyspepsia. We have had 14 of approximately 400 JRA patients develop duodenal ulcer disease in the context of JRA and salicylate therapy (J.G. Schaller, D. Christie, unpublished data). All had a history of dyspepsia prior to the recognition of duodenal ulcer. No child has had a gastric ulcer. Relationships of the

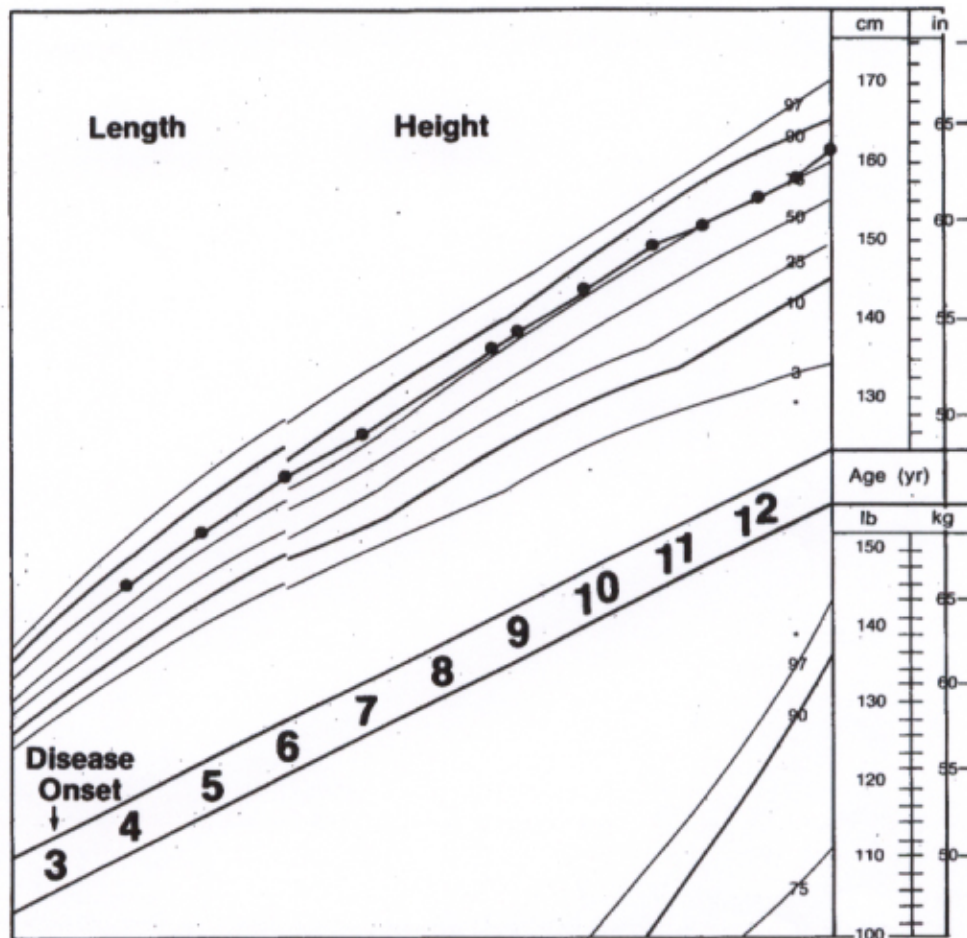


FIG. 2. Growth of girl who received therapeutic doses of salicylates for seronegative polyarthritis between ages 4 and 13 years.

ulcers to salicylate therapy are uncertain; however, it has been our policy to suspect ulcer disease in any JRA patient who complains of stomach aches. Gastrointestinal blood loss due to salicylate therapy has rarely been a major clinical problem in our patient group unless ulcer disease is present. However, iron deficiency should be suspected and appropriately treated in JRA patients who are anemic.

#### Other Possible Untoward Effects of Chronic Salicylism in JRA

Effects of salicylism bleeding are described by Pearson in another Symposium article (p 926). We have had only one JRA patient with serious bleeding problems in the context of chronic salicylate administration. We routinely change from aspirin to another ester of salicylic acid such as choline salicylate two or more weeks prior to any anticipated surgical procedures.

Hypersensitivity manifestations of salicylate administration have been rarely recognized in our

group of JRA patients. However, the sensitivity of some asthmatic children to salicylates seems to be well established, as noted in another Symposium article by Weinberger (p 910) and in other reports.<sup>47,48</sup> This may be a matter worthy of further attention.

Chronic renal disease is not recognized as a problem of chronic salicylate administration in children, although the occurrence of mild hematuria and renal tubular celluria is well documented in association with salicylate administration,<sup>49</sup> and minor renal changes have been noted in children with JRA.<sup>50,51</sup> Adults with rheumatoid arthritis may have significant renal disease.<sup>52</sup> The relationships of such observations of renal disease in rheumatoid patients to drug therapy are unknown.

It has been suggested that salicylates may have effects on growth (G.A. Limbeck, V.C. Kelley, oral communication, 1965); however, in JRA, growth suppression appears to be related to active disease or to corticosteroid therapy and not

to salicylate therapy.<sup>53,54</sup> Figure 2 demonstrates the growth curve of a child whose disease was well controlled with salicylates and who grew rapidly during a number of years of continuing salicylate administration.

#### Serious Toxicity of Salicylates

In our experience with some 400 children with JRA treated with chronic salicylates, we have never had to hospitalize a child because of salicylism, nor have any patients had severe salicylate toxicity. Two children (cases 1 and 2) had what might be termed serious hepatotoxicity, believed to contraindicate further salicylate administration. One child had a serious bleeding episode, and DIC has been noted in two additional children with JRA, only one of whom (case 2) was receiving salicylates at the time. One child has had a chronic rash that appeared to be related to salicylate administration. Fourteen children had duodenal ulcer disease of uncertain relationship to salicylate therapy.

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