Salsalate: Its Role in the Management of Rheumatic Disease

Peter T. Singleton, Jr.

University of California Medical Center and The Letterman Medical Center, San Francisco, California

ABSTRACT

Our present array of nonsteroidal anti-inflammatory drugs (NSAIDs) provides many more avenues for the long-term management of rheumatic disease. Their clinical efficacy notwithstanding, these drugs possess significant iatrogenic potential. These risks are typified by aspirin side effects, basically gastrointestinal, hematologic, and thrombopathic. Most of the NSAIDs share these liabilities. However, there is now wider appreciation of recent findings that nonacetylated salicylates, particularly salsalate,* provide the benefits of aspirin and other NSAIDs but not their dangers. Salsalate is a prototypic drug of this class; it is reviewed in detail with appropriate comment concerning its present and potential clinical contributions to anti-rheumatic therapy.

INTRODUCTION

The most significant clinical development in the management of inflammatory joint disease lies in the evolution of nonsteroidal anti-inflammatory drugs (NSAIDs). This evolution has grown apace with that of enhanced understanding of the immunopathogenesis of rheumatic disease, classically modeled by rheumatoid arthritis. A salient achievement of NSAIDs is a general reduction of the limiting side effects seen with standard aspirin therapy.

However, the rapid emergence of these newer agents has produced a schism among clinicians. Many still favor aspirin as the primary agent in the management of rheumatoid arthritis, but a growing number of clinicians are considering newer NSAIDs for initiating treatment in these patients. The first group considers aspirin to be the most effective drug for long-term management of this disease; the second group lauds the clinical efficacy and safety of newer NSAIDs, as well as improved patient compliance with treatment guidelines.

This divergence of clinical opinion has led to renewed evaluation of nonacetylated salicylate preparations as a major alternative. Among these, salsalate (salicylsalicylic acid) has gained increasing support. In clinical trials it has been proven effective and especially safe in the management of patients with

*Trademark: Disalcid® (Riker Laboratories, Inc., Northridge, California).

rheumatoid arthritis or other inflammatory joint disease. Although technically classified as an NSAID, salsalate does not share, as do most drugs in this class, the *in vitro* propensity to inhibit prostaglandin biosynthesis (Figure 1). The efficacy of salsalate probably derives from its behavior as a prodrug of salicylic acid—the active moiety of all salicylate formulations—and leads to important safety considerations. Chief among these are lack of major gastrotoxicity or bleeding and thrombopathic effects. Thus the clinician is freed of concern about the principal shortcomings of regular aspirin treatment.

Salsalate, in contrast to several newer NSAIDs, seems to provide better patient tolerance and equal clinical efficacy in management of rheumatoid arthritis.[1] Armed with these data, physicians treating rheumatic diseases should consider four basic questions when choosing as drug for the management of a patient with arthritis: 1) Is the drug effective in all critical areas of management (e.g., pain, inflammation, joint dysfunction)? 2) Is it safe? 3) Does it have a high risk-benefit ratio? and 4) Is it cost-effective compared with other drugs? Affirmative answers to the first three questions are possible with salsalate. In the context of all nonsteroid anti-inflammatory drugs (Figure 2), including precursors of salicylic acid, only aspirin is less expensive.

The choice of the appropriate drug, although extremely important, is only part of a holistic approach to the management of rheumatoid arthritis. The use of physical modalities (e.g., heat, range of motion exercises, local and systemic rest, and hydrotherapy) also represents a fundamental element of management at all levels of disease activity and extent of joint destruction. So-called remitting agents (Table I) — chloroquine, gold salts, D-penicillinamine — are slow acting and seek to reduce synovial-based inflammation. These drugs should be used in concert with NSAIDs in any complete treatment program. Immunoregulatory

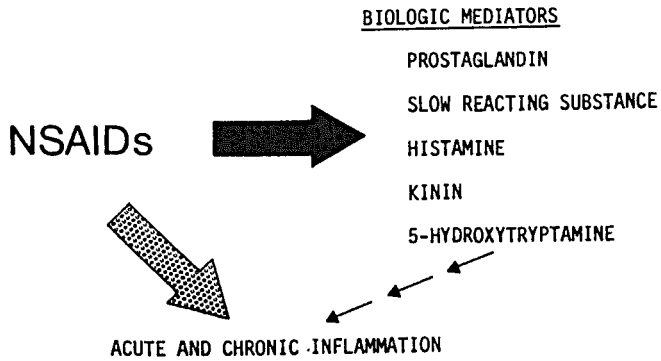

Figure 1. Some nonsteroidal anti-inflammatory drugs (NSAIDs) modify or inhibit biologic mediator activity in addition to exerting possibly more direct influence on acute and chronic inflammation.

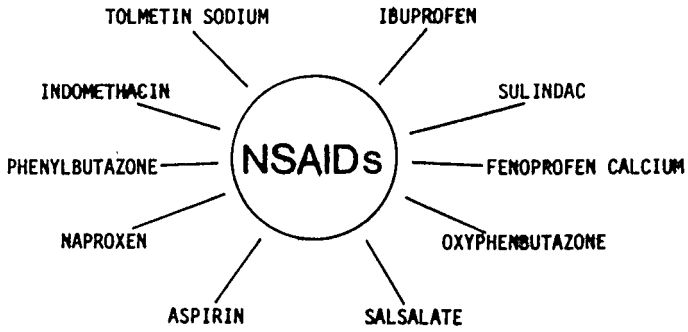

Figure 2. Nonsteroidal anti-inflammatory drugs (NSAIDs).

drugs, such as azathioprine, cyclophosphamide, chlorambucil and levamisole, are restricted to use in patients who have failed to respond to the aforementioned agents.

Table I. Remitting and immunomodulation drugs and experimental techniques.

Remitting Drugs
Hydroxychloroquin sulfate
Chrysotherapy
Penicillamine
Zinc-histidine
Immunomodulation Agents
Immunosuppressives
Cyclophosphamide
Chlorambucil
Azathioprine
Immunostimulants
Levamisole
BCG
Transfer factor
Experimental
Thoracic duct drainage
Plasmaphoresis
Radionuclide synovectomy

Corticosteroids are usually reserved for rheumatoid arthritis patients demonstrating serious extra-articular features of the disease (e.g., rheumatoid lung disease and vasculitis) or acute exacerbations uncontrolled by NSAIDs. Intra-articular steroids are particularly helpful in reducing pain and inflammation when only a few joints remain symptomatic. From surgical research has evolved an increasing array of reconstructive procedures and prostheses to relieve pain, correct joint deformities, and restore functional capabilities in those patients with major limitations secondary to severe articular destruction.

The complete scheme of the management of arthritis patients incorporates the various roles of allied health professionals. We cannot overemphasize the contributions of physical therapists, occupational therapists, clinical social workers, clinical psychologists, and nurses trained in the management of the arthritis patient. Only by a judicious integration of each of these resources can a full impact be made in arthritis care. Toward that end, the following review will focus on ad-

vantages and disadvantages of primary treatment of these patients with non-acetylated salicylate formulations, particularly salsalate.

CHEMISTRY

Salsalate is a stable, white crystalline powder that melts at 140 C. Chemically, it is a dimer of salicylic acid in which the carboxyl group of one molecule is covalently linked to the hydroxyl group of a second molecule (Figure 3A). Its commercial synthesis is carried out by several methods using salicylic acid as the starting material.

Salsalate can be considered as a prodrug of salicylic acid, since *in vivo* the dimer is readily hydrolyzed to two molecules of salicylic acid (Figure 3B). It is, however, more resistant to hydrolysis than aspirin at the physiologic pH. The ester group of salsalate apparently does not transesterify proteins, as happens with the acetyl ester in aspirin (Figure 3C). This may explain its lack of platelet effect or other hemotologic perturbations, as discussed in the section on safety.

The acid strengths of salsalate, salicylic acid, and aspirin are very similar. Their solubilities at neutral or acid pHs, however, are quite different. Salsalate is only one twentieth as soluble as aspirin. Because of this lower solubility, salsalate is less likely to interact with the gastric mucosa than is salicylic acid or aspirin.

Salsalate becomes solubilized and absorbed in the basic media of the small intestine. The delay in absorption as a result of gastric insolubility[2,3] may ac-

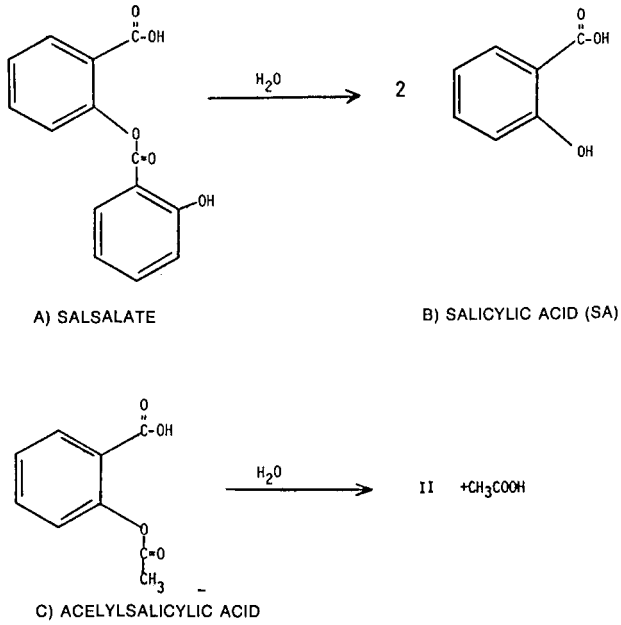

Figure 3. Hydrolytic cleavage of salsalate and aspirin molecules.

count for the somewhat delayed peak time of circulating salicylic acid levels following single-dose administrations.

PHARMACOKINETICS

Wide familiarity among practitioners with the clinical use of aspirin facilitates understanding of salicylic acid derivatives, which are generally thought to provide most of the advantages of aspirin without the unwanted side effects. Salsalate, a prototypic salicylic acid derivative, was originally formulated to achieve this objective.[4]

Absorption

As mentioned, ingested salsalate is virtually insoluble in acidic gastric fluids (less than 0.1 mg/ml at ph 1.0[5]) and is readily soluble in the small intestine. Although it is a weakly acidic drug, there is no tendency for it to precipitate in acidic media; rather, it is maintained in a state of supersaturation by the gastric fluids.[6] Salsalate hydrolysis is known to begin intraluminally, although Hicklin[7] considers the extent of intraluminal hydrolysis to be negligible. This accords with Nordqvist's earlier view[8] that the molecule is at least partially hydrolyzed by intravascular esterases. The drug, either in tablet or capsule formulations, provides similar peak plasma concentrations of both unchanged salsalate and salicylic acid. In addition, the time required to attain peak concentrations and steady-state levels is also similar.[9] Salsalate is thought to undergo continuing hydrolysis during transmucosal transit, as Humphreys[10] has shown with other salicylates. Unchanged salsalate continually undergoes hydrolysis to salicylic acid in all body fluids (Figure 4).

During the absorptive phase, plasma salsalate and salicylic acid concentrations rise more slowly than plasma levels of the more soluble salicylates. Goff[11] has shown this clearly in studies with rats, where 100 mg single doses of salsalate and aspirin were compared by following blood levels for 24 hours after administration. Corroborative studies[12,13] in man (Figure 5) show this same general relationship of salsalate to more soluble salicylates after single-dose administration. These studies merely confirm that salsalate has significantly slower absorptive characteristics after a single dose. However, Fixley et al.[14] noted that for chronically administered drugs the amount absorbed is much more crucial than rate of absorption. After repeated dosing with salsalate, no clinically significant differences occur in steady-state blood concentrations between salsalate and the more soluble salicylates.[7,15-20] This is borne out by recent studies of Dromgoole et al.[21] No statistical difference was observed in the steady-state plasma salicylic acid levels after molar equivalent doses of aspirin (5 gm daily) and salsalate (3.6 gm daily) were administered for five days. Consequently, areas under the curve of plasma concentration versus time (AUC), although slightly higher following aspirin, were also similar.

Apparent differences in blood levels between salsalate and other salicylic acid pro-drugs are explainable. On a milligram-for-milligram basis,[20,22] salsalate provides higher blood concentrations than does aspirin. However,

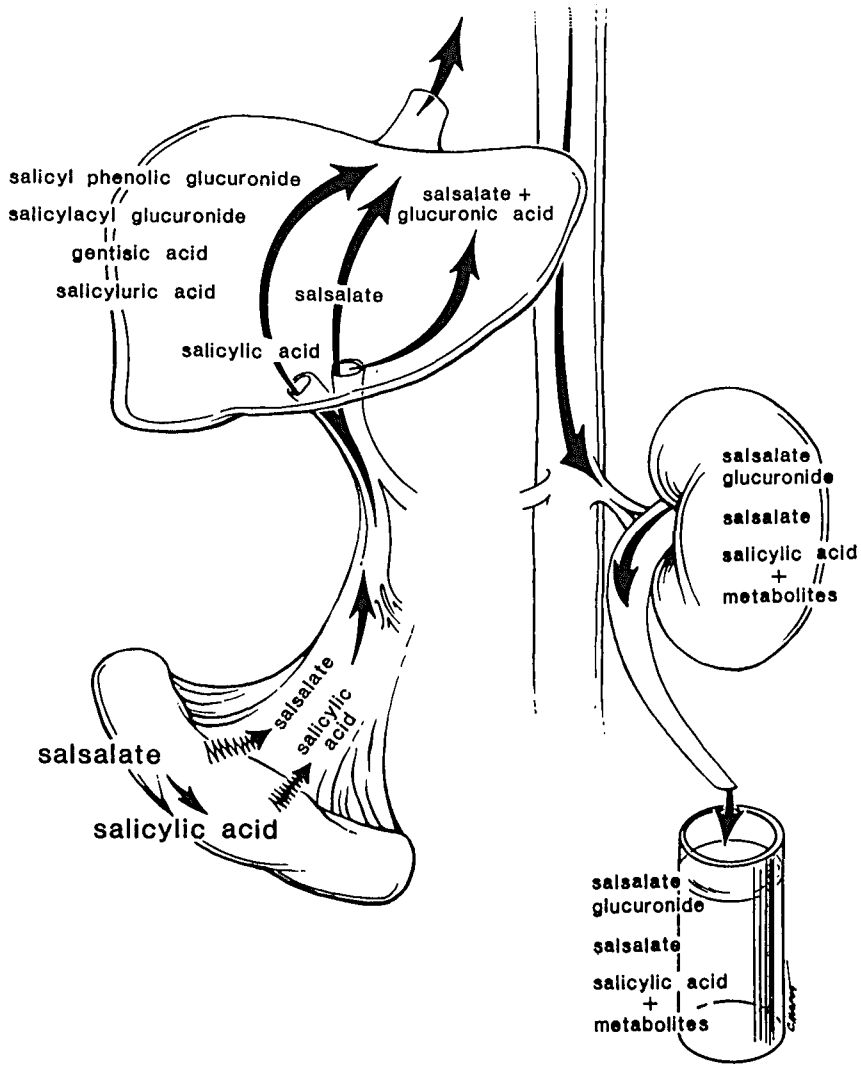

Figure 4. Proposed scheme for salsalate absorption, metabolism, and excretion.

when studied on the basis of molar equivalents of salicylic acid, salsalate shows about a 15 to 20% lower salicylic acid concentration than aspirin,[15,21,23] suggesting that some salsalate follows a metabolic pathway other than hydrolysis to salicylic acid[21] (Figure 4). In practice, therapeutic concentrations of salicylic acid are achieved by titration, irrespective of its precursor (Table II).

Metabolism

Although an early study by Hanzlik

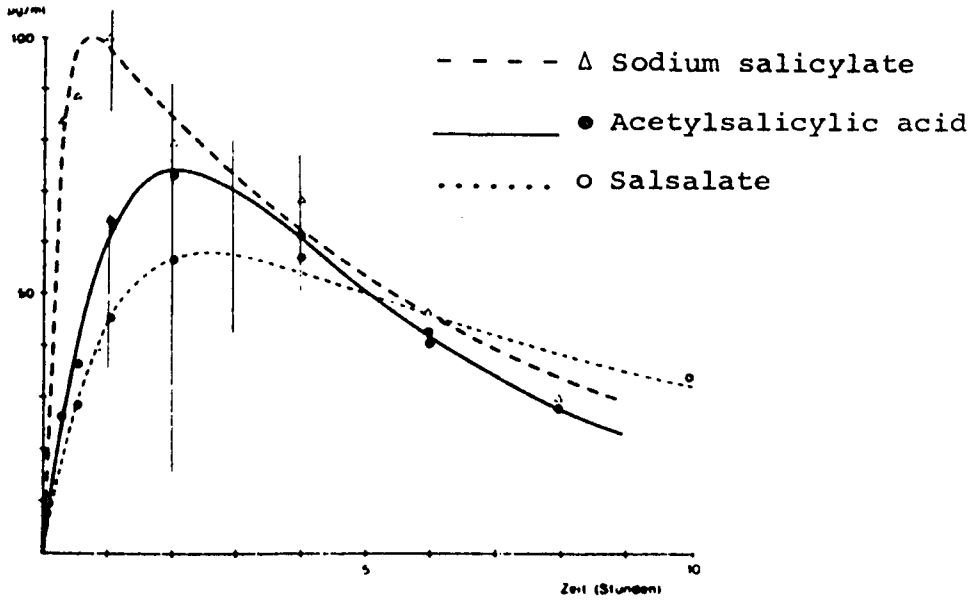

Figure 5. Comparative blood levels (man) of salicylic acid from salsalate and two highly soluble salicylate formulations

and Presho[3] demonstrated only negligible intraluminal hydrolysis of salsalate, the possibility of transmucosal metabolic change of the molecule is not precluded. Nevertheless, Nordqvist[24] has purportedly shown that 30 to 40% of the total concentration of salicylates in the blood is unhydrolyzed salsalate. Although both salsalate and aspirin are apparently well absorbed into the systemic circulation, aspirin is acted upon more rapidly by esterases and first-pass hepatic excursions; indeed, 32% of the drug is lost during its passage through the liver.[25] On the other hand, ester bonding of salsalate in whole blood and plasma is disrupted more slowly than that of aspirin. Further, salsalate hydrolysis occurs more slowly in whole blood than in plasma, and this may in part explain observed differences in the biological half-life of these two parent drugs.[26] The half-life of salicylic acid is the same despite its origin. These observations indicate that hepatic clearance, vascular and extravascular degradation, and elimination are less rapid for salsalate than for aspirin.

Assuming no further drug absorption, salicylic acid either rapidly conjugates with glycine (to form the major salicylic acid metabolite) or enters another slower conjugation-excretion route. (Figure 6).[27] These events are well documented and need no additional comment here. However, a recent study by Dromgoole et al[21] has revealed the presence of a glucuronide conjugate of intact salsalate in urine and plasma. Expressed as the percentage of total

Table II. Steady-state salicylic acid (SA) blood levels reported by various investigators.

Reference	Pro-drug Dose*		Steady-State Day	Mean Blood Level SA (mg%)		Elimination half-life SA		Subjects/ Patients
	SSA	ASA		SSA	ASA	SSA	ASA	
Jeretin[15]	3.0 gm/day	3.9 gm/day	4-6**	18.1	25.8	5.1	4.4	Subjects
French and Mildon[20]	3.0 gm/day	3.306 gm/day	3	19.49	18.3	***	***	Subjects
Santillan[22]	4.0 gm/day	4.2 gm/day	3	32.02	25.68	†	†	Subjects
Dromgoole et al.[21]	3.6 gm/day	5.0 gm/day	12	22.5	26.2	—	—	Patients
Paulus et al.[31]	—	4.0 gm/day††	3	—	16.2	—	6-16‡	Patients
Cohen[53]	3.0 gm/day	3.9 gm/day	5	15.9	17.4	—	—	Subjects
Leonards[16]	3.0 gm/day	4.2 gm/day	8	‡‡	‡‡	—	—	Subjects
Liyange and Tambar[19]	3.0 gm/day	3.6 gm/day	14	13.5	12.9	—	—	Patients

*SSA = salsalate; ASA = acetylsalicylic acid.
**Means of three days.
***Elimination rate/hour for SSA = 0.498 mg%; ASA = 0.73 mg%. These were less than theoretical rates for arthritis patients (i.e., 0.83 mg%/n) reported by Paulus et al.[31] $T_{1/2}$ not calculated.
†Elimination rate/hour for SSA = 0.837 mg%; ASA = 0.562 mg%. $T_{1/2}$ not calculated.
††65 mg/kg/day.
‡Serum levels 10 to 26 mg%, respectively.
‡‡Serum levels (not reported) stated by author to be "of the same order of magnitude."

urinary salicylate, the salsalate-metabolite ranged to as much as 13% (Figure 6).

Protein binding (especially albumin[27]) accounts for 50 to 80% of plasma salicylic acid, although the free-drug concentration may change in proportion to serum albumin changes, as in rheumatoid arthritis. Unchanged prodrug and its various metabolites at certain concentrations may compete for available binding sites, each moiety having different binding characteristics. This is probably dose-concentration related; Smith[28] found unbound plasma salicylate to increase with dose. Similarly, urinary elimination varies inversely with an increase in plasma protein concentration.[29]

Salicylic acid does not follow first-order kinetics: Its biological half-life increases with dose. Levy[30] and Paulus[31] have shown that such capacity-limited metabolism can increase usual salicylic acid half-life from about 3.5 hours to as long as 30 or more hours. Thus dosage frequency can be reduced from three or four times daily to twice daily when adequate steady-state blood levels are attained.

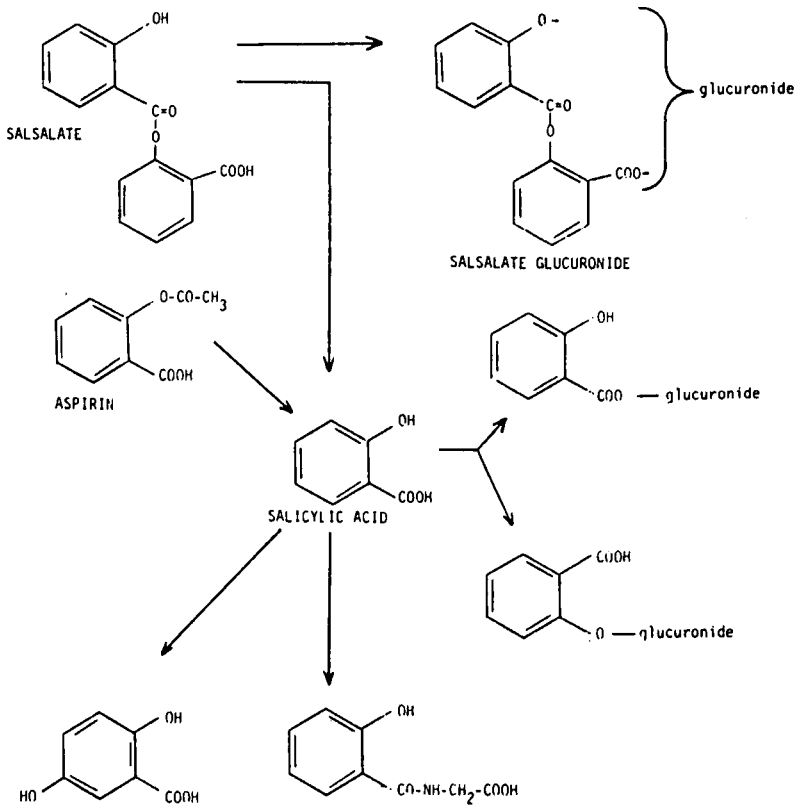

Figure 6. Known metabolism of salsalate, aspirin, and salicylic acid. Recent study[21] has revealed a new metabolite of salsalate (salsalate glucuronide).

Distribution

Volume of distribution is a function of: 1) the ester bond, 2) protein binding, 3) ionization, and 4) pH of body fluids and tissues. Absorbed salicylates are widely distributed to all body tissues.[27] However, Nordqvist[32] and Jeretin[15] cite differences in distribution between aspirin and salsalate, with faster rates for the nonacetylated compound thought to account for lower AUC values.[21,23] This may be due either to a shift of intact salsalate into other body compartments or to its prompt conjugation with glucuronic acid.

Salsalate has an affinity for tissues that synthesize mucopolysaccharides (especially connective tissue and cartilage.[13] It was shown by Aberg and Larsson[33] to be superior to aspirin for inhibiting *in vitro* absorption by cartilage of S_3 sulphate—a test of antirheumatic effect. However, the study by Dromgoole et al.[21] revealed no differences between aspirin and salsalate; the volume of distribution was 11.2 liters and 11.0 liters, respectively, with no statistically significant difference noted.

Excretion

Salsalate is excreted primarily by the kidneys in the form of small amounts of unchanged drug, a glucuronide conjugate, salicylic acid, and various salicylic acid metabolites (Figure 4). As with aspirin and other salicylic acid prodrugs, salsalate excretion is influenced by the presence of kidney disease, inhibitors that compete for the transport system in the proximal tubules (e.g., probenecide, para-aminohippurate, and acetazolamide,[27] and urinary pH changes toward alkalinity.

MODE OF ANTIRHEUMATIC ACTION

Because of the wide use of aspirin and other salicylic acid pro-drugs in rheumatic diseases, their anti-inflammatory actions are coming under increasing scientific investigation. Such study has presented a conceptual grasp of the pertinent physiologic events. Horan[34] noted that acute inflammatory edema develops phasically over about a three-hour period. The first phase, 30 minutes to one hour, is mediated by histamine and serotonin, and the transudate is cell- and protein-poor. At one hour it becomes richer in granulocytes and protein and is thought to be mediated by kinins (perhaps partly as a result of polymorphonuclear cells). Prostaglandins (PG) may mediate the response at three hours; indeed, it was noted by Zurier[35] in a carrageen edema preparation that PGE_2 appeared at three hours and was maximal at 12 to 24 hours. A fourth mitotic phase characterizes repair of the injury.

Aspirin is active only in the delayed phases, after one hour. The exact mechanism is unknown, but the wealth of recent data regarding this drug's demonstrable inhibition of cyclooxygenase and prostaglandins synthetase must certainly be involved. Salsalate, with clinically comparable antirheumatic actions, does not exert similar inhibition during *in vitro* tests, but the likelihood still exists that such inhibition may be exerted *in vivo* by its metabolite (i.e., salicylic acid). Indeed, Hamberg[36] has shown that sodium salicylate and aspirin are equally effective in suppressing prostaglandins formation in man.

This does not suggest any unanimity of findings correlating inhibitory effects on prostaglandin biosynthesis with anti-

inflammatory activity. In certain animal models, aspirin and nonacetylated salicylates do not behave similarly in this regard.[34,37,38] However, in carrageenin-induced rat paw edema, virtually all NSAIDs are active. But Glenn et al.[37] reported an interesting dissociation: Both phenacetin and acetaminophen do not inhibit prostaglandin biosynthesis yet are equipotent to aspirin in anti-inflammatory action in this test.

These recent reports have not quieted the considerable speculation and differing views concerning the biochemical mechanisms by which NSAIDs act as anti-inflammatory agents. Earlier hypotheses proposed effects on oxidative phosphorylation,[39] leukocyte migration,[40] lysosomal membrane stabilization,[41] and other suggested mechanisms described by Ferreira.[42] In addition, there is no evidence that NSAIDs are effective through production of endogenous steroids by pituitary-adrenal stimulation. In 1971, Vane[43] drew attention to prostaglandin biosynthesis, following his discovery that aspirin-like drugs inhibited potent biochemical mediators of inflammation. He found that most NSAIDs with known clinical antirheumatic activity had correlative effects in several *in vitro* and *in vivo* prostaglandin tests. These effects are presumably mediated by inhibition of cyclooxygenase and synthetase.

A discrepant finding of early *in vitro* experiments, as noted above, showed that nonacetylated salicylates, including salsalate, did not inhibit the prostaglandin enzymatic system. In response, Willis et al.[44] advanced the idea that salicylic acid *in vivo* must be converted to an "active metabolite" possessing these desirable inhibitory qualities. But efforts thus far to identify this metabolite have not succeeded. Possibly, the active metabolite is salicylic acid itself, as suggested by Smith,[38] in accordance with Hamberg's above mentioned report[36] that prostaglandin biosynthesis is equally suppressed by aspirin, sodium salicylate and indomethacin. Smith[38] and Vane[45] recently exchanged views on the anomalous behavior of salicylic acid in *in vitro* prostaglandins tests (i.e., lack of enzyme inhibition). Both investigators allow that salicylic acid may exert anti-inflammatory effects other than those mediated through the prostaglandin system.

Further distinctions between acetylated and nonacetylated salicylate drugs are observed in platelet function regulated by the prostaglandins. Nonacetylated forms do not inhibit platelet function (see *Safety* below) whereas about one fortieth of the effective antirheumatic dose of aspirin irreversibly acetylates platelet cellular cyclooxygenase. Active enzyme returns with a time course reflecting platelet turnover (approximately 8.2 days[46]) and may indicate an effect on megakaryocyte cyclooxygenase. Thus aspirin is unique among NSAIDs. It is the only drug to irreversibly inactivate prostaglandin enzyme systems by transfer of its chemically labile acetyl group (transacetylation) to a protein component of this system.[47] This effect may cause the prolonged bleeding time and gastrointestinal blood loss widely reported after aspirin use; in contrast, even high antirheumatic doses of nonacetylated salicylates apparently do not share these liabilities.

SAFETY

Toxicity

Oral administration of salsalate or aspirin to MMRI mice indicated that the LD_{50} was in the same range for both drugs, at least 20 times an average daily dose. Child et al.[48] gave both drugs by oral and subcutaneous routes to rats. Determinations of the LD_{50} were similar, as was gross pathology, despite the route of administration. Using Shay rats, these investigators then evaluated potential gastric irritation liabilities for salsalate, aspirin, and placebo. Results indicated a greater protective action by salsalate against gastric ulcer production. Long-term comparative teratogenic studies by Eriksson[49] concluded that the fetus-damaging effects were not different for salsalate, aspirin, and sodium salicylate. Phillips[50] has demonstrated a clear dose-related gastrointestinal bleeding response in dogs given the equivalent of one, two or three 5-grain tablets twice daily. Other symptoms of toxicity attributable to salicylic acid are essentially the same, irrespective of the precursor drug used.

Laboratory

Unlike NSAIDs in general, prolonged use of salsalate is not regularly associated with blood or urological abnormalities. The lack of acetylation reduces both sensitivity reactions and the induced alteration of plasma proteins[51] with its consequences. So-called transaminitis or salicylate hepatitis, an occasional complication of salicylate therapy,[52] has not been detected in any clinical trials with salsalate. Indeed, significant laboratory abnormalities with this agent are the exception. Cohen[53] reported that two subjects in his study had elevated SGOT values while taking placebo; these abnormal values gradually returned to normal during and following subsequent treatment with salsalate. A recent study by Golje[54] with 18 rheumatoid arthritic patients provides further evidence of safety. Salsalate was taken for three months at recommended doses. Eleven patients who completed 12 weeks of follow-up had mean transaminase values of SGOT 13.09 units/ml and SGPT 12.45 units/ml (Sigma Frankel units).

Salsalate is not only virtually free of gastric bleeding liability,[4,5,16,19,53,55] but also appears to cause none of the hematological changes of aspirin.[4,5] In addition to lack of any apparent adverse impact on the gastrointestinal tract, salsalate does not alter platelet aggregation or bleeding time.[13,14] Estes[56] recently studied a small group of rheumatoid and osteoarthritis patients (including one patient with lupus erythematosus) to evaluate potential salsalate effects vs those of aspirin and placebo on bleeding time and platelet aggregation. Patients had been on long-term salsalate therapy. Bleeding time was demonstrably prolonged and platelet aggregation impaired following aspirin but not after salsalate or placebo. Thus, as Hume suggests,[57] salsalate might be used instead of aspirin in circumstances where there is any tendency to gastrointestinal or genitourinary bleeding, in the presence of anticoagulant therapy, or prior to surgery of the central nervous system. Also, Salick[58] has noted no significant hematologic

changes during one month of careful observation of rheumatoid arthritis patients taking salsalate.

Clinical

The safety and efficacy of salsalate promote compliance and enhance the doctor-patient relationship because a degree of clinical response can be expected. Even arthritic individuals with peptic ulcers seem able to tolerate salsalate without the bother of also taking antacids, which add significantly to the difficulty of controlling blood salicylate levels. The lack of acetylation of the salsalate molecule reduces certain allergic phenomena, such as skin rash, angioedema, asthma, and nasal polyps. If acetylated proteins are antigenic, as Farr postulated,[59] then such "antigens" may work in concert on immunological mechanisms with aspirin anhydride, an impurity present in many aspirin preparations now available.[60] Jeretin[15] also scores the allergenic potential of this anhydride but suggests that more recent aspirin formulations are free of this contaminant.

Preliminary clinical experience with salsalate in patients with lupus erythematosus and juvenile rheumatoid arthritis has turned up no evidence of liver toxicity.[61] However, nonacetylated salicylates have produced laboratory changes indicative of such toxicity. In this regard, the lack of transaminitis cited above is encouraging, as is the impressive safety record shown for salsalate in numerous clinical efficacy trials in the United States and in Europe. Large multicenter trials conducted in these two areas found salsalate particularly well tolerated in terms of gastrointestinal effects; more than 90% of 1,283 mostly arthritic patients were free of such complaints.[62,63]

Commenting on salsalate safety, Liyanage and Tambar[19] compared it with aspirin and placebo in 20 patients with osteoarthritis of the hip or knee. Salsalate and aspirin produced comparable clinical improvement and serum salicylate levels, but salsalate was significantly better in terms of side effects and gastrointestinal blood loss. Fecal blood loss from aspirin is apparently independent of HCl. St. John and MacDermott[64] found significant blood loss in both patients with pernicious anemia and control patients.

In one of the multicenter trials[62] with salsalate less than 4% of patients had detectable fecal blood (not controlled for dietary intake, gum abrasion from toothbrush, etc.). Hicklin[7] noted that even patients with detectable blood in their stool became negative during treatment with salsalate. Further controlled studies by many investigators here and abroad confirm empirical clinical observations that salsalate has far less predilection for gastric irritation or erosion than aspirin and perhaps other salicylates as well (Table III).

CLINICAL EFFICACY

Available data concerning clinical experiences with salsalate in almost 2,000 patients who were mostly arthritic suggest several important facts useful to doctors concerned with long-term management. The effective daily dose of salsalate is, on average, 3 gm. This dose consistently provides steady-state blood levels of salicylic acid of approximately 10 to 30 mg (Table II) but, as Paulus[31]

Table III. Gastrointestinal blood loss studies conducted in animals and man by various investigators.

Reference	Species	Method	Subjects/ Patients	No. of Patients	Drugs*/Dose	Plasma Concentrations of Salicylic Acid	Results
Aberg[67]	Guinea pigs	Visual and photographic	—	24	ASA/100 mg/kg SSA/100 mg/kg	—	Mucosal erosions/animal: ASA 31.6, SSA 0.9
Aberg[67]	Guinea pigs	Direct: microscopic	—	25 ea.	**/100 mg/kg	—	Mucosal erosion/animal: ASA 31.9, SSA 2.4, CaASA 10.4, NaSal. 5.0, Salicylamide 2.4
Thune[4]	Man	Modified: benzidene	Patients	22	ASA/3.0 gm/day SSA/3.0 gm/day	—	ASA > SSA—difference statistically significant
Edmar[55]	Man	X-ray gastro-camera	Subjects	8	ASA/4.0 gm/day SSA/4.0 gm/day	—	ASA produced widespread erosions; SSA, minor changes in one subject
Cohen[53]	Man	^{51}Cr-tagged RBCs	Subjects	20	ASA/3.9 gm/day SSA/3.0 gm/day	17.4 mg%*** 16.0 mg%	ASA > placebo ($P < 0.01$) SSA = placebo
Liyanage and Tumbar[19]	Man	—	Patients	20	ASA/3.6 gm/day SSA/3.0 gm/day	12.9 mg% 13.5 mg%	ASA > SSA ($P < 0.02$)†
Leonards[16]	Man	^{51}Cr-tagged RBCs	Subjects	12	ASA/4.2 gm/day SSA/3.01 gm/day	††	ASA > placebo—difference statistically significant SSA = placebo

*ASA = aspirin; SSA = salsalate.
**SSA vs ASA, Ca ASA, Na salicylate, salicylamide.
***Day 5, 12 hours after last dose.
†Four patients positive for fecal blood on placebo reverted to negative while taking SSA. Another four became positive on ASA, and of these three became negative while taking SSA.
††Serum levels were "same order of magnitude."

and others clearly point out, attainment of such concentrations of salsalate is best achieved by individual titration of daily dosage.

An acceptable daily dosage is well within the tolerance of most patients, as was clearly indicated in two large multicenter trials in mostly arthritic patients.[62,63] If patient compliance is linked to drug efficacy, as Rooney et al.[65] suggest,[61] the 92 and 96% rates found in these two studies augur well. Virtually every clinical study reviewed (Table IV) concluded that salsalate and aspirin were therapeutically equivalent. This conclusion is augmented by a fairly unanimous judgment of investigators that salsalate is fairly safe when compared to other salicylates. These two observations indicate the drug is suited for the intense and prolonged treatment required in managing arthritic patients.

In addition to comparable clinical effectiveness with aspirin, salsalate has several important advantages. Fewer significant side effects related to the gastrointestinal tract permit greater confidence in the presence of peptic ulcer or other irritative disorders of the gastric mucosa, or in the treatment of patients with asymptomatic gastrointestinal disease. Safe use of the drug before and after surgery results from its demonstrated lack of adverse hematologic effect. Improved control of night pain and morning stiffness combine with a simplified daily dosage schedule to improve patient compliance, so vital to any successful management of these disorders.

PERSONAL CLINICAL EXPERIENCE

The role of NSAIDs in management of a group of 15 patients was reviewed with respect to the number of different agents used and the efficacy/toxicity ratio of each. All 15 patients had taken full-dose aspirin for a mean period of 3.6 months, with maintenance of serum salicylate levels between 20 and 28 mg%. Twelve of the 15 patients experienced limiting side effects ranging from tinnitus and transient deafness to nausea and epigastric pain. Stool guaiacs were positive in every patient and peptic ulceration complicated therapy in one patient. Because of side effects aspirin use was abandoned, and each patient was administered various other NSAIDs under close supervision for trial periods averaging 1.5 months. All such drugs were discontinued for a variety of reasons including the following: 1) recurrence of gastrointestinal and/or CNS symptoms (epigastric pain, flatulence, headache, and unusual disturbances); 2) worsening of synovitis and increased morning gel phenomenon; 3) edema and weight gain; 4) major GI bleeding with endoscopic evidence of erosive gastritis.

Salsalate was subsequently prescribed for these patients in daily dosages ranging from 2 to 4 gm. After an average of six months, 12 of the 15 patients reported improvement: shorter duration of morning stiffness, decrease in the number of painful, swollen joints, increase in grip strength, and general enhancement of well-being.

Two additional rheumatoid arthritis patients not included in this group of 15 were initially found to have classic problems with respect to management. A 54-year-old woman with severe seropositive, nodular-erosive rheumatoid arthritis developed upper gastrointestinal bleeding with radiographic

corroboration of gastric ulceration. She had been taking only acetaminophen. In addition to suffering serious side effects, her joint symptoms were not measurably improved. Salsalate was begun in a divided dosage of 3 gm per day. After a year of therapy her joint disease was well controlled with no recurrence of gastrointestinal bleeding or symptoms. The other patient, a 62-year-old woman with known severe coronary artery disease and rheumatoid arthritis, was given concomitant warfarin and salsalate at the full daily recommended dose. Close monitoring of prothrombin times revealed no interference of salsalate with her anticoagulant therapy.

Experience with both patients bears out what has been well established in the literature: the safety of salsalate with respect to gastrointestinal ulceration and bleeding, and a lack of clinically significant interaction with long-term use of anticoagulant drugs. Global assessment of these rheumatoid arthritic patients with chronic active synovitis lends clinical support to the reported efficacy of salsalate in major inflammatory joint disease and suggests remarkable safety and tolerance.

QUESTIONS AND ANSWERS

Some pertinent questions relevant to this topic are answered below.

Are there any elements of rheumatoid arthritis that predict a severe disease course?

Certain, discrete prognostic markers should alert clinicians to the possibility of more severe disease: rheumatoid nodules, generally seen in 20 to 50% of RA patients; high titer of rheumatoid factor; persistent high sedimentation rates; and development of extraarticular lesions. Particularly alarming are systemic implications of rheumatoid arthritis—extraarticular disease; pleuritis, pericarditis, iridocyclitis, pneumonitis, and digital infarction—which often spell systemic necrotizing vasculitis and are grave findings. In my experience, males with onset of classic nodular-erosive rheumatoid arthritis with high titer rheumatoid factor activity in serum are the greatest challenge.

Should all rheumatoid arthritic patients in remission while on chrysotherapy have treatment discontinued?

There is an emerging concept that chrysotherapy should be continued on a low-dose maintenance level once remission is achieved. Also, according to the Empire Rheumatism Council Study,[68] the old 20-week standard course of gold usually will not induce sustained remission of disease activity. Accordingly, I suggest continuing gold injections, barring toxicity (i.e., dermatitis, mucosal ulcerations, hematuria/proteinuria, and hemopoietic disturbances), ultimately changing from a regimen of 50 mg intramuscularly (IM) per week to one of 50 to 100 mg IM per month (maintenance level).

What is known of the pathogeneses of rheumatoid arthritis?

Rheumatoid arthritis is a classic model of autoimmune disease. An initiating event, possibly of viral cause, leads early to the local alteration of native IgG in the environs of the synovial membrane. This appears to elicit a plasmacytic response with subsequent production of antialtered IgG, IgM rheumatoid factors. Complexes of rheumatoid factor and IgG form and elicit

Table IV. Salsalate (SSA) clinical efficacy reported by various investigators.

Reference	Diagnoses	No. of Patients	Daily Pro-drug Dose*		Results	Side Effects	Comments
			SSA	ASA (other)			
Nordqvist[8]	RA, OA, other	96	3.0 gm	3.0 gm	Comparable, less morning stiffness with SSA	Less GI with SSA	30-day trial. Longer duration of SA** blood levels with SSA
Thune[4]	RA, OA	22	3.0 gm	3.0 gm	Significantly less GI with SSA	—	Therapeutic efficacy not evaluated
Deodhar et al.[1]	RA (classical)	15	3.0 gm	75.0 gm (indo-meth-acin)	Both drugs significantly better than placebo in most indices	Comparable between drugs & placebo	1-week crossover trial
Liyanage & Tambor[19]	OA (hip, knee)	20	3.0 gm	3.6 gm	Comparable	ASA > SSA (including blood loss)	2-week crossover trial
Regaldo[66]	RA, OA, other	66	3.0 gm	—	Marked improvement in joint pain and morning stiffness	Mostly dyspepsia	6-week trial

(Multi-clinic[63])	RA, OA, other	1,181	3.0 gm	—	75% efficacy	Present in 27%	4-week trial. Marked improvement in pain and stiffness (morn./night)
Ré[62]	RA, OA, other	102	3.0 gm	—	67% efficacy	Present in 24 patients	15-day trial. Only 2 of 54 patients monitored had demonstrable fecal blood loss.
Droomgoole et al.[21]	RA (hospitalized)	6	3.6 gm	5.0 gm	Comparable	> GI complaints with ASA	7-day crossover trial. (SSA dose may be increased owing owing to lower bioavailability)
Hicklin[7]	RA, OA	61	3.0 gm	—	Satisfactory pain relief	High incidence (mostly salicylism)	4-week trial
Hicklin[7]	OA	20	3.0 gm	0.5 gm (diflunisal)***	Comparable	Minor	2-week trial with SSA versus 4-week trial with diflunisal. Data biased against SSA.

*ASA = acetylsalicylic acid.
**SA = salicylic acid.
***Diflunisal, a nonionizing salicylic acid precursor.

complement activation. Chemotaxis of inflammatory polymorphonuclear leukocytes ensues with immune adherence of the complex and phagacytosis. The formation of lysosomal vacuoles about the immune complex eventually leads to rupture of the PMN cell membrane, releasing multiple lytic enzymes on articular cartilage. Erosion of cartilage, pannus formation, and ultimate derangement of joint function follow. This general scheme simplistically explains part of the pathogenetic mechanism in rheumatoid arthritis.

The vicious cycle of autoimmune aberrations precipitating acute and chronic inflammation has histopathologic correlates: chronic synovitis, rheumatoid nodulosis, erosive destruction of cartilage, and the demonstration of immune complexes (RF and C_3) in the synovial membrane. Cellular immune dysfunction, too, participates in the perpetuating cycle of chronic synovitis, as seen in the model of rheumatoid arthritis. Through refinement of knowledge based on our concept of pathogenesis, we may better understand and control these local and systemic immunologic dysfunctions.

Should anti-inflammatory agents be used with gold or D-penicillamine in the patient with rheumatoid arthritis?

Absolutely yes. We consider anti-inflammatory drugs the primary step as well as the backbone of chronic therapy programs in rheumatoid arthritis. Where there is uncontrolled synovitis and steady progression of disease activity, we turn to the "remitting" or "slow-acting" therapeutic agents. This group comprises antimalarials, gold salts, D-penicillamine, and immunosuppressive drugs. I suggest that anti-inflammatory drugs are an essential part of the management of patients throughout the natural history of their disease. Slow-acting agents, including D-penicillamine, represent a complementary extension of anti-inflammatory treatment in a holistic approach to drug therapy aspects of management.

Where does salsalate fit in the scheme of drug therapy for arthritic patients?

A long-standing concept of management in patients with rheumatoid arthritis and degenerative joint disease is that aspirin represents the initial approach to drug therapy. This remains true in 1980, with some qualifications. The vast majority of patients treated with aspirin dosages sufficient to achieve serum salicylic acid levels between 15 and 30 mg% experience some degree of side effects, principally gastrointestinal. I have also found that many patients have great difficulty taking full-dose aspirin and will admit to very poor compliance.

When there is intolerance to aspirin, poor patient compliance, or major contraindications to aspirin usage (i.e., peptic ulcer disease or anticoagulant drug therapy), I have used salsalate as the primary drug therapy. Most of these patients had satisfactory clinical improvement and found it easier to comply with prescribed dosage regimens. Thus re-emergence of nonacetylated salicylic acid derivatives as alternatives to aspirin therapy in the intolerant patient is a great step forward.

Is salicylate therapy ever effective in other rheumatic diseases such as sys-

temic lupus erythematosus?

Yes. Salicylates have been considered the cornerstone of management, not only in rheumatoid arthritis and degenerative joint disease, but also in acute rheumatic fever and mild systemic lupus erythematosus. Lupus patients regularly present arthralgia as a major symptom. Frequently, such arthralgia responds favorably to salicylic acid pro-drugs. For those who complain of major aspirin intolerance or bothersome transaminitis, I have used salsalate to relieve side effects, with equally effective control of symptoms.

REFERENCES

1. Deodhar, S.D., McLeod, N.M., and Dick, W.C. (1977): A short-term comparative trial of salsalate and indomethacin in rheumatoid arthritis. *Curr. Med. Res. Opin. 5,* 185–88.
2. Stevens, L.A. (1977): Some physical, chemical and biopharmaceutical studies on salicylsalicylic acid, pp. 5–14, 309, 312. Ph. D. dissertation, University of Bath, Bath, England.
3. Hanzlik, P.J., and Presho N.E. (1926): The salicylates, XV, Liberation of salicyl from and excretion of salicylsalicylate. *J. Pharmacol. Exp. Ther. 26,* 61–70.
4. Thune, S. (1968): Gastrointestinal bleeding and salicylates. *Nord. Med. 79,* 352–54.
5. Rothschild, B.M. (1979): Commentary: Hematologic perturbations associated with salicylate. *Clin. Pharmacol. Ther. 26,* 145–52.
6. Stevens, L.A., and Padfield, J.M. (1976): The crystallization characteristics of salicylsalicylic acid (SSA) in different media: their biopharmaceutical significance. *J. Pharm. Pharmacol. 28–1P (Suppl).*
7. Hicklin, J.A. (1978): Relationship of plasma salicylate levels to pain relief with two different salicylates. *Curr. Med. Res. Opin. 5,* 572–79.
8. Nordqvist, P. (1964): Salicylsalicylic acid in the treatment of rheumatoid diseases and pain. Lecture held at the yearly congress of the Swed. Med. Soc., Stockholm.
9. Unpublished clinical study. Data on file, Medical Affairs Section, Riker Laboratories, Inc.
10. Humphrey, K.J. and Smy, J.R. (1975): The absorption of benorylate from everted sacs of rat intestine. *J. Pharm. Pharmacol. 27,* 962–64.
11. Goff, S. and Grelis, E. (1955): Rat blood salicylate levels following single oral doses of salicylsalicylic acid and acetylsalicylic acid. *Fed. Proc. 14,* 344.
12. Unpublished clinical study. Data on file. Medical Affairs Section, Riker Laboratories, Inc.
13. Nordqvist, P. (1976): Disalicylic acid. *Aktuel. Gerontol. 6,* 31–36.
14. Fixley, M., Shen, D.D., and Azarnoff, D.L. (1977): Theophylline Bioavailability. *Am. Rev. Respir. Dis. 115,* 955–62.
15. Unpublished clinical study. Data on file, Medical Affairs Section, Riker Laboratories, Inc.
16. Leonards, J.R. (1969): Absence of gastrointestinal bleeding following administration of salicylsalicylic acid. *J. Clin. Lab. Med. 74,* 911–14.
17. Unpublished clinical study. Data on file, Medical Affairs Section, Riker Laboratories, Inc.

18. Nordqvist, P., Harthon, J.G.L., and Karlsson, R. (1968): The relation between body weight and concentration of salicylate in plasma in adults. *Nobel-Pharma No. 2.*

19. Liyanage, S.P. and Tambar, P.K. (1978): Comparative study of salsalate and aspirin in osteoarthritis of the hip and knee. *Curr. Med. Res. Opin. 5,* 450–53.

20. French, I.W. and Mildon, C.A. (1978): Salsalate (S-S) and acetylsalicylic acid: Overnight maintenance of therapeutic serum salicylate levels. *Clin. Therap. 1,* 353–58.

21. Unpublished clinical study. Data on file, Medical Affairs Section, Riker Laboratories, Inc.

22. Santillan, I. (1978): Overnight serum salicylate levels: A comparison of salicylsalicylic acid and acetylsalicylic acid. *Curr. Therap. Res. 23,* 345–50.

23. Cohen, A. (1978): A comparative blood salicylate study of two salicylate tablet formulations utilizing normal volunteers. *Curr. Therap. Res. 23,* 772–79.

24. Nordqvist, P. (1964): Lecture, Svenska Läkarsälskapets Riksstämma. Stockholm.

25. Rowland, M., Riegelman, S., and Harris, P.A. (1972): Absorption kinetics of aspirin in man following oral administration of an aqueous solution. *J. Pharm. Sci. 61,* 379–85.

26. Harthon, L. and Hodstrom, M. (1971): Hydrolysis of salicylsalicylic acid in human blood and plasma: A comparison with acetylsalicylic acid. *Acta Pharmacol. Toxicol. 29,* 155–63.

27. Goodman, L.S., and Gilman, A. (1970): *The Pharmacological Basis of Therapeutics.* The MacMillan Company, London.

28. Smith, P.K., and Gleason, N.L. (1946): Study of pharmacology of salicylates. *J. Pharmacol. Exp. Ther. 87,* 237–55.

29. Hollister, L. and Levy, G. (1965): Some aspects of salicylate distribution and metabolism in man. *J. Pharm. Sci. 54,* 1126–29.

30. Levy, G. and Leonards, J.R. (1966): Absorption, metabolism and excretion of salicylates. In: *The Salicytes,* pp. 5–48. Editors: M.J.H. Smith and P.K. Smith. John Wiley and Sons, New York.

31. Paulus, H.E., Siegel, M., and Morgan, E. (1971): Variations of serum concentrations and half-life of salicylate in patients with rheumatoid arthritis. *Arthritis Rheum. 14,* 527–532.

32. Nordqvist, P., Harthon, J.G.L., and Karlsson, R. (1965): Metabolic kinetics of salicylsalicylic acid, aspirin and sodium salicylate in man. *Nord. Med. 74,* 1074–76.

33. Aberg, G. and Larsson, K.S. (1970): Pharmacological properties of some antirheumatic salicylates. *Acta Pharmacol. Toxicol. 28,* 249–57.

34. Horan, A.H. (1974): Can salicylates affect decidual cell reaction? *Obstet. Gynecol. 4,* 13–16.

35. Zurier, R.B. (1974): Prostaglandins inflammation and asthma. *Arch. Intern. Med. 133,* 101–10.

36. Hamberg, M. (1972): Inhibition of prostaglandin synthesis in man. *Biochem. Biophys. Res. Commun. 49,* 720–26.

37. Glenn, E.M., Bowman, B.J., and Rohloff, N.A. (1979): Anomolous biological effects of salicylates and prostaglandins. *Agents Actions 9,* 257–64.

38. Smith, M.J.H. (1978): Aspirin and prostaglandins: Some recent developments. *Agents Actions 8,* 427–29.

39. Whitehouse, M.W. and Haslam, J.M. (1962): Ability of some antirheumatic

drugs to uncouple oxidative phosphorylation. *Nature 196,* 1323–24.

40. McArthur, J.N., Dawkins, P.D., and Smith, M.J.H. (1971): The displacement of L-Tryptophan and dipeptides from bovine albumen *in vitro* and from human plasma *in vivo* by antirheumatic drugs. *J. Pharm. Pharmacol. 23,* 393–98.
41. Ignarro, J.L. and Colombo, C. (1972): Enzyme release from guinea pig polymorphonuclear leucocyte lysosome inhibited *in vitro* by anti-inflammatory drugs. *Nature (New Biol.) 239,* 155–57.
42. Ferreira, S.H. and Vane, J.R. (1974): New aspects of the mode of action of non-steroid anti-inflammatory drugs. *Ann. Rev. Pharmacol. 14,* 57–71.
43. Vane, J.R. (1971): Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature (New Biol.) 231,* 232–35.
44. Willis, A.L., Davison, P., Ramwell, P.W., et al. (1972): *Relief and actions of prostaglandins in inflammation and fever: Inhibition by anti-inflammatory and antipyretic drugs,* pp. 227–68. Editors: P.W. Ramwell, B.B. Pharris. Plenum, New York-London.
45. Vane, J. (1978): The mode of action of aspirin-like drugs. *Agents Actions 8,* 430–31.
46. Burch, J.W., Stanford, N., and Majerus, P.W. (1978): Inhibition of platelet prostaglandin synthetase by oral aspirin. *J. Clin. Invest. 61,* 314–19.
47. Roth, J.G., Stanford, N., and Majerus, P.W. (1975): Acetylation of prostaglandin synthetase by aspirin. *Proc. Natl. Acad. Sci. U.S.A. 72,* 3073–76.
48. Child, G.P., Larson, M., and Brisk, T. (1955): Acute toxicity and gastric irritation of acetyl and salicylsalicylic acids in the rat. *Fed. Proc. 14,* 326.
49. Ericksson, M. (1971): Salicylate-induced foetal damage during late pregnancy in mice: A comparison between sodium salicylate, acetylsalicylic acid and salicylsalicylic acid. *Acta Pharmacol. Toxicol. 29,* 250–55.
50. Phillips, B.M. (1973): Aspirin-induced gastrointestinal microbleeding in dogs. *Toxicol. Appl. Pharmacol. 24,* 182–89.
51. Pinkard, R.N., Hawkins, D., and Farr, R.S. (1968): *In vitro* acetylation of plasma proteins, enzymes and DNA by aspirin. *Nature 219,* 68–69.
52. Zucker, P., Daum, F., and Cohen, M.L. (1975): Aspirin hepatitis. *Am. J. Dis. Child. 129,* 1433–34.
53. Cohen, A. (1979): Fecal blood loss and plasma salicylate study of salicylsalicylic acid and aspirin. *J. Clin. Pharmacol. 19,* 242–47.
54. Golje: Personal communication. Manuscript in preparation.
55. Edmar, D. (1971): Effects of salicylates on the gastric mucosa as revealed by roentgen examination and the gastrocamera. *Acta Radiol. 11,* 57–66.
56. Personal communication. Manuscript in preparation.
57. Hume: Letter to editor (submitted).
58. Salick, A. (1978): Salicylates in the management of arthritis, a roundtable discussion. Medical Services Section, Riker Laboratories, Inc.
59. Farr, R.S. (1970): The need to re-evaluate acetylsalicylic acid (aspirin). *J. Allergy 45,* 321–28.
60. De Weck, A.L. (1971): Immunological effects of aspirin anhydride, a contaminant of commercial acetylsalicylic acid preparations. *Int. Arch. Allergy 41,* 393–418.
61. Personal communication.

62. Ré, O.N. (1979): Salicylsalicylic acid revisited: A multicenter study. *J. Int. Med. Res. 7,* 90–95.

63. Unpublished clinical study. Data on file, Medical Affairs Section, Riker Laboratories, Inc.

64. St. John, D.J.B. and MacDermott, F.T. (1970): Influence of achlorhydria on aspirin-induced occult gastrointestinal blood loss: Studies in Addisonian pernicious enemia. *Br. Med. J. 2,* 450–52.

65. Rooney, P.J., Capell, H.A., Paterson, S., et al. (1978): Continual use of non-steroidal anti-inflammatory drugs: An index of clinical efficacy. *Br. J. Clin. Pharmacol. 5,* 453–55.

66. Regaldo, R.G. (1978): The use of salsalate for control of long-term musculo-skeletal pain: an open, non-comparative assessment. *Curr. Med. Res. Opin. 5,* 454–60.

67. Aberg, G., Larsson, K.S. (1970): Pharmacological properties of some anti-rheumatic salicylates. *Acta Pharmacol. Toxicol. 28,* 249–257.

68. Empire Rheumatism Council Study (1957): Multicenter controlled trial comparing cortisone acetate and acetylsalicylic acid in the long-term treatment of rheumatoid arthritis. *Ann. Rheum. Dis. 16,* 277.