Chapter 49

Aspirin and Salicylate

by

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INTRODUCTION

The salicylates have a recorded history of over two millennia of continuous medicinal use. Probably because they are so widespread in common plants, so easily extracted, and so free of major toxicity, they were independently discovered to be useful by many cultures. Hippocrates, Celsus, Pliny, Galen, and many medieval herbalists recorded their use of salicylates. In a superb historical bibliography, Gross and Greenberg document this early history, including some of the amusing and now forgotten indications cited by early physicians.[1] For over two centuries the salicylates have been used to treat fever, and for over a century to treat rheumatism.

The happy outcome of a misguided experiment played an important role in the modern use of salicylates, as it has in the history of almost every antirheumatic drug we use today. In 1763, the Reverend Edward Stone wrote about his success in treating fevers with willow bark. He had tried willow bark because, like quinine-containing Peruvian bark which cured fever, it had a bitter taste, and because willows grow in the damp and might therefore be expected to cure fever, whose origin could often be traced to the damp. An active principle, salicylin, was isolated in 1826, and salicylic acid was derived from salicylin in 1838 and synthesized in 1852. Only when it was synthesized commercially in 1874, however, did its modern pharmacologic history begin. Acetylsalicylate was synthesized in 1853, but its modern pharmacologic history began only in the last decade of the century when F. Hoffmann of Bayer gave it to his arthritic father who could not tolerate salicylic acid for prolonged use. It was introduced widely in 1899 and was first used in the United States in that year.[2] Today salicylates are available in hundreds of forms,[3] and the annual consumption of pills is measured in the billions.

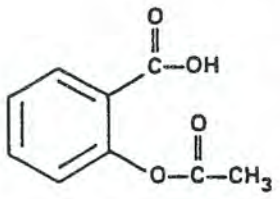
In the last quarter of this century the ancient salicylate family and its most successful member, aspirin (acetylsalicylic acid), are threatened by obsolescence. Drugs with similar or even equal therapeutic potency have been developed and may, if they prove safer, replace the salicylates. Never more than today, however, there is vigorous research on the action and toxicity of the salicylates, stimulated not only by the seminal discovery that they inhibit prostaglandin synthetase[4] but also by a desire to rescue them from oblivion by perfecting them.

STRUCTURE, ABSORPTION, AND METABOLISM*

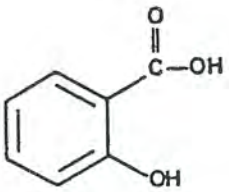
Salicylic acid is the common name for 2-hydroxybenzoic acid, and aspirin was originally a trade name but is now the common name for the salicylate ester of acetic acid (Fig. 49–1). Both are white powders relatively insoluble in aqueous solutions. Their sodium salts are more soluble, particularly in a slightly alkaline solution. The ionization constant, pKa, for the carboxyl hydrogen is 3.5 for aspirin and 3.0 for salicylic acid. Consequently, in the highly acid stomach both will be un-ionized, and in the body fluids, both will be largely ionized, though aspirin slightly less so. Because it is probable that the un-ionized rather than the ionized form of both drugs diffuses across cell membranes, it is worth remembering that, even far from the pKa, changes in pH can have marked changes in the proportion of drug which is ionized.[5]

When aspirin or salicylate tablets are placed in an aqueous solution, they visibly disintegrate with a speed that depends largely on various factors in their manufacture but in all events faster than the active drug goes into solution. The dissolution rate, too, is controlled by factors in tablet manufacture and plays a role in the subsequent fate of both aspirin and salicylate, since once dissolved the drug is absorbed very rapidly.[5] Generally aspirin or salicylate taken as a solution (for example, effervescent buffered aspirin) or

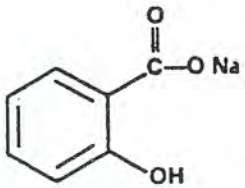
*This subject is well reviewed in Reference 5.



Aspirin



Salicylic Acid



Sodium Salicylate

Figure 49–1. The chemical structure of the principal salicylates.

in an easily soluble form such as sodium aspirin is more rapidly absorbed than standard aspirin.[6-8] Buffering may also accelerate dissolution.[9, 10] The drugs are available in many guises, none demonstrably better than the others for treating connective tissue diseases.

Acid in the stomach may cause the un-ionized form of the drug to form and precipitate, or the drug may remain in supersaturated solution,[6] but relatively little is known of the physical state of aspirin or salicylate in either the secreting or the nonsecreting stomach. Studies on the state of the drug in the overnight fasted stomach from which secretions have been aspirated may bear little relation to its state in a subject who eats and drinks and takes drug in irregular relation to food. Early observations of particles of aspirin in the stomach wall of patients who ingested drug just prior to gastrectomy have so many possibilities for artifact that they cannot be taken as having generality.[11] When awake subjects are gastroscoped after taking aspirin, such particles are not usually visible.

Aspirin and salicylate are absorbed to a certain extent by the gastric mucosa,[12-14] and it is likely that the low pH of the stomach contents, by causing the drugs to be un-ionized, facilitates absorption.[15, 16] Nevertheless, they can be absorbed from the neutralized stomach at a considerable rate.[17] Both drugs become ionized as they pass into the small intestine, because the pH is near neutrality. While this enhances solubility, it obviously diminishes the amount of un-ionized drug. Since the drugs are well absorbed from the intestine, either the ionized form is absorbed or the effective pH in the unstirred layer near the wall is much lower, thus allowing the proportion of un-ionized drug to rise,[15] or the enormous surface allows the rapid absorption of any un-ionized drug so that the drugs are continually pushed toward the un-ionized form. Although aspirin can spontaneously hydrolyze to acetate and salicylate in aqueous solution, the rate of spontaneous hydrolysis is low enough so that little or no free salicylate is found in the intestine; it is absorbed as aspirin, not as salicylate.[6]

Aspirin after absorption is metabolized exclusively to salicylate, and thereafter its fate is that of the salicylate ion; but because many clinicians believe that aspirin and salicylate differ in their effects in arthritis, because in some animal experiments the two drugs clearly differ in their antipyretic and analgesic properties (see below), and because their relative potency of inhibition of prostaglandin synthetase varies enormously from tissue to tissue,[18] it is important to understand the metabolism of both drugs.

Aspirin is the dominant form of the drug in plasma within the first 10 to 20 minutes after ingestion;[6, 19, 20] it can be detected for several minutes before there is any measurable salicylate;[21] and it even appears in joint fluid before salicylate. But it disappears very fast ($T_{1/2}$ 15 minutes), and consequently the blood level of aspirin is quite sensitive to the rate of absorption.[5]

Aspirin disappears by deacetylating to salicylate by one of three routes. It spontaneously deacetylates in plasma as it will in vitro in aqueous solution. It acetylates proteins, of which prostaglandin synthetase is the most notable example[22] but by no means the only one. Both hemoglobin[23] and albumin[24] have been shown to be acetylated, and doubtless other proteins and macromolecules are, too, including perhaps some cell surface macromolecules. And it is hydrolyzed enzymatically to salicylate, although it is by no means clear that this enzymatic activity is specific in any way for aspirin.[25] Since hepatic venous salicylate exceeds portal venous salicylate after an oral dose of aspirin, the enzymatic hydrolysis probably takes place in the liver, but it has not been localized to a well-characterized enzyme.[6, 26]

Aspirin and salicylate are partially bound to serum proteins, mainly albumin.[27] They diffuse into cells and across various membranes into body fluids such as the cerebrospinal fluid[28] and synovial fluid,[21] and they freely cross the placenta.[27] The diffusion is fairly rapid, and joint fluid levels, although never so high as serum levels, do reach 60 to 75 percent of serum levels in acute experiments, and drug can be detected there within 20 minutes of ingestion.[21] With increasing dose, the proportion of drug in plasma that is not protein-bound increases. Likewise, when plasma albumin is low, as in severe rheumatoid arthritis, less drug is protein bound. Since it is the free drug that diffuses to the site of its action, the pharmacologic and toxic effects of an increment in dose are greater when the dose is already high and when the plasma albumin is low. It is likely that many other factors influence the rates of passage of the drugs across biological membranes, for example, the proportion of un-ionized drug, which is sensitive to pH, and local protein binding.[29] The influence of these factors on the subsequent metabolism of salicylate, particularly during drug intoxication, is poorly understood but doubtless important.

Salicylate appears to be metabolized principally if not exclusively by the liver, although formal proof of this is lacking. There are three major and several minor metabolites of the drug which together satisfactorily account for its fate. They are all excreted into the urine, and drug recovery in the urine after an acute ingestion approaches 100 percent of the ingested drug. The major metabolite is the glycine conjugate, called salicyluric acid, and there are two glucuronide conjugates, one on the phenolic hydroxyl and one on the carboxyl group. At no time do these principal metabolites reach any significant proportion of the circulating salicylate.[30] The metabolites appear to be excreted quantitatively as soon as they reach the kidneys and can be found in the plasma only by sensitive chemical techniques. Their excretion depends on glomerular filtration and tubular secretion, is independent of urine flow or urine pH, and approaches but does not exceed renal plasma flow.[30] The quantitatively minor metabolite, gentisic acid, is important only because it has occasionally been shown to have prostaglandin synthetase–inhibiting properties,[31] but it is highly unlikely that it contributes to the clinical effects of aspirin.

It has long been known that serum levels of salicylate (it is impractical to measure serum levels of aspirin in a clinical setting) bear only the crudest relationship to the dose ingested even when corrected for body size, and that the full effect on serum level of an increase in dose may be reflected only after several days. Most strikingly, a small increment in dose may lead to a profound increment in serum level (for example, in one study the mean serum level was three-fold higher when the dose was 100 mg per kilogram per day than when it was 65 mg per kilogram per day),[32] and marked fluctuations in serum level may be observed without a change in dose. Furthermore, in contrast to aspirin, the plasma half-life of salicylate is many hours and is directly proportional to the serum levels; *the higher the serum level, the slower the disappearance*. The mystery of this erratic behavior has been solved by a number of excellent studies which have shown that the two major determinants of the serum level of salicylate are the urinary pH[33-35] and the activity of the enzyme which synthesizes salicylurate by conjugating glycine to salicylate.[36-39]

Urinary pH variations over the normal range profoundly affect clearance of salicylate by the kidneys. Salicylate is filtered at the glomerulus, and is both reabsorbed and secreted by the tubules. Below pH 6, salicylate clearance is about one tenth of creatinine clearance.[30] Above neutrality, salicylate clearance rises steeply and may reach almost twice the creatinine clearance in a slightly alkaline urine. Consequently, salicylate excretion may change from hour to hour, depending on the quantity and composition of ingested food, exercise, the normal diurnal fluctuations of urinary pH, pulmonary events, and the ingestion of antacids.[40] Because of these factors, and because below pH 6 there is no significant variation of salicylate clearance, metabolic studies are often carried out with concomitant urinary acidification.

The ingestion of antacid not only facilitates absorption by solubilizing drug in the intestines and accelerating gastric emptying; it also facilitates excretion by the kidneys. This property is found with both absorbable and the "nonabsorbable" antacids, which can lower steady-state serum salicylate levels despite a constant salicylate dose by their effect on urinary pH.[35] Likewise, withdrawal of antacids can cause a sudden rise in salicylate levels.

The other major determinant of serum salicylate is the rate of conjugation to glycine. Since the glycine conjugate salicylurate is the major metabolite when salicylate excretion is suppressed by acidification, the serum level is determined principally by the rate of production of salicylurate. In acute metabolic studies it has been found that above a serum level of about 6 mg per deciliter the rate of fall of serum salicylate is constant because there is a constant rate of production of salicylurate independent of the serum level.[32, 36] It appears that the extraordinary variation in serum levels among different individuals on a similar dose (serum levels ranged from 4 to 33 mg per deciliter in a group of patients with rheumatoid arthritis who took 50 mg per kilogram per day)[38] reflects variation in the level of the conjugating enzyme rather than in the kinetic parameters of the enzyme. The level of enzyme seems to be at least partially under genetic control; identical twins have very closely matched rates of salicylurate formation, while fraternal twins do not.[39] But the matter is not so simple, since with the continued ingestion of salicylate or aspirin, at least over several days, the level of enzyme rises somewhat.[38] There may be other determinants of the level of this enzyme too, for example, the ingestion of other drugs. The production of salicylate phenolic glucuronide is also saturable within the clinical dose range,[36] but since it accounts for only about a fifth of excreted metabolites when salicylate excretion is suppressed, variation in its metabolism will have little effect on serum levels. It should be noted that because of the limited capacity of the two major metabolic pathways of salicylate, as the serum level rises the proportion of salicylate that is not conjugated will rise, and hence the effect of urinary pH on excretion will be more profound.

Although aspirin and salicylate are rapidly absorbed and metabolized, under steady-state chronic ingestion with as many variables as possible removed, the serum salicylate level fluctuates little between doses. With a 4-hour dosing interval, the mean fluctuation is only 1 mg per deciliter, and with an 8-hour interval, 2.5 mg per deciliter, although individual patients may vary as much as 3 and 6.3 mg per deciliter, respectively.[32] The overall kinetic model for the metabolism of single doses of aspirin developed by Levy, Tsuchiya, and Amsel[36] is well substantiated by experimental results.[37]

What is the clinical importance to the rheuma-

tologist of the studies on the absorption and metabolism of the various salicylates? The studies have uncovered a good deal about the pharmacology of this important and fascinating drug family, but still little is known about the absorption and metabolism of the drugs in patients who take them regularly over long periods,[41] and nothing whatever is known of the serum aspirin level and changes in the conversion of aspirin to salicylate with long-term therapy. It is of possible merit that a single dose of a salicylate achieves a given serum level a few minutes before another, and it is even of possible merit that slightly more analgesia results from a marginally higher serum level achieved with one or another pill. There is no serious reason to believe, however, that differences demonstrable in acute single dose experiments mean much in the treatment of chronic pain or inflammation. The goals of long-term and short-term therapy are different, and it is not even known whether the goals in long-term therapy in rheumatoid arthritis are better achieved with occasional spikes in the serum level of aspirin or of salicylate or with a steady moderate level. It can be safely said that the symptoms and signs of most inflammatory arthritides fluctuate more in response to physical activity and emotional state than in response to fluctuations in the serum salicylate level, that some patients are symptomatically sensitive to the dosing interval, and that if the drugs are stopped for a day or so, the disease will measurably flare.

MAJOR THERAPEUTIC ACTIONS

Antipyresis. Although fever has doubtless developed for powerful evolutionary reasons, including perhaps as a mechanism of fighting infections,[42] and although fever therapy has had a vogue from time to time, fever has no such evident benevolent role in the connective tissue diseases, and may be not only the first clinical manifestation but also the most troublesome one. The antipyretic property of the salicylates was known by the middle of the eighteenth century, and today antipyresis is a prime indication for salicylates. By the 1940's, it appeared likely that the antipyretic action was central, not peripheral, and the details have unfolded beautifully over the past decade.

Jackson established in 1967 that endotoxin caused fever only after a considerable latency but that a substance liberated from leukocytes did so rapidly.[43] In the same year Cooper et al. showed that the leukocyte pyrogen but not endotoxin was 100-fold more potent when given into the brain than intravenously and established that a neurotransmitter other than epinephrine or norepinephrine was involved.[44] When Milton and Wendlandt showed that prostaglandin E_1 injected into the third ventricle of a cat caused an immediate fever which acetaminophen could not affect,[45] the broad outlines of the story were evident. Over the next 2 years it was shown that aspirin injected into the anterior hypothalamus was more potent than aspirin injected into the third ventricle and that injections into the carotid artery and intravenously were progressively less potent.[46, 47] Soon after Flower and Vane discovered the prostaglandin story, they showed not only that rabbit brain prostaglandin synthetase was blocked by aspirin, indomethacin, and acetaminophen, but also that their relative potencies were far different from their potencies in other enzyme systems.[48] In particular, acetaminophen and aspirin were almost equipotent and only about 10-fold less potent than indomethacin against the brain enzyme, whereas they were spread over a greater than 5000-fold potency range for dog spleen enzyme. Furthermore, it had long been known that sodium salicylate was almost as potent as aspirin in lowering fever despite doubts about their equivalence in other respects.[49]

It is now evident that PGE_1-like material appears in the third ventricle when fever is produced by an endotoxin,[50] that antipyretics of the PG-synthetase inhibiting class block that appearance,[50] that aspirin can block leukocyte pyrogen–induced but not PGE_1-induced fever,[50-52] that in vitro leukocyte pyrogen production is unaffected by high levels of salicylate,[53] that leukocyte pyrogen and aspirin do not compete for a common binding site, that in the brain as elsewhere PGE may mediate its effects through cyclic nucleotides,[54] and that the anterior hypothalamus is the principal site of action of this class of antipyretics[55] (Fig. 49–2).

Whether or not prostaglandins play a role in the normal temperature regulation in primates is uncertain. In some animal models under some circumstances aspirin can produce hypothermia,[56] but not usually.[57] In normal man, hypothermia does not occur when aspirin is given in the afebrile state, but under some clinical conditions it does, suggesting that keeping the temperature normal, like keeping renal blood flow normal, may under certain circumstances call prostaglandin mechanisms into play.

Although the mechanism of fever in the connective tissue diseases is unknown and may or may not depend upon the release of leukocyte pyrogen from sites of inflammation, the efficacy of salicylates and other prostaglandin synthetase–inhibiting drugs does suggest that prostaglandins serve as mediators of fever. Because of the sensitivity of fever to aspirin (inhibition of fever is maximal with about 600 mg every 4 hours), the antipyretic effects in many inflammatory conditions are achieved at doses below those necessary to suppress other measures of inflammation.

In adult rheumatoid arthritis, fever is unusual, and hypothermia is not a consequence of aspirin therapy. In rheumatic fever and in juvenile rheumatoid arthritis, in which fever may be the most prominent feature early in the illness, aspirin and other salicylates are powerful antipyretics and do not usually cause hypothermia. The antipyretic action is a principal indication for salicylates in lupus and often succeeds in lowering

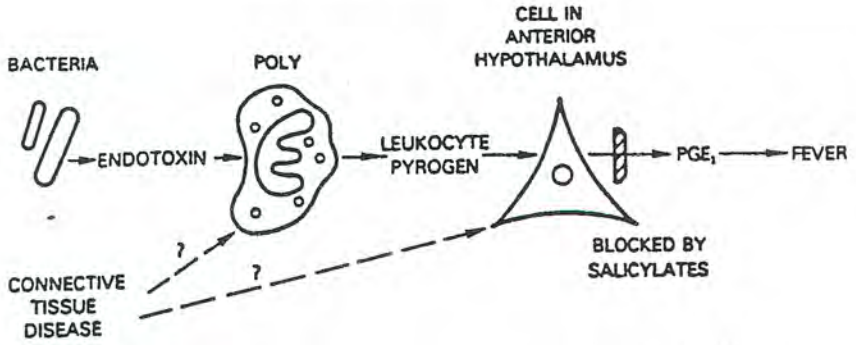


Figure 49–2. Leukocyte pyrogen liberated by peripheral leukocytes in response to bacteria stimulates the synthesis of prostaglandins in the anterior hypothalamus. The antipyretic action of salicylates is to block this synthesis.

a fever in lupus when steroids fail. In fact, fever in lupus should preferentially be treated with nonsteroidal drugs.

Analgesia.* Even the most skeptical can usually attest from their own experience that aspirin is an effective analgesic for various kinds of pain. Although experiments on the analgesia of aspirin and salicylate in man are quite limited, there is formal proof of their efficacy in some double-blind studies against placebo.[59] There are also studies, some hidden in the files of the Food and Drug Administration, showing that aspirin (as well as an investigational analgesic drug given to other patients) is more potent than a placebo for treating pain in arthritis. In general, aspirin and salicylate are properly classified as mild analgesics, equivalent to moderate doses of codeine, and less potent than full doses of narcotic analgesics,[60] but more effective than narcotics against inflammatory pain.[61]

Because of the difficulties in designing such studies, almost nothing is known of the dose-response curve for analgesia in man. It is likely that a maximum response is reached with 600 or 625 mg in an adult; with this dose, the serum salicylate level will not usually exceed 5 mg per deciliter. It has been asserted, though without published proof, that aspirin is a more effective analgesic than sodium salicylate in man.[62] Aspirin is clearly four times more potent than salicylate in blocking the painful response to intraperitoneal or intrasplenic bradykinin in dogs (see below),[63, 64] and the period of analgesia in man does correspond roughly with the period when unhydrolyzed acetylsalicylic acid is still present in the blood after oral ingestion.[58] Nevertheless, as the long and successful history of salicylates prior to the synthesis of aspirin establishes, salicylate itself is analgesic in man.

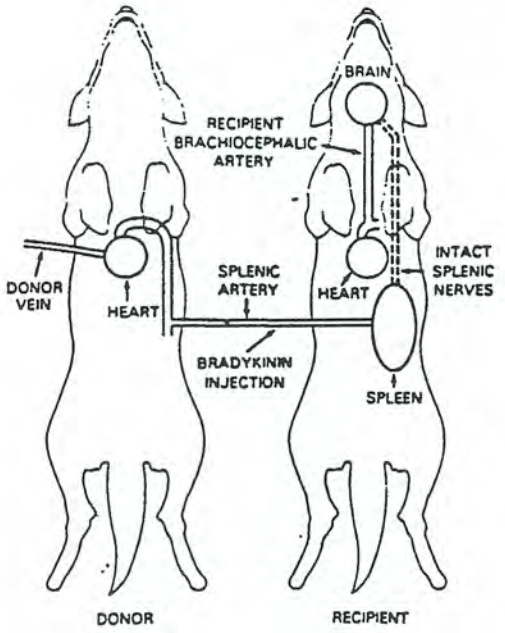
The study of pain in humans is fraught with the difficulty of translating into a one-dimensional scale a sensation composed of many dimensions. The study of pain in animals supposes that the measurement of a response (barking, writhing, hypertension) to a stimulus represents the one-dimensional equivalent of that multidimensional human concept. Since the reduction of pain can occur at so many levels, it is hazardous to believe that a response in an animal system has an exact human equivalent.[65]

Aspirin can act as an analgesic peripherally to reduce the inflow to the central nervous system of nerve impulses from a painful stimulus. This has been shown in an elegant series of cross-circulation experiments in dogs.[63, 64] The spleen of a recipient dog, with its nerve supply intact, received its arterial blood supply from a donor dog (Fig. 49–3). An injection of bradykinin into that splenic artery caused pain in the recipient as manifested by barking. An injection of aspirin into the donor dog blocked the pain, whereas an injection into the recipient (but not into the spleen) was ineffective. With narcotic analgesics, the reverse was true. If aspirin was injected directly into the splenic artery, the effective dose was 3.8 mg per kilogram, whereas it was 50 mg per kilogram if it was injected intravenously into the donor. Drug administered into the recipient's carotid artery was not analgesic. Again, with morphine the opposite was true. Propoxyphene was active by both routes. Furthermore, aspirin but not morphine blocked nerve impulses evoked in the splenic nerve by the bradykinin injection. In these experiments, sodium salicylate was an effective analgesic in doses four-fold higher than aspirin. In analogous experiments, in which a leg was supplied with arterial blood from a donor dog, intra-arterial sodium salicylate blocked the bradykinin-evoked pressor response in the recipient.[66] In an assay in which rats writhe in response to a bradykinin injection, aspirin was the most potent of a number of salicylate derivatives and analogues.[67] None of aspirin's metabolites beyond salicylate has analgesic action.[58]

What is known of the mechanism of the analgesic action? In response to an intra-arterial injection of bradykinin into the dog spleen, the splenic venous circulation had an increased output of prostaglandin-like material, and there was a rise in systemic blood pressure.[68] If PGE_1 or PGE_2 was given along with the bradykinin, the hypertension was augmented, although alone these prostaglandins lower the blood pressure. Indomethacin, a powerful inhibitor of pros-

*This subject is well reviewed in Reference 58.

ANALGESIA FOLLOWING BRADYKININ-INDUCED PAIN



ANALGESIA

	SPLENIC ARTERY	DONOR VEIN	BRACHIOCEPHALIC ARTERY
SALICYLATES	+++	+	0
MORPHINE	0	0	+++

Figure 49–3. Bradykinin injected into the splenic blood supply of a vascularly isolated spleen causes the recipient dog to bark if the nervous connections of the spleen are left intact. Aspirin injected with the bradykinin blocks the pain response, but is without effect if injected into the brachiocephalic artery. With morphine, the opposite is true. (See Reference 64.)

taglandin synthesis, blocked the hypertension induced by bradykinin. Thus, prostaglandins appear to mediate some bradykinin effects. Experiments in rats showed that prostaglandins lowered the threshold to pain from a mechanical stimulus,[69] and in humans that intradermal PGE_1 lowered the threshold to pain from a subsequent injection of bradykinin or histamine.[70] Aspirin cannot interfere with the pain induced by an intra-arterial injection of either PGE_1 or PGE_2 in the dog.[71] Salicylates are generally ineffective against nonpathologic pain: that is, they appear to work only on some painful process already underway. For example, they raise the pain threshold to mechanical pressure in a rat's paw inflamed by an injection of yeast without altering the pain threshold in a normal paw.[69] A plausible case can thus be made for the view that part of the pain of inflammation is due to the stimulation by mediators such as bradykinin of the synthesis of prostaglandins which sensitize nerves to painful stimuli, and that salicylates are effective analgesics because they block that synthesis. Their analgesic property, however, is not identical to their anti-inflammatory property, since in both animal experiments and human experience analgesia occurs in doses below those which reduce heat and edema.

However plausible and satisfying the case may be for a unitary hypothesis of action of these drugs, the experiments are so far from providing the details necessary for verisimilitude that skepticism is unavoidable. One cannot yet dismiss theories concerning the direct effect of salicylates on nerve cell membranes,[72] or a central action under certain circumstances. For example, aspirin given to the rat so alters histamine metabolism that there is an increase in the production of indoleacetic acid, which has narcotic properties in that species.[73, 74] Furthermore, many individuals, particularly the elderly, experience apparently central effects of aspirin such as dizziness, somnolence, and slurred speech, not to mention that hyperpnea and antipyresis are clearly central effects of the drugs. Any unitary hypothesis of aspirin and salicylate analgesic action must account for their ability to counteract pain of diverse sorts: headache, both vascular and muscular, and deep visceral or skeletal pain, whether neoplastic or mechanical, as well as pain related to inflammation. It seems likely that the proof of such a hypothesis will have to rest on a deeper understanding of the mechanism of pain than presently exists.

Anti-inflammation. In favoring aspirin and its pharmacologic relatives (and steroids) over propoxyphene, pentazocine, codeine, morphine, or even acetaminophen in the treatment of connective tissue diseases, especially arthritis, rheumatologists lean upon the belief that they provide not only freedom from addiction but the positive property of suppressing inflammation. Since one can obtain analgesia without measurably affecting other aspects of inflammation, the optimal use of these drugs in inflammatory disease may depend on using them so as to obtain the anti-inflammatory effects.

What is the reason for believing that aspirin and salicylates have anti-inflammatory effects over and above analgesia? Inflammation is a term used to describe a global reaction which involves vascular events leading to the translocation of blood cells, protein, electrolytes, and fluid to the extracellular space; stimulation, proliferation, and transformation of cells; the production, diffusion, and destruction of mediators of great variety; the stimulation of nerve endings; the destruction of tissues; and ultimately a return to the uninflamed state. The inciting cause, the location, the species, the chronicity, and many other factors determine the course of inflammation and doubtless the response to intervention. Measuring the effects of intervention might therefore appear to be despairingly difficult, but in fact a good deal of useful information has been gathered on the global response and its less subtle manifestations, edema, erythema, and pain (see Analgesia).

The evidence for a reduction of edema and effusion in human arthritis is relatively limited. The clearest effect was in a study with patients with rheumatoid

arthritis in which it was shown that aspirin at 5.3 grams per day reduced both joint pain and joint swelling as measured by jeweler's rings, whereas aspirin at 2.6 grams per day and acetaminophen affected only pain.[75] In other studies, some unpublished, aspirin has been shown to reduce swelling or increase joint motion, presumably measures of inflammation. There is evidence, too, that prostaglandins are elevated in the active synovial effusion of rheumatoid arthritis and even that therapy with aspirin can reduce that level, but the story is distinctly incomplete.[76] There is no useful, independent evidence on the mechanism or anti-inflammatory effects of aspirin or salicylate in any nonarthritic condition, although any clinician who has treated the serositis of lupus erythematosus with them will attest to their efficacy.

Animal models have provided substantial evidence for anti-inflammatory effects of aspirin and salicylate. Aspirin or salicylate reduced edema in rat paws injected with the algal polysaccharide carrageenan as a subacute irritant.[77-80] Furthermore they reduced the accumulation of effusion and cells when carrageenan was injected intrapleurally.[81] They reduced edema and warmth as well as the hyperesthesis of yeast-induced inflammation in the rat paw.[82, 83] Urate-induced edema and ellagic acid–induced edema in both the rat paws and the dog stifle joint were reduced by aspirin.[84] Chemical- or ultraviolet-induced skin erythema was reduced only by very large doses.[85] Among chronic models of inflammation, aspirin effectively inhibited and also treated established adjuvant arthritis in the rat.[86-88] It did not have a beneficial effect on the inflammation of a traumatized joint,[89] and it had a variable effect in an antigen-induced arthritis.[90] Although it is likely that prostaglandins are important in the inflammation in some of these models, and that the interaction between bradykinin and prostaglandins is important in edema as well as pain, it is premature to suggest that aspirin works in them solely because of its effects of prostaglandin synthesis, or, conversely, that prostaglandin synthesis does or does not have a role in inflammation because inhibition of synthesis affects the process. Aspirin is not effective against inflammation caused by histamine or by injected or previously synthesized prostaglandins.

Recent tissue culture experiments have shed new light on the role of prostaglandin in rheumatoid inflammation. Human rheumatoid synovial fragments produced PGE_2 and a collagenase and can accelerate the release of calcium from mouse fetal bones; furthermore, mitogen-activated lymphocytes produce a substance or substances which stimulate these fragments to produce more prostaglandin.[91, 92] It might seem possible, then, that adequate long-term suppression of prostaglandin synthesis would inhibit the bone destruction process in rheumatoid joints. Unfortunately, although such a possibility has not been formally ruled out, there is no clinical evidence on which to build such a hope.

In mechanistic terms, the influence of aspirin and salicylate upon the migration of neutrophils and monocytes seems to be important, particularly since prostaglandins can influence migration.[93, 94] The complex effects of various prostaglandins on vascular permeability offer another point of intervention. There appears to be a direct effect of aspirin on the surface of granulocytes which might influence their ability to enter the extravascular space.[95]

Inflammation doubtless has an important beneficial role so that interference with it might be hazardous as well as helpful. Such is the case with corticosteroids. With aspirin, salicylate, and other prostaglandin synthesis–inhibiting drugs, however, the course of infection, both chronic and acute, is unaffected, demonstrating the limitations of those drugs in the face of a powerful stimulus.[96]

Aspirin and sodium salicylate have rarely been compared for potency in animal models of inflammation; investigators tend to prefer to use aspirin, but sodium salicylate has been effective in some studies. In humans with arthritis, only the undocumented assertion by several investigators can be cited to support a greater anti-inflammatory potency for aspirin, although many clinicians favor it.[62] Even if the unitary hypothesis for the action of these drugs on prostaglandin synthesis is correct, it is unlikely that the inhibition of a single enzyme is solely responsible for anti-inflammatory effects. In view of the great range of tissue sensitivities to inhibition, one should not a priori expect that the overall inhibition by salicylate will be appreciably less than that by aspirin.

However unproved and uncertain the unitary prostaglandin theory,[97, 98] none of the other proposed theories of aspirin's anti-inflammatory action has plausible evidence in support of it. The possibility that aspirin works by inhibiting phosphodiesterase is remote, since only high levels are inhibitory.[99] Some of the older theories on the interactions of aspirin with various parts of the inflammatory system have been well reviewed.[85]

THE CLINICAL USE OF ASPIRIN AND SALICYLATES IN THE RHEUMATIC DISEASES

The major indications for aspirin and salicylate in the rheumatic diseases are fever, pain, and inflammation. They are useful for the fevers which commonly accompany rheumatic fever, systemic lupus erythematosus, and juvenile polyarthritis and, less commonly, rheumatoid arthritis, the spondyloarthritides, and other connective tissue diseases. They are useful for the pain of arthritis of any origin, including osteoarthritis and mechanical joint pain even when inflammation is not evident, and they are useful for the inflammatory arthritis, pleurisy, and pericarditis which accompany rheumatoid arthritis, lupus erythematosus, and occasionally other connective tissue diseases.

They are not in general useful for the treatment of myositis, rash, nodules, renal disease, or serologic tests. It should be noted, however, that the anti-inflammatory effect in systemic lupus erythematosus, juvenile arthritis, and rheumatic fever may be accompanied by the fading of rash, and the sedimentation rate, too, responds as inflammation recedes in many diseases.

The antipyretic action and simple analgesia require relatively small doses of either aspirin or salicylate. One or two 300 mg tablets four to six times a day suffices for all but the largest adults. When the drugs are used to combat inflammation, higher doses are necessary, and although salicylate itself may not be so powerful and anti-inflammatory as aspirin, the serum level of salicylate is best used to guide therapy.

Plain aspirin, the cheapest USP formulation available, is the most sensible place to start. Provided it is kept dry, it will remain as aspirin; otherwise it will slowly decay to salicylic acid and acetic acid and acquire a vinegary smell. Such preparations are not unsafe to use and are no less efficacious than the salicylate they contain. The starting dose should be about 8 tablets per day in adults, since the abrupt introduction of higher doses often leads to patient resistance because of gastrointestinal side effects. Recalling the unusual metabolism of salicylates, in which the serum half-life gets longer as the serum level goes higher, the dose should be raised at one or two tablets per day no more often than once per week until tinnitus occurs or until the salicylate level is between 20 and 30 mg per deciliter. A slow-release form used at bedtime sometimes reduces early morning stiffness and pain. Since the drugs are most often introduced outside the hospital, and since frequent determinations of serum salicylate are impractical or impossible, older patients should raise the dose even more slowly, and all patients should be told about tinnitus, diminished hearing, and hyperpnea that accompany high serum salicylate levels. Patients know about the gastrointestinal side effects well enough, but if a physician is committed to the use of salicylates, he can help a patient avoid them by a variety of maneuvers which may not make pharmacologic sense or be supported by controlled trials, but work. The drug can be given only with meals, only with antacids, crushed in milk, dissolved in water, or even crushed with Jell-O. The hour can be varied and the brand can be varied; a buffered preparation, sodium salicylate, enteric-coated aspirin, timed-release aspirin, choline salicylate, and even various magnesium and calcium salts are available substitutes and will overcome gastrointestinal side effects in some patients. They can be used interchangeably except for enteric-coated aspirin which, in the United States, at least, is quite variably absorbed by some patients. If it is used, salicylate levels should be checked if the pharmacologic effect is less than expected.

It has often been observed that for some reason, pharmacological or psychological, individual patients may respond differently to different formulations. There are many variations in the formulation of aspirin and salicylate designed to reduce the symptoms of gastrointestinal upset, to accelerate the absorption of the drug, or to reduce the microbleeding (see below). There is good evidence that sufficient buffering with either bicarbonate, citrate, or nonabsorbable alkali to bring the intragastric pH to neutrality will reduce microbleeding and accelerate absorption. The price, however, is a level of sodium intake unacceptable for long-term therapy (521 mg of sodium per 322 mg of aspirin in the most popular effervescent form, Alka-Seltzer) and/or accelerated excretion of the drug so that serum levels with long-term therapy are lower. Although the small amounts of buffering in commonly sold buffered aspirin may marginally accelerate absorption, they do not alter microbleeding. No formulation has proved dependably better at reducing gastric upset in blinded trials and, most important, no formulation is free of an association with gastric ulcer or gastritis and hemorrhage. In practical terms, if a patient has good symptomatic relief of arthritis with aspirin or salicylate but complains of gastrointestinal side effects, it is sensible to switch preparations; it is not necessary to abandon salicylates.

If the patient also takes corticosteroids or drinks any alcohol, nonabsorbable antacids should be used, bearing in mind that higher doses of the salicylate may then be necessary to maintain an adequate serum salicylate level.

Although it may be irrational, other nonsteroidal drugs can be added to aspirin with psychological if not pharmacological therapeutic benefit and no harm.

In rheumatoid arthritis, aspirin should be used in full anti-inflammatory doses, which means until a salicylate level of at least 20 mg per deciliter is reached or until tinnitus or diminished hearing occurs. Indeed, aspirin or another nonsteroidal anti-inflammatory drug should be given in anti-inflammatory doses along with all other classes of antirheumatic drug if inflammation is present.

Generally a reduction in dose suffices to reverse most symptomatic toxicities, although some require that the drug be stopped (see following page). The elderly patient is particularly susceptible to salicylism. The hepatic and renal side effects of the drug can be safely ignored in rheumatoid arthritis unless frank symptoms of hepatitis develop. It is unnecessary to monitor transaminase levels, creatinine, or urea in the patient on long-term therapy.

In juvenile arthritis and in rheumatic fever, aspirin is usually used in doses of 80 to 100 mg per kilogram per day, although sometimes doses up to 130 mg per kilogram per day are used. Children seem to tolerate high serum levels of salicylates better than adults, and therapeutic levels of over 30 mg percent are considered tolerable. The mild hepatitis that can be detected by blood tests is not a contraindication to continuing the drug, but any signs of bleeding or jaundice are (see following page).[100]

In osteoarthritis and fibrositis, doses well short of supposed anti-inflammatory doses are usually adequate for analgesia, and there is no reason to push higher in the absence of overt inflammation.

In systemic lupus erythematosus, aspirin is often as good as or even better than corticosteroids for fever, arthritis, pleurisy, and pericarditis, and it is the drug of first choice in many clinics.[101] The starting dose should not exceed 12 tablets per day, but it can be raised to anti-inflammatory levels for arthritis and serositis. It is uncertain (see Side Effects and Toxicities) whether chronic liver damage occurs as a very rare sequel to salicylate-induced hepatitis, and it is true that the hepatitis may fade away as disease activity recedes, but it is safest to reduce the dose or stop temporarily if the serum transaminase rises rapidly in a hospitalized patient or is found to exceed about ten times normal in an ambulatory patient. If a random elevation of less than that is found in an otherwise reasonably well patient, the drug can be safely continued if the observation will be close. Alterations in renal function can occur with all the prostaglandin synthetase–inhibiting anti-inflammatory drugs and are not an indication for stopping therapy. Measurements of renal function to be used in therapeutic decisions, however, should not be made while a patient is taking those drugs.[102]

In ankylosing spondylitis, some patients will respond to anti-inflammatory doses of aspirin, and it is worth trying. The same is true for the other spondyloarthritides and psoriatic arthritis.

Aspirin and salicylates no longer have a place in the treatment of crystal-induced disease. Not only are they not as effective as other drugs, but the peculiar effect of salicylates on the serum uric acid and urinary urate excretion can complicate evaluation and management.

Aspirin or salicylate can be tried for symptomatic relief in a variety of other connective tissue diseases, but is likely to be ineffective for the major manifestations of scleroderma, dermatopolymyositis, polyarteritis, polymyalgia rheumatica, and temporal arteritis.

INTERACTIONS WITH OTHER DRUGS*

Of the many drugs likely to be given with aspirin or salicylates, with few are there significant interactions. Much of the writing on the subject deals with the interactions of aspirin with acetaminophen, with indomethacin, and with the newer nonsteroidal anti-inflammatory drugs, and is concerned with the influence of one drug on the absorption or half-life of the other, not with their clinical interactions. These writings generally teach that there is little pharmacologic reason to give these drugs in combination but even less to forbid them. There are other interactions which are occasionally important: with coumarin anticoagulants, with uricosurics, with corticosteroids, with methotrexate, and with oral hypoglycemics.

Salicylate displaces indomethacin from a plasma protein binding site, raising the unbound drug level, and thereby accelerating its clearance and metabolism.[104] Thus, aspirin at a dose of 3 to 6 grams per day slightly lowers the peak serum indomethacin level when the two drugs are given simultaneously and has an inconstant effect on the serum disappearance.[105-108] This is altogether a small effect of no clinical significance. Indomethacin does not alter serum salicylate levels.[109] Both drugs are potent inhibitors of prostaglandin synthetase, and they may act at the same site on the enzyme, since indomethacin inhibits acetylation of the platelet enzyme by aspirin.[110] Since this

*This subject is well reviewed in Reference 103.

TABLE 49–1. INTERACTIONS OF ASPIRIN (A) AND SALICYLATES (S) WITH OTHER DRUGS

Drugs or Class of Drugs	Interaction	Clinical Implications
Nonsteroidal anti-inflammatory		
Indomethacin	A lowers serum levels slightly; not vice versa	None
Ibuprofen	Protein-bound S level reduced	None
Naproxen	A lowers serum levels slightly	None
Fenoprofen	A lowers serum levels slightly; not vice versa	None
Acetaminophen	Raises serum A level but leaves total S level unchanged	None
Coumarin anticoagulants	A variably reduces prothrombin time further when added	Reduction of anticoagulant dose
Uricosuric agents	A/S blocks uricosuric effect	A/S should not be used with them
Sulfonylurea oral hypoglycemics	A/S variably potentiates hypoglycemic action	Reduction of sulfonylurea dose
Corticosteroids	Lower serum S levels	Observe S level when steroids reduced
Antacids	Accelerate both adsorption and excretion of A/S	Overall tendency to lower serum S levels when added
Methotrexate	A displaces methotrexate from protein-binding sites and enhances marrow depression	Caution, especially when using large doses of methotrexate
Ethanol	Synergistic effect with aspirin on gastrointestinal bleeding	Do not mix

ızyme inhibition is responsible for some or perhaps l the pharmacologic action of both drugs, and since full doses of either roughly the same effects are ·hieved, they would be expected neither to be addi- ve nor significantly to interfere with one another. ıch is the case in the few human and animal studies which their clinical interaction has been measured. he finding in a model adjuvant arthritis of a long- sting anti-inflammatory effect of both drugs is so far :moved from other known actions of the drugs as to ·ouse skepticism about their relevance.[87] Despite ɔme common side effects, there is no evidence that ɔxicities are additive.

Aspirin has minor effects on the metabolism of cetaminophen,[111, 112] including a reduction in cetaminophen-induced hepatotoxicity in mice.[113] Of reater interest is the finding in man that when a single ose of acetaminophen (650 mg) is given simultaneous- / with a single dose of aspirin (650 mg), total serum cetylsalicylic acid levels are higher and remain high ıuch longer than when aspirin is given alone, but total alicylate levels are unchanged. At 1 hour, the serum evel of aspirin was 3.32 μg per milliliter when the drug vas given alone and 9.33 μg per milliliter when given vith acetaminophen.[114] The mechanism for this effect ɔn deacetylation is unknown and its clinical value ınexplored. Although it would be useful to prolong the ɔharmacological effects of aspirin, possible adverse :ffects on the liver of such combination therapy would ;uggest caution.

What is true of the similarity in pharmacologic :ffects between aspirin and indomethacin is true also ɔf the similarities among all the newer nonsteroidal ınti-inflammatory drugs which can inhibit prostaglan- din synthesis, although doubtless there will be subtle differences which are due to different sensitivities of the enzymes in various tissues. Consequently there is little interest in details of their interaction. Of the few clinical studies, ibuprofen can increase the level of free as opposed to protein-bound salicylate as measured in vitro by equilibrium dialysis;[115] a single dose of aspirin could slightly lower peak naproxen levels, probably by displacement from protein, leading to further excre- tion, but there was no effect on salicylate levels;[116] and aspirin lowered fenoprofen levels both acutely and chronically, possibly by increasing hydroxylation of the drug, but fenoprofen did not affect salicylate levels.[117] None of these interactions appear to be of any clinical significance. There is no indication that toxicities of drugs in this class are additive.

The interaction with the coumarin family of anti- coagulants is variable and often not significant in an individual patient. Aspirin alone may have minor effects on prothrombin time and may reduce the amount of anticoagulant necessary to maintain a given prothrombin time.[103, 118, 119] Of far greater importance is the fact that they are inhibitors of different steps in the coagulation scheme and consequently may in- crease the tendency for bleeding as a side effect of oral anticoagulant therapy. It is for this reason that these drugs should be given together only when necessary and that aspirin should be avoided when any other defect in the coagulation system, inherited or ac- quired, is present.

Salicylate has complicated dose-dependent effects on both uric acid reabsorption and secretion, probably in part through its competition as an organic anion. In low doses, these actions raise serum uric acid, and in high doses they may lower it. Any dose of aspirin or salicylate can block the uricosuric action of both probenecid and sulfinpyrazone and consequently should not be used together with them.[120] The newer uricosuric, benzbromarone, is less affected.[121]

Although aspirin and salicylates do not lower blood sugar in normal subjects, they may potentiate the hypoglycemic effects of the sulfonylurea drugs by unknown mechanisms, and doses may have to be modified accordingly.[103]

Any drugs which markedly alter urine pH can have an effect on salicylate levels, since salicylate excretion is markedly accelerated at high urine pH. Theoreti- cally, ascorbate or other urine acidifiers could raise serum salicylate levels, but this does not appear to be a problem. A problem with ascorbate potentially related to aspirin is that it can make the routine tests for stool occult blood falsely negative, thus obscuring a gastro- intestinal blood loss.[122] Nonabsorbable as well as absorbable antacids can influence both the absorption and excretion of salicylates (see above).

Corticosteroids can lower the level of serum sali- cylate so that, when they are withdrawn, the serum level as a constant dose may rise substantially, even into the toxic range.[123] It is the impression of many clinicians that adverse effects of the two drugs on the gastrointestinal tract are additive or even synergistic.

Ethanol in the form of alcoholic beverages and aspirin probably are synergistic in their tendency to cause gastrointestinal bleeding from gastritis and gas- tric ulcer (see below).

Aspirin, probably by displacing methotrexate from protein binding sites, enhances the bone marrow de- pressing effects of the antimetabolite. This has been shown clinically in studies with patients given large intra-arterial doses of methotrexate for malignan- cies.[124] Bone marrow depression, usually on the day after the injection, occurred almost exclusively in those patients who also received aspirin during the infusion. Studies in mice have confirmed this interac- tion experimentally.[125]

ASPIRIN AND SALICYLATES IN PREGNANCY

In this day it is unnecessary to caution against the use in pregnancy of a drug even so apparently benign as aspirin. The issue is how to assess the risk to the pregnant woman whose own illness demands anti- inflammatory therapy. The risk of congenital malfor- mation that can be attributed to aspirin is negligible,[126] and neither hypoglycemia nor bleeding problems are

more common in babies born of mothers taking salicylates.[127] In a large study of women taking aspirin at least twice a week, no increased incidence of stillbirth or perinatal mortality was found, and mean birth weight was unaffected.[128] That study, however, did not focus on women who took aspirin daily. In a smaller study of women in Australia who took salicylate-containing powders daily more for social than for genuine medical indications, mean birth weight, even corrected for the high incidence of smoking in this population, was significantly lower (3283 grams vs. 3502 grams in controls), and there were four stillbirths near term compared to none in a control group.[127] Pregnancy was an average of a week longer, antepartum and postpartum hemorrhage were more common, and anemia in the mother was more frequent (uncorrected for other factors such as smoking), but labor was not significantly prolonged.[129]

The only study to focus on women who took aspirin for rheumatologic disease during pregnancy was a retrospective chart survey covering a 20-year period, so its findings must be accepted cautiously.[130] Gestation was prolonged by about a week, labor prolonged by about 5 hours, and estimated blood loss increased by about 100 ml in aspirin-takers with rheumatologic disease compared to normal women or to women with rheumatologic disease not taking aspirin. Reduced birth weight was common to women with rheumatologic disease whether or not they took aspirin. In both studies of women who took aspirin daily, there was an increased incidence of pregnancies lasting more than 42 weeks.

For the woman who must take an anti-inflammatory agent during pregnancy, aspirin can be relied on not to increase the risk of congenital malformation but does add some risk of prolonged gestation and labor and an increase of perinatal maternal bleeding. Since these risks are probably related to the prostaglandin synthetase–inhibiting properties of the drug, they are likely to depend on continued use of the drug. For the same reason, other drugs which inhibit prostaglandin synthetase are likely to share those effects. A sensible course would seem to be to stop anti-inflammatory medication if possible in the last month.

The infants born to women taking salicylates until term pose no special medical problems, although it is interesting to note that they have higher serum salicylate levels then their mothers.[27]

SIDE EFFECTS AND TOXICITIES

Under this heading I will discuss those effects of aspirin which are extratherapeutic. They are not all toxicities and they are not all unwanted. Aside from the relation to major gastrointestinal hemorrhage and a controversial and doubtful relation to analgesic nephropathy, the toxicities of aspirin and salicylate are neither chronic nor cumulative. Furthermore, they are rapidly and completely reversible with a reduction of dose or cessation of therapy.

Allergy. For the many rheumatologists who have never or only rarely seen an allergic response to aspirin, the problem may seem remote, but a patient with a tale of an allergic response to aspirin is not rare in the office of the allergist. The earliest good description is of four cases of severe asthma, one fatal, induced, ironically, by "M. Matte's German Asthma Powder," which contained aspirin and caffeine.[131] By the early 1950's the essential immunologic facts of aspirin "allergy" were clear:[132] skin tests are negative for aspirin;[133, 134] sodium salicylate does not provoke the allergy;[133] and there is no antibody detectable by passive cutaneous anaphylaxis (and presumably, therefore, no IgE or homocytotropic IgG antibody).[134, 135] Later studies have confirmed these findings more elegantly. By the end of the preprostaglandin era, a nonimmune mechanism already seemed likely. It is now apparent that the "allergy"-inducing potential of the class of drugs is related to their ability to affect prostaglandin synthesis; not only aspirin (as little as 30 mg)[136] but other prostaglandin synthetase inhibitors, indomethacin (as little as 5 mg), mefenamic acid, flufenamic acid, fenoprofen, ibuprofen, and phenylbutazone reduce air flow in aspirin-sensitive patients, whereas salicylamide, paracetamol, and propoxyphene do not.[137, 138] What remain unknown are the site of the affected enzyme, the identity of the active prostaglandin, and the mechanisms by which the prostaglandins affect the airways.

Clinically, the patients fall roughly into two categories: those who react to aspirin with bronchospasm and those who react with urticaria and angioedema. About half of those who have the bronchospastic type also have nasal polyps, in contrast to fewer than 15 percent of those with the urticaria-angioedema reaction.[139] Of those with the asthmatic response, at least half can be classified as having "intrinsic" asthma (normal IgE, normal skin tests, no recognizable environmental provocation or seasonal variation).[140] It seems likely that these patients have a metabolic defect either making them unusually sensitive to inhibition of prostaglandin synthetase because of a property of the enzyme itself or causing their airflow regulation to be abnormally dependent on prostaglandins to remain adequate.

In a large series of patients attending an allergy clinic, 3.8 percent of the asthmatics had aspirin allergy, the rate being higher for those with intrinsic (4.7 percent) than extrinsic (3.5 percent) asthma.[140] Most asthmatics who react to aspirin get the bronchospastic response, whereas among the 1.4 percent of rhinitis patients with aspirin allergy, the angioedema response predominated. Tartrazine sensitivity occurred in fewer than 20 percent of aspirin-allergic patients. The reported rate of 0.9 percent of "allergic" aspirin intolerance among normals seems to me inordinately high.[140]

Because aspirin is used so widely and because the

"allergic" response requires only small not full rheumatologic doses to provoke it, aspirin allergy is virtually never discovered by the rheumatologist. If a patient gives a convincing history of bronchospasm, urticaria, or angioedema in relation to taking aspirin, however, it is likely that indomethacin, ibuprofen, fenoprofen, naproxen, tolectin, and probably phenylbutazone will provoke a similar response and ought to be avoided.

Tinnitus and Hearing Loss. Patients treated with salicylates will often note a high-pitched ringing in the ear and diminished hearing. Occasionally, they will also have vertigo, dizziness, and loss of balance. These toxicities are dose related and are probably all due to effects on the inner ear rather than on the central nervous system.

A raised threshold for all sound frequencies can be demonstrated by audiometry.[141] The change is roughly proportional to the serum salicylate level and is rapidly and completely reversible within 24 to 72 hours even if the drug has been taken for many years. The loss amounts to 20 to 40 decibels and occurs preferentially in the frequency range in which hearing is normal in those with pre-existing high tone deafness, thus leading to a flatter audiogram. Salicylates have little or no effect on presbycusis in which there is already a flat depressed acuity. The hearing loss is sensorineural, can be produced in several animal species.[142–146] and is unassociated with any recognizable morphologic changes in either animals or man, even if the drugs have been taken for many years with a known effect on hearing.[147] Salicylate-intoxicated cats show some biochemical changes in enzymes of the endolymph and perilymph, but what relationship this has to the ototoxicity is unknown.[142] Vestibular changes can be measured in humans as changes in the nystagmus induced by caloric stimulation and presumably account for the dizziness, vertigo, and imbalance.[147]

Tinnitus occurs universally in patients with normal hearing who take sufficient salicylate or aspirin. It comes on only when the serum salicylate exceeds 20 mg per deciliter, occurring on the average at about 30 mg per deciliter.[148] In these patients it is a useful guide to dosage, since it appears when the serum level is in the supposed anti-inflammatory range; the dose can be raised gradually until the appearance of tinnitus and then held steady at a slightly lower dose. Patients who have a high-tone hearing loss prior to salicylates often do not experience tinnitus even with very high salicylate levels. If there is any suspicion of a hearing deficit, or in any older patient, serum salicylate ought to be measured rather than waiting for tinnitus to occur.

Gastrointestinal Effects. The effects of aspirin and salicylate on the gastrointestinal tract have played a large role in their history. Aspirin itself was first popularized as a salicylate with less tendency to irritate the gastrointestinal tract; then attempts were made to reduce the gastric irritancy of aspirin; and now the newer nonsteroidal anti-inflammatory drugs claim to be no better than aspirin, merely less irritating to the gastrointestinal tract.

Because of the confusion concerning the gastrointestinal effects of aspirin and salicylate, it is helpful to examine separately the three major effects: symptomatic gastrointestinal distress, microbleeding, and frank gastritis or ulcer.

GASTROINTESTINAL SYMPTOMS. Gastrointestinal symptoms following use of aspirin occur occasionally and range from a very mild discomfort elicited only by direct or repeated questioning to heartburn, nausea, or severe discomfort occurring after a single tablet. Many patients with rheumatoid arthritis will tolerate a minor gastrointestinal discomfort as they will tolerate tinnitus in order to keep the beneficial effects of aspirin or salicylate. In various surveys the incidence of complaint has ranged from less than 2 percent to almost 40 percent, reflecting many factors related to the study design: whether or not the subjects knew they were getting aspirin, how a history of side effects was elicited, what condition the drug was given for, the age of the subjects, the dose of the drug, and doubtless sometimes the expectation or prejudice of the investigator.[149–153] Toxicities as well as benefit are subject to a placebo effect.

The form of aspirin does not appear to influence the incidence of gastrointestinal distress; in several controlled studies, aspirin and buffered aspirin have been found equally guilty.[150, 151, 154] Nor do symptoms correlate with the presence of or amount of microbleeding or gastroscopic abnormalities.[155–158]

The mechanisms responsible for gastrointestinal symptoms are largely unknown, but probably a direct irritation to the mucosa, psychological expectations, and a central nervous system effect of salicylate all contribute. A dose of sodium salicylate given intravenously caused nausea at the same serum salicylate level as when the drug was given by mouth.[159] Since it is known that salicylate does not diffuse from the serum into the gastrointestinal tract, an extraluminal, probably extraintestinal central nervous system effect must have been responsible.

In practical terms, if gastrointestinal intolerance occurs when aspirin or salicylate is begun or when the dose is raised, and if the drug is otherwise having a therapeutic benefit, it is wisest to switch preparations to buffered, to enteric-coated, or to a liquid form, or to use one of the maneuvers suggested above (see Clinical Use). A substantial proportion of patients will be able to continue the drug with such switches from time to time. It has been repeatedly observed that some people who claim gastric intolerance to aspirin are able to tolerate it if they are unaware that it is being given or if it is given in another form. Of course switching to another nonsteroidal drug is sensible if intolerance persists. Combining two nonsteroidals (including aspirin) in submaximal doses sometimes works, too.

MICROBLEEDING AND GASTROSCOPIC CHANGES. The ingestion of aspirin causes the loss of small amounts of blood (about 2.5 ml per day above a back-

ground loss of about 0.5 ml per day) into the stool in about 70 percent of people.[155, 157, 160-166] Although a sensitive qualitative test may sometimes detect losses this small,[167] most patients taking aspirin will not have occult blood on routine testing, and investigation of the circumstances of this loss has required the measurement of fecal radioactivity after the injection of ^{51}Cr-labeled autologous red blood cells. There is a large literature devoted to studies of this sort, most predicated upon the view that this blood loss is somehow related to other gastrointestinal effects of aspirin and salicylates, a view that is open to serious doubt.

Aspirin, soluble aspirin, calcium aspirin, aspirin in solution, aspirin in suspension, aspirin given with milk, and some "enteric-coated" and over-the-counter buffered aspirins are roughly equivalent in their ability to cause blood loss.[160, 168] Sodium salicylate, choline salicylate, effervescent aspirin, or aspirin given with enough sodium bicarbonate or nonabsorbable, nonsodium-containing buffers causes little or no blood loss,[7, 157, 167, 169-173] and the presence of achlorhydria markedly diminishes the loss.[165, 166] No minimum dose for this toxicity has been found, but the loss does increase with increasing dose in the clinical range.[160] Furthermore, some subjects lose a great deal more than the average and are probably those few whose chronic iron deficiency anemia may be due to aspirin.[157, 174] Ethanol, which itself does not cause this sort of microbleeding, does potentiate aspirin's effect.[163, 175] There does not appear to be any adaptation, since microbleeding at 4 weeks or even as long as a year after starting therapy continues at about the same rate.[176, 177] Intravenous aspirin in doses leading to the same serum salicylate level and the same effect on bleeding time causes a negligibly small increment blood loss in subjects with a normal gastrointestinal tract.[168, 178] Nor does the ingestion of coumarin anticoagulants increase the rate of blood loss.[179]

Normal volunteers and patients with rheumatoid arthritis have the same frequency of microbleeding (about 70 percent) and the same range of blood loss.[157] Even patients who have recently had a major gastrointestinal hemorrhage from peptic ulcer disease have a similar frequency and degree of microbleeding.[174] Most patients with rheumatoid arthritis do not develop a chronic anemia that can be attributed to aspirin. On the contrary, patients who take aspirin over the course of a year for arthritis are likely to have a slightly higher hemoglobin than before they began the drug, probably because their disease activity has been diminished.[180]

Gastroscopic abnormalities after aspirin have been known for over 40 years, although much has been made of them recently with the advent of easier endoscopy.[111] There has been controversy over their actual incidence, location, nature, and even their relation to drug ingestion, but there is no doubt that aspirin given to a fasting subject with an empty stomach can lead to visible abnormalities ranging from hyperemia, petechiae, and submucocal hemorrhage to superficial erosion or even frank ulceration with visible intraluminal blood.[111, 181-188] This is not a placebo effect, although occasionally placebo-treated subjects show some abnormalities. It occurs more frequently with aspirin than with other nonsteroidal prostaglandin synthetase inhibitors, although like microbleeding, it is by no means absent with them,[187, 188] and tolerance does not develop over several weeks. The reported incidence has varied considerably, even to as high as 100 percent,[185] but all observers do not use equivalent language to describe their findings; one observer's hyperemia may well be another's superficial erosion. From both animal and human studies, the microscopic damage that accompanies the visible abnormalities is extremely quick to reverse, being largely gone within an hour of the dose of drug and completely gone by 6 hours.[186]

In view of their similar frequency, the fact that tolerance develops to neither, and the fact that adequate buffering can prevent both of them, it is reasonable to conclude that the microscopic blood loss originates in the visible lesions.

Their mechanism is mysterious. They are clearly not due to platelet effects or other effects on the measurable coagulation factors. Despite earlier evidence that particles of undissolved drug might be involved in mucosal damage, soluble aspirin can cause microbleeding (although it may be argued that, in the acid environment of the stomach, aspirin might be precipitated from sodium aspirin solutions). Acid does seem necessary, since adequate buffering prevents it.[183] The fact that achlorhydria is also protective may reflect not only the absence of acid but also the more rapid cell turnover of the gastric mucosa characteristic of that condition, thus allowing more rapid repair.[189] The Davenport model (see below) postulates that the back-diffusion of acid into the gastric wall caused by an effect of aspirin on the gastric mucosal barrier liberates histamine locally, which dilates capillaries, presumably leading to diapedesis of red cells, some of which make their way to the gastric lumen through ruptured intercellular bridges.[190]

Do they relate to major blood loss, either chronic or acute? They are probably responsible, in the rare person with a large asymptomatic daily loss, for a chronic iron deficiency anemia. If the visible lesions are the precursor of the rare gastric ulcer or gastritis leading to major blood loss, it is easy to imagine that any condition which impedes the repair process, such as uremia, stress, ingestion of ethanol or corticosteroids, or an intercurrent illness, could potentiate the danger of aspirin.[189, 191] There is no direct evidence, however, to link them to acute gastrointestinal bleeding caused by gastritis or peptic ulcer. Major hemorrhage retrospectively related to aspirin ingestion is as likely to have occurred with buffered or even effervescent aspirin,[192-194] which does not cause microbleeding, as with plain aspirin, and while the visible mucosal changes and the microbleeding are very common, major gastrointestinal hemorrhage is uncommon or even rare. The relation among them remains uncertain.

Do microbleeding or the visible gastroscopic changes

relate in any way to complaints of gastrointestinal distress? In every series in which microbleeding or mucosal changes and symptoms have been recorded there has been a dissociation; some have distress without microbleeding or changes, and most have microbleeding or changes without distress.[155-158]

Both microbleeding and visible gastroscopic changes can be prevented by adequate buffering with sodium-containing buffers as in effervescent aspirin, but only at a cost of a prohibitive sodium intake for the chronic aspirin taker, and it is difficult to incorporate sufficient nonabsorbable buffer into an oral tablet. Sodium salicylate is thought by many to be pharmacologically inferior to aspirin, and enteric-coated aspirin is variably absorbed. With sufficient ingenuity, a preparation of aspirin that caused little microbleeding or visible mucosal changes could probably be developed,[172] but it is unlikely that it would reduce the incidence of gastrotintestinal distress and it would be almost impossible to prove that it would reduce the already very low incidence of major gastrointestinal hemorrhage.

Neither microbleeding nor visible mucosal changes are the more dangerous for our being able to measure them or see them. If the gastrointestinal effects of aspirin and salicylate are to influence the way we use them, then it must, in my opinion, be those which relate to patient comfort, for which appropriate individual adjustments are made, or those which relate to clear-cut morbidity or mortality, such as ulcer or major hemorrhage, for which there is yet no evidence that aspirin is a worse offender than any of the alternatives.

ULCER, GASTRITIS, AND GASTROINTESTINAL BLEEDING. Does aspirin cause major gastrointestinal bleeding? Ulcer? How often? Who is particularly susceptible? Can anything prevent it? What should be done if it occurs? Does anything potentiate the risk? What is safer than aspirin?

The evidence that aspirin causes major gastrointestinal bleeding is roughly as follows: In a large number of surveys of patients admitted to the hospital or studied as outpatients for major gastrointestinal bleeding and/or ulcer, the patients have been from two to five times more likely to have taken aspirin in the few days prior to admission than a group of control patients.[149, 192-199] The choice of controls has varied in the studies and been the focal point for much criticism. It may be, for example, that patients with any gastrointestinal problem more readily remember taking aspirin because of its publicized gastrointestinal effects; or that they have taken aspirin (usually effervescent) to treat the early symptoms of their bleed; or that controls are more likely to have diseases which, like stroke, impair their ability to take part in a survey. Even more remarkable is the extraordinary range of frequency of aspirin ingestion in the various populations — from 25 percent to over 90 percent.[200] Despite the imperfections of such studies, the qualitative conclusion is inescapable: a proportion of major gastrointestinal bleeding or ulcer is related to the recent ingestion of aspirin.[201] Such surveys also have established that buffered aspirin and effervescent aspirins are often the culprits, probably no less often than plain aspirin,[192-194, 202] and that alcohol ingestion increases the risk of aspirin.[192, 196, 197] The episodes have been gastrointestinal bleeding without a visible source and therefore attributed to gastritis, gastric ulcer with bleeding, or gastric ulcer without bleeding.[202] Duodenal ulcer does not appear related.

In another type of survey, chronic gastric ulcer in young women in Australia was found to be quite common and highly likely to be associated with the chronic ingestion of headache powders; the incidence of gastric ulcer in women rose markedly as these powders came into vogue.[203] Furthermore, ulcer disease leading to gastrectomy is very common in analgesic abusers who have developed analgesic nephropathy, although it is difficult in that population to point a finger with any assurance at any particular drug or to ignore psychological factors.[204]

In a survey of hospitalized patients, habitual aspirin ingestion (four or more times per week) contributed to uncomplicated benign gastric ulcer and to new episodes of gastointestinal bleeding not due to duodenal ulcer.[202] In that study, it was estimated, based on the known populations from which the patients were drawn, that the drug added a total of 25 cases per 100,000 users of aspirin per year. This is a very small risk indeed.

While aspirin does not appear to cause duodenal ulcer, patients with duodenal ulcer are not immune from its effects on the stomach. No formal survey proves that such patients are unusually susceptible to aspirin, but most physicians are properly cautious about using it. The hypersecretion of acid and pylorospasm characteristic of duodenal ulcer disease might be expected to contribute to a gastric toxicity of aspirin. In the absence of a strong indication (see below), it should be avoided.

Factors such as stress, alcohol ingestion, concurrent illness, other medications, diet, age, sex, and season as well as others probably contribute to the tendency of aspirin to cause gastric ulcer and gastritis with or without bleeding. Increased acid secretion may be a factor; however, ulcer and bleeding may occur, although rarely, in the patient with achlorhydria, too.[205, 206]

There is no evidence that regular antacid ingestion or a switch to salicylate can prevent a risk of major gastrointestinal bleeding, but establishing a change in the frequency of a rare event is extremely difficult. *Most importantly, there is no evidence whatever that the incidence of ulcer or major gastrointestinal bleeding is any different with any other nonsteroidal anti-inflammatory drug from what it is with aspirin.*

Are rheumatologic patients or any subgroup of them particularly susceptible to the gastrointestinal effects of aspirin? There is no evidence that this is so. The incidence of ulcer disease in patients with rheumatic diseases may be higher than in the general population, but not all studies are in agreement on this point, and in particular they have not adequately assessed the role of drugs. Patients with rheumatoid arthritis are not more

susceptible to aspirin-related gastrointestinal discomfort or microbleeding.

Clinically, gastric ulcer and gastritis in the patient with arthritis and in the normal individual are no different. It is my impression that gastric ulcer is more common than symptomatic gastritis with bleeding or silent gastrointestinal hemorrhage among rheumatologic patients. Major gastrointestinal bleeding related to aspirin is probably very rare in children, although a report of 12 children with melena, hematemesis, or anemia but no ulcer following therapeutic doses of aspirin suggests that it does occur.[207]

What should be done when ulcer or gastrointestinal bleeding occurs in the rheumatologic patient taking aspirin? We have successfully treated active ulcer disease in a substantial number of patients with rheumatoid arthritis with a standard ulcer regimen *while continuing aspirin*, and believe it can safely be done in the hospitalized patient or the reliable outpatient. We do so when aspirin appears necessary to the management of arthritis. With the availability of potentially equivalent anti-inflammatory drugs, it is reasonable to switch. It is reasonable to add cimetidine to an ulcer regimen while continuing aspirin (or other drugs), since it does appear to reduce the gastric irritation caused by aspirin.[208-211] When the ulcer is healed, there is no contraindication to a return to aspirin with antacid.

Potential Difference. When unbuffered aspirin is instilled into the stomach of man or experimental animals, the electrial potential difference between the gastric mucosa and the skin or a peripheral vein is reduced from its normal of −40 mV to about −30 mV.[212, 213] It is likely that this change in potential reflects a change in the mucosal barrier which protects the stomach from the high acid concentrations of gastric secretion: in experimental animals, particularly the dog with an isolated gastric pouch, the potential changes induced by aspirin parallel a back-diffusion of hydrogen ions into the stomach wall and leakage of sodium and chloride into the lumen.[214, 215] Davenport's theory of the gastric damaging effects of aspirin postulates that this back-diffusion leads to the release of histamine, capillary dilatation, increased acid production, and, if there is a sufficient concentration of acid in the lumen initially, gastric erosion and bleeding. Because of the difficulty of measuring ion fluxes in man, measurement of changes in the potential difference has been used as a surrogate for changes in the gastric mucosal barrier.

Aspirin causes a reduction in potential, but not if accompanied by adequate buffer (effervescent aspirin, nonabsorbable antacids, or sodium bicarbonate).[216, 217] Ethanol alone reduces the potential and potentiates the reduction induced by aspirin.[216, 218] Indomethacin, prednisone, and phenylbutazone do not alter the potential.[218] Bile acids, which cause gastric damage in animals and exacerbate aspirin's tendency to do so, also reduce the potential difference.[216] Glucagon, PGE_2, and cimetidine all increase the potential difference and, in the proper dose, block the potential reduction induced by aspirin.[206, 210, 219] In the case of glucagon, the intragastric pH is unaltered (i.e., it remains low) but gastric damage is prevented. In the case of cimetidine, the pH is raised to 7 and cell damage is blocked.

Animal Studies. Gastrointestinal effects of aspirin and salicylate have been studied in dogs, cats, rabbits, guinea pigs, rats, and even frogs. There are pronounced differences among different species in their susceptibility so that extrapolation to man is hazardous.

The most useful studies have been by Davenport, using the dog with a Heidenhain pouch, an exteriorized isolated gastric pouch with intact blood supplied that can easily be filled and emptied. In his experiments, he instilled drugs with or without acid at various concentrations and measured the changes in ion concentration and the appearance of blood in the gastric fluid over time. He showed that aspirin or sodium salicylate in a weakly acid solution (0.001 M HCl) breaks the mucosal barrier to ion fluxes, allowing hydrogen ions to back-diffuse into the gastric mucosa and sodium to leak into the lumen, but only with strong acid (0.1 M HCl) does bleeding occur.[220] Ethanol potentiates the effect of aspirin by lowering the concentration of acid at which bleeding appears. Davenport has summarized his findings and his model in an excellent review.[190]

Studies in rats, which develop ulcers easily with aspirin, have shown that stress,[221, 222] starvation,[223] and bile acids[224, 225] potentiate its effect, while bicarbonate,[226] vagotomy, atropine,[226, 227] metiamide,[209] and cimetidine[221] ameliorate it. Giving very large quantities of glutamine[228] or cupric sulfate[229] or giving aspirin methyl ester[230] prevents the ulcers without inhibiting the beneficial pharmacological effects.

Although it has been established in animals that aspirin does reduce both gastric venous[231] and gastric juice prostaglandin levels,[232] what relation this has to changes in the mucosal barrier, to ion fluxes, and to cell damage remains unknown. Gastric blood flow may increase,[233] decrease,[234] or remain unchanged after aspirin, depending on the animal model;[191] likewise acid production is inconstantly affected.[191, 234] Most attention has focused on the stomach, but permeability changes also occur in the small intestine.[235-237]

Platelet and Coagulation Effects. Aspirin's effects on platelets and coagulation have commanded attention because they were discovered early, have been easy to study, and have raised the hope of safe and effective prophylaxis against venous and arterial thrombosis. The principal effects are on platelets and bleeding time; there is a minor effect on synthesis of the vitamin K dependent clotting factors.

Aspirin prolongs the bleeding time as tested by any of the standard assays. Most subjects, normal or rheumatoid, can be shown to respond, although the final bleeding time may remain within the normal range.[238-243] On the average, the bleeding time is prolonged 1.5- to 2-fold. Sodium salicylate is without effect.[241] A minimal effective dose of aspirin has not been defined, although less than 1 gram a day can do it.[243] The crudeness of the assay has limited the information that can be extracted from these studies, and it is, in fact, not

certain that the effects on platelet cyclooxygenase described below rather than other effects on platelets, capillaries, arterioles, or local tissues are responsible for the altered bleeding time.

Soon after the discovery of the effects on bleeding time, several laboratories discovered that aspirin in vitro entirely blocked the aggregation of platelets by collagen or connective tissue fragments, and blocked a second wave of aggregation when platelets were exposed to ADP or epinephrine, while not blocking the initial aggregation these substances caused.[244-247] Later it was shown that aspirin blocked the release from platelets of serotonin and ADP from the dense granules,[248, 249] that the initial adherence of aspirin-treated platelets to an injured vascular endothelium was unaffected but subsequent build-up of larger aggregates was blocked,[249-252] and that all these effects occurred with doses or levels of aspirin well below what are achieved in vivo after aspirin ingestion.[253-255] Although details in the picture of platelet aggregation remain to be worked out, the broad outline is roughly as follows. Various mechanical and chemical stimuli, including exposure to collagen, to damaged vascular endothelium, to excessive agitation, and to thrombin, ADP, and epinephrine, cause platelets to adhere to surfaces and to each other. During that process, arachidonate is mobilized, and is metabolized by the enzyme platelet cyclooxygenase to the cyclic endoperoxide PGG_2, which is converted successively to thromboxane A_2 and PGE_2 and PGF_2, as well as to a number of other substances whose functions are not known. Thromboxane A_2 and probably also PGG_2 are released from the platelet into the surrounding fluid, where they cause the release of ADP and serotonin from the dense granules of other platelets.[256-258] The released ADP in turn aggregates these other platelets, causing them to adhere to the nearby initial aggregate.[259] The mechanism of dense granule release probably involves both GMP and calcium but is not presently well understood.[260, 261] Aspirin, by blocking the initial step of synthesis in the prostaglandin pathway, blocks the release of PGG_2 and thromboxane A_2, thereby preventing the so-called release reaction and secondary aggregation. Platelets exposed to aspirin in vivo or in vitro demonstrate this lesion, and it is irreversible. If PGG_2 or additional ADP is provided, however, secondary aggregation can take place.

It is now clear that the acetyl group of the aspirin specifically acetylates a single platelet microsomal protein of molecular weight 85,000, the cyclooxygenase, and that the acetylation stoichiometrically irreversibly inactivates the enzyme.[22, 262, 263] Sodium salicylate is virtually without effect; indomethecin is likewise highly effective at blocking the enzyme. The human platelet cyclooxygenase is peculiarly sensitive to this inactivation, at least 30 times as sensitive as the only other cyclooxygenase studied in detail.[258] Studies on the effects of aspirin, salicylates, indomethacin, and other drugs of this class on many different tissues confirm that there are indeed major differences of the cyclooxygenases to these drugs.[264]

One 300 mg tablet of aspirin by mouth has a demonstrable effect on human platelets within 5 minutes and is maximally effective by 15 minutes; no further effect is achieved by a greater dose.[253] With a tablet a day, the effect remains unchanged indefinitely. It takes 2 days to begin to wear off, suggesting that megakaryocyte cyclooxygenase is acetylated, and platelet function is returned to normal only after the affected platelets have lived out their normal life span.[258] Aspirin-treated platelets appear normal.[265, 266] The single tablet inactivates about 90 percent of the enzyme.[258] As little as 20 mg has a substantial effect and will, in time, block about 60 percent of the enzyme. The effective in vitro concentration is about 10^{-5}M.[267]

Several investigators have described effects of aspirin on other platelet functions, particularly in activating platelet factors 3 and 4.[247, 268] Although they are of rapid onset, they may require somewhat larger doses. The consequences of this aspect of aspirin's action are not known.

Aspirin has a small inconsistent effect on the synthesis of the vitamin K dependent clotting factors.[118, 240] Some investigators have not found it at all. Rarely a patient will demonstrate bleeding and prolonged prothrombin time as a manifestation of aspirin toxicity.[100] Several of the reported cases occurred in people with a probable nutritional deficiency which may have contributed to the prothrombin problem.[269]

Of what clinical importance are the effects on coagulation, particularly on platelet function? Under ordinary conditions of aspirin use in the rheumatic diseases, none. The effect on prothrombin time is so weak and variable that it need be considered only when coumarin anticoagulants are administered simultaneously because the dose of anticoagulant sometimes but not always needs to be reduced (see above). The effect on platelets cannot be wholly responsible for the anti-inflammatory action of aspirin, since it occurs at doses at least 10-fold below anti-inflammatory doses. It might be argued that the anti-platelet effect contributes to the gastrointestinal microbleeding. That is exceedingly unlikely, since aspirin administered by other routes or so that it can be absorbed only beyond the stomach has just as much platelet effect but does not cause gastric microbleeding. Finally, there is no evidence, clinical or epidemiologic, that patients with rheumatic disease and taking aspirin, even at the time of operation or even if another coagulation problem is present simultaneously, are disposed to bleed excessively. In a rare exception, aspirin appears to have been responsible for well-documentated intravascular coagulation and aspirin-induced hepatitis in a young boy with Still's disease[270] and in a 17-year-old girl with "adult onset" juvenile rheumatoid arthritis.[271]

It is interesting to note that there exist patients whose platelets closely mimic aspirin-treated platelets.[249] In fact, a patient with deficient or absent platelet cyclooxygenase had no significant clinical illness.[256] This reflects, I believe, the happy natural redundancy of the coagulation system; under normal circumstances and sometimes in fact under any circumstances, deficits in

the coagulation scheme can go unnoticed throughout a lifetime unless special tests uncover them.

Aspirin and other drugs which depress platelet function, such as dipyridamole and sulfinpyrazone, have been explored for their ability to prevent arterial and venous thrombosis, especially in patients with coronary and cerebral circulatory insufficiency and in bedridden patients after major surgery. It is beyond the scope of this chapter to review the evidence of these studies except to say that they show some modest promise in several clinical circumstances[272] but almost surely will not prove to prevent major arteriosclerotic and thrombotic arterial disease which occur all too often in patients who have taken aspirin for decades. Aspirin's effects on the vascular system are not confined to effects on platelets, and it may well turn out that inhibition of other prostaglandin pathways, in the vascular wall, for example, counterbalance any beneficial effects on platelets or so restrict the beneficial dose range that prophylactic therapy is impractical.

Hematologic and Immunologic Effects. WHITE CELL EFFECTS. Some investigators have found that aspirin or salicylate inhibits various in vitro functions of human or animal lymphocytes, including transformation in response to mitogens,[273] the allogeneic mixed lymphocyte reaction,[273] transformation in response to antigens,[274] and the production of migration inhibitory factor.[275, 276] In some but not all experiments, the lymphocytes isolated from subjects taking aspirin have been found to respond subnormally.[277, 278] The inhibition was sometimes related to serum level. The in vitro effects do occur in the range of drug levels found in the serum of patients, but it should be noted that when drug is added in vitro to a culture containing 20 percent plasma the proportion of unbound drug is higher since the albumin concentration is lower. Data on the reversibility of the effect are inconsistent. These effects may be in some way related to the depressed levels of cyclic AMP found in the lymphocytes of subjects taking aspirin.[279]

In the only experiments in which lymphocyte responses to mitogen and antigens and corresponding skin tests were performed in a double-blind trial of aspirin and placebo administration to normals, aspirin showed no effect despite substantial serum levels.[280] Thus a healthy skepticism for claims that aspirin's anti-inflammatory effects are mediated by direct effects on lymphocytes is warranted, but indirect effects are still possible.

There have been a number of early studies of other immunologic effects of aspirin which were well reviewed some years ago.[281] These studies do not support a primary action on antibody synthesis; effects which have been reported such as protection against the Shwartzman phenomenon in the rabbit are more reasonably attributable to other actions of this class of drugs or occur at doses far from the clinical range.

Aspirin ingested by normal volunteers modestly decreased the ability of their granulocytes to adhere to nylon fibers in vitro for several hours after a 1.2 gram dose, although sodium salicylate added in vitro had no effect.[282] The mechanism is unknown, but the changes in migration of leukocytes into inflammatory lesions in several animal models may be related to the adherence and movement of leukocytes.

ASPIRIN IN GENETIC HEMOLYTIC ANEMIAS. In a large careful study, 22 patients with glucose-6-phosphate dehydrogenase deficiency did not show signs of hemolysis when given a 4-day course of aspirin at 50 mg per kilogram per day.[283] Glutathione levels in deficient red cells were not altered in vitro by exposure to aspirin or the metabolite gentisic acid, and Heinz bodies did not form. Neither chemical altered the hexose monophosphate shunt activity of normal red cells. There is a single case report alleging that a large dose of aspirin (6 grams per day) shortened the half-life of red cells to 16 days in an enzyme-deficient subject.[284] Because of the heterogeneity of the enzyme-deficiency state, caution is necessary in applying the results of observations to all patients. It is likely that aspirin can be safely administered when clinically indicated to most deficient individuals.

A much rarer genetic defect, the severe anemia form of pyruvate kinase deficiency, may cause the red cells of affected individuals to be unusually susceptible to salicylates.[285] When exposed in vitro to aspirin, intracellular ATP falls and the cells have altered permeability and a decreased hexose monophosphate shunt, thereby diminishing their ability to manufacture glutathione. Consequently detoxification of other drugs may be impaired. The clinical importance of this is unknown.

CYTOPENIA. Aspirin and salicylate have almost never been convincingly implicated as a cause of anemia, leukopenia, or thrombocytopenia resulting from peripheral destruction of cells or marrow depression.[286]

Pulmonary and Cardiovascular Effects. PULMONARY EDEMA. The rare complication of pulmonary edema caused by salicylates was first recognized in patients being treated with full doses of salicylates for rheumatic fever, with or without carditis. It was described as "rheumatoid pneumonia," with the typical roentgenographic appearance of pulmonary edema.[287] The patients in whom it was originally described had an increased plasma volume which was thought to account for the pulmonary edema. The presence of actual or possible carditis resulting from rheumatic fever clouded the early description,[288, 289] although it was noted that a patient taking salicylates who had a roentgenographic picture of pulmonary edema might have no other signs of heart failure.[290, 291] With the description of cases in otherwise healthy individuals, it became apparent that underlying heart disease was not a requirement.[292, 293] In addition, there have been autopsies of two patients with fatal pulmonary edema which showed only congested lungs; the hearts were normal.[294] In one previously normal patient with pulmonary edema, catheterization showed a normal pulmonary artery pressure, normal pulmonary capillary wedge

...re, and normal pulmonary atrioventricular oxy- ...fference. The pathophysiology is most reminis- ...of noncardiogenic pulmonary edema of the sort ...d by morphine, heroin, and propoxyphene.[295] ...ly experimental evidence of a similar lesion was ...e sheep infused with aspirin.[296] They developed ...ased pulmonary lymph flow and leakage of serum ...ins into pulmonary lymph but had normal cardiac ...tion and pulmonary artery pressure. Thus, by a ...chanism unknown, there is an outpouring of fluid ... the pulmonary air spaces at a time when cardiac ...tion is unimpaired. The physiologic consequences ... dyspnea and cyanosis, and the radiologic con- ...uence is pulmonary edema.

...e serum salicylate level is usually greater than 40 ...rcent. The lesion is rare, but it may be the ...ting manifestation of occult salicylism in the ... and must therefore be kept in mind.[297] Although ...mechanism of the hyperpnea regularly seen with ...therapeutic doses of salicylates is central stimula- ... the clinical appearance may also be that of ...ed dyspnea.

CARDIOVASCULAR EFFECTS. Aspirin and salicylate ... of cardiac effects except as related to the anoxia ... drug-related pulmonary edema and acid-base ...rbances. From the discovery that prostaglandin ... could keep open a patent ductus in the new- ... when that shunt was necessary for survival,[299, 300] ... but a short step to the use of the prostaglandin ...stase inhibitors aspirin and indomethacin to ... the duct in newborns in whom surgery might ...se be necessary.[301, 302] This simple and ap- ... benign therapy is now in wide use. In these ... marked transient renal effects occur, probably ...ection of an unusual dependence on prostaglan- ... to maintain renal perfusion. In levels larger than ... encountered even in severe intoxication there is a ... suppression of cardiac conduction tissue.[303] ... other vascular effects are probably of no clinical ...ance.[304]

...matic Effects. The hepatitis caused by aspirin is in ... a disease of advancing medical science; it was ...overed when the serum transaminase test became ...[305, 306] and usually is discovered today only ... that test is ordered routinely, not because ...matic liver disease develops. It first was thought ... a chemical manifestation of liver disease in chil- ...n with active rheumatic fever with carditis, and only ... it realized that the common factor was aspirin ... salicylate therapy rather than the disease. Subse- ... children with rheumatoid arthritis,[307, 308] espe- ... females and those with the systemic type,[100] ... with active systemic lupus erythematosus,[309] ... patients with any underlying liver disease have ... found particularly but not exclusively susceptible. Those with other forms of connective tissue ... and even otherwise healthy individuals may ... hepatic injury, although often of but a trivial ...[305, 311-313]

...ically, abnormal transaminase occurs in the second or third week of therapy or after an increase of dose. A high proportion of patients who have active lupus erythematosus and some patients with juvenile rheumatoid arthritis will develop abnormalities, sometimes within a week of an increase in dose, and often rising to levels in the hundreds or even thousands. Most often the bilirubin remains normal even if transaminase is high for extended periods; the alkaline phosphatase may rise just into the abnormal range. Except in a few patients, usually children, prothrombin time is unaffected.[100] In those few, ecchymoses and frank bleeding may occur quite rapidly and drug should be immediately stopped and vitamin K and/or plasma given.

Although most patients with this hepatitis are asymptomatic, some develop nausea, anorexia, a loss of taste for cigarettes, and even an enlarging or tender liver.[309, 313] Biopsies in cases of acute aspirin-related injury have generally shown a nonspecific toxic hepatitis with single cell necrosis, anisocytosis and aniso-nucleosis, and a mononuclear cell infiltrate in the lobule and in the portal areas.[311, 314, 315] Several patients have been seen in whom the lesion developed in the face of a recent normal liver biopsy, thereby establishing that underlying liver disease is not a precondition. There have been two patients reported in whom histologic chronic hepatitis has been found to be the probable result of long-term aspirin therapy.[310, 314] Although this is probably a rare event, aspirin should be added to the list of potential inciting agents of idiopathic chronic hepatitis, especially if immunologic phenomena are a prominent feature, since systemic lupus erythematosus with aspirin-induced hepatitis may closely resemble chronic active hepatitis with immunologic features.

Early papers stressed the relationship to high serum salicylate levels, often over 30 mg per deciliter, but the hepatitis clearly can occur with a serum level below the therapeutic range, as low as 10 mg per deciliter. If abnormalities occur, they will disappear within a week or rarely up to 2 weeks when the drug is stopped or the dose is lowered. In addition, however, they will often disappear if the drug is continued in children with arthritis.[100, 316] If aspirin is continued in a patient with active lupus who develops hepatitis, the abnormalities will occasionally disappear if the disease becomes less active. There are apparently spontaneous fluctuations, particularly in children with arthritis; if children are tested often enough, abnormal liver function tests will appear at some time or other in more than half of those on aspirin.[317]

The mechanism of this lesion is unknown. Eosinophilia and rash are not regularly associated with the hepatitis, and the toxicity is dose related. Together, these observations make a hypersensitivity type reaction very unlikely. Animal studies have not shed any light: it is possible to show only trivial hepatic changes in rabbits despite long-term high-dose therapy with salicylate.[318] It is true that patients with liver disease are more susceptible and that such patients have a reduced level of aspirin esterase,[319] but it is unlikely that those observations are related, since hepatitis is caused as

readily by salicylate as by aspirin.[308] It is possible that a metabolite, perhaps an otherwise minor metabolite, achieves toxic levels in certain disease states, but there is no evidence of this yet. Salicylate does appear to be directly toxic to rat hepatocytes in short-term tissue culture, causing the liberation of a cytoplasmic enzyme, LDH; this system may provide a window on the mechanism of the toxicity.[320]

In clinical practice, the best way to avoid aspirin hepatitis in adult rheumatoid arthritis is to avoid measuring transaminase levels unless frank symptoms related to the liver or upper abdomen are present. In children, the drug can be continued safely if there is no evidence of bleeding or ecchymosis and if any transaminase abnormalities do not suddenly worsen or reach levels above several hundred. Lowering the dose or temporarily stopping and then resuming it at a lower dose is usually adequate therapy. When transaminase levels rise sharply in lupus, we tend to stop and switch temporarily to another drug, although some patients do improve without lowering the dose. It should be borne in mind that the administration of two hepatotoxic drugs can be unusually dangerous and ought in general to be avoided.

Reye's syndrome, the catastrophic illness of children in which an apparently metabolic encephalopathy is coupled to hepatocellular failure and fatty degeneration, has been attributed to salicylates[321] and has even been described in a girl being treated in hospital with aspirin for polyarthritis.[322] It is not possible in this or in the other cases in which a role for salicylate has been proposed to incriminate it with certainty, because the drug had been given at a time when there were symptoms of an upper respiratory illness. Since there is an epidemiologic association of Reye's syndrome with viral illness, it is more likely that salicylate has only an auxiliary role. The liver pathology of Reye's syndrome is quite different from that found in aspirin-induced hepatotoxicity.

Renal Effects. There are five renal effects of aspirin or salicylates which may, under certain circumstances, be clinically significant: a transient shedding of tubular cells when therapy is begun; a possible relation to analgesic nephropathy; reduced glomerular filtration and renal blood flow, probably related to prostaglandin synthetase inhibition; interaction with aldosterone and spironolactone; and alteration of urate excretion (see above).

When aspirin or salicylate administration is begun, there is an outpouring of cells into the urine which is due to the shedding of tubular cells.[323, 324] The effect lasts several days and disappears. Its mechanism is obscure; in fact it defies easy speculation because none of the actions of salicylates or aspirin are known to attenuate so quickly. Perhaps it is caused by effects on prostaglandin biosynthesis for which compensatory mechanisms exist. Besides being recognized for its own sake, its importance lies in its possible relation to analgesic nephropathy. While hematuria may also occur in association with salicylate therapy, the mechanism remains unclear.

Although analgesic nephropathy has been recognized for over 20 years, it continues to arouse heated debate. It has been studied mainly in those countries where social patterns of drug use have encouraged many young women to ingest large quantities of proprietary analgesic powders or pills,[325] but it may cause as much as 20 percent of obscure renal failure in the United States.[326] It escapes notice because a history of analgesic abuse is often not sought and may be hard to elicit when it is.

The controversy surrounds the issue of which drug or drugs are responsible. Without trying to unravel its entirety, the following considerations are relevant to aspirin: (1) Although most studies implicate phenacetin in combination with other drugs, it is where phenacetin consumption is high that the nephropathy has been most evident, and when phenacetin was removed from analgesic powder in New Zealand, the incidence of interstitial nephritis fell dramatically.[325] (2) There have been a very few cases of interstitial nephritis and papillary necrosis which have occurred in patients who have taken only aspirin.[326] (3) It is possible in animals to produce a lesion with aspirin and/or phenacetin that more or less resembles analgesic nephropathy, but the circumstances of drug administration are remote from the clinical setting of analgesic nephropathy.[327, 328] (4) Renal disease characteristic of analgesic nephropathy is exceedingly rare in those populations in which aspirin is taken for adequate rheumatologic reasons.[329, 330] In summary, the virtually hypothetical relationship of aspirin to analgesic nephropathy suggests that a physician should not consider it in selecting long-term therapy for rheumatologic diseases, and, indeed, most rheumatologists wisely do not.

Effects on renal function were first discovered in a series of dramatic experiments performed by Hanzlick and Scott and their colleagues over 60 years ago.[331, 332] They described mild albuminuria, edema, and a rising blood nitrogen after giving 1 gram of sodium salicylate hourly until intolerance, usually about 12 grams. Recent experiments showed that aspirin or salicylate could alter creatinine clearance acutely in humans, and that patients with renal disease are more susceptible to these effects.[102, 309, 333-336] These effects may arouse clinical concern in patients with systemic lupus erythematosus even in the absence of detectable renal disease.[102] In patients with active lupus with or without renal disease, the administration of anti-inflammatory doses of aspirin regularly raises the BUN and serum creatinine and sometimes raises the serum K+ and reduces the serum Na+.[337] The effect can be dramatic and misleading in the patient with lupus; if aspirin or indeed any of the other prostaglandin synthetase–inhibiting anti-inflammatory agents are administered to a patient with lupus for the management of arthritis, fever, or serositis, any changes in BUN, creatinine, and creatinine clearance must be recognized as possibly due to the drugs in order to avoid unnecessary renal biopsies and therapy. When the drugs are stopped, the changes rapidly recede. Sometimes the changes recede while the drugs are continued, and much clinical experi-

ence in lupus suggests that chronic renal changes are not a consequence of continued aspirin therapy. Nevertheless, it is important to recognize that advancing renal disease may sensitize the kidney to the renal effects of this class of drug.

The mechanism probably involves the inhibition of intrarenal prostaglandin synthesis:[338] urinary prostaglandins fall before creatinine clearance does; the fall in creatinine clearance correlates with a fall in renal blood flow and a fall in inulin clearance; plasma renin falls; and a number of drugs which inhibit prostaglandin synthesis, including indomethacin, ibuprofen, fenoprofen, and naproxen, have the same effect.[337] Although it is possible to demonstrate aspirin-induced changes in creatinine clearance in patients with rheumatoid arthritis and indeed in normals, they are smaller than the changes in lupus and clinically insignificant.[102] Such a difference in susceptibility supports the view that under certain conditions of renal function, renal blood flow is maintained to a greater than normal extent by mechanisms involving prostaglandin synthesis.[339] The prostaglandin synthetase–inhibiting properties of aspirin and indomethacin have been used to advantage to probe the mechanism of and successfully treat the rare Bartter's syndrome.[340]

The relationship between aspirin and the mineralocorticoids is probably complicated and fortunately rarely of clinical interest. Aspirin can compete with aldosterone receptors in some experimental models[341] and it can inhibit the action of spironolactone administered to man.[342] The latter action is worth noting for those situations in which the drugs are given together.

The relation to urate excretion is discussed under Interactions with Other Drugs.

In summary, with the exception of the reversible but occasionally dramatic effects of aspirin (and other prostaglandin synthetase–inhibiting drugs) on BUN, creatinine, and creatinine clearance in active lupus, the renal effects of aspirin, although interesting and controversial, are clinically rarely important.

Aspirin or Salicylate Overdose or Accidental Intoxication. The problem of salicylate toxicity caused by accidental overdosage in infants and in children lies beyond the scope of this book and beyond the experience of most rheumatologists. Aspirin or salicylate overdosage in adults occurs in a different setting and presents different metabolic problems. Overdose with suicidal intent is met in the emergency ward. Although the complicating late acidosis of children is not usually a problem in managing adults, and although with modern techniques of rapid laboratory determinations and dialysis fatality is uncommon, death may occur with blood levels less than twice therapeutic levels.[29, 343] When it is recognized that the therapeutic serum level of salicylate is in the range of 10^{-3}M, far higher than almost any other drug, it is not difficult to understand that an organic anion at 4×10^{-3}M (the mean serum level in a group of fatal cases)[344] might have many effects beyond its sometimes subtle therapeutic effects.

Salicylate intoxication in adults, however, is by no means limited to the suicidal. On a medical or rheumatology ward, the new appearance of dyspnea, confusion, ataxia, oliguria, or a rising BUN or creatinine in a hospitalized patient who is taking aspirin ought to suggest the possibility of salicylism.[297] After recognition, temporary withdrawal of the drug is usually adequate therapy. In the emergency ward, salicylism should be considered in the differential diagnosis of cardiopulmonary disease presenting dyspnea, tachypnea, or pulmonary edema, or of almost any central nervous system problem, including seizures. Older individuals taking salicylates or aspirin, often for a good reason, are the usual victims of this syndrome. It probably arises when a supervening event alters the already peculiar metabolism of salicylate to cause a sudden rise in serum level. Among the events which may do so are acidosis, e.g., from fasting, dehydration, and the ingestion of drugs which displace salicylate from protein-binding sites. In a series of 20 patients with an average age of 53 in whom diagnosis had not been made until 6 or more hours after admission, six died, a far higher mortality than among 53 patients who took the drug with suicide in mind. Therapy consists of a forced diuresis maintaining the urinary pH in the alkaline range, hemodialysis if diuresis is unsatisfactory, and any other appropriate supportive measures, including removing residual drug from the gastrointestinal tract by emesis, a large bore stomach tube, or the administration of activated charcoal if that seems indicated by the history. Keeping the urine alkaline abets the excretion of salicylate. Vitamin K has also been recommended because large doses of salicylate may interfere with the synthesis of the vitamin K dependent clotting factors.

The near-universal tachypnea of salicylism is due not to a metabolic acidosis but to a direct effect on the central nervous system in the medullary respiratory center.[298] Salicylate given intravenously will cause tachypnea, an increase in oxygen consumption and pH, and a decrease in pCO_2 within 1 or 2 minutes, well before any measurable blood acidosis. It has even been proposed that this action of salicylates be harnessed to increased pO_2 and lower pCO_2 in patients with emphysema,[345] but it is doubtless too variable and hazardous, particularly as an effect of salicylate of less rapid onset is increased oxygen consumption and CO_2 production.

There are probably many causes of the diverse central effects of salicylate intoxication. Local brain hypoglycemia may occur, as it does in experimental animals, because high doses of salicylate uncouple oxidative phosphorylation, forcing the brain to maintain its energy supply by markedly increasing glycolysis.[346, 347] Indeed, glucose prevents death from salicylate intoxication of experimental animals.

Miscellaneous Effects. Aspirin has been shown to inhibit RNA synthesis of the mouse oocyte,[348] to reduce the growth rate of several mouse tumors,[349] and to alter tumor induction by a mouse tumor virus.[350] These effects have not been shown to depend on those fea-

tures of the aspirin molecule known to be related to its pharmacology in man. It is likely that they are irrelevant to the clinical action of the salicylates.

CONCLUSION

The recent pharmacologic history of the drugs whose action in man depends on inhibition of the synthesis of prostaglandin strongly suggests that no new drug in this class will exceed in clinical efficacy those already in use, although a new drug might show a different spectrum of side effects and toxicities. What appears to limit efficacy is not the power of the drug but the extent to which the prostaglandin system is involved in the inflammation of the connective tissue diseases.

The durability of the salicylates is no accident. Just as the survival of buildings of earlier civilizations is most often rooted in strong materials and sound structure, so is the survival of salicylates rooted in their clear and powerful action and their safety. If they become obsolete in this century, it will be not an indictment of them, but a tribute to the ingenuity of chemists and pharmacologists.

REFERENCES

1. Gross, M., and Greenberg, L. A.: The Salicylates. A Critical Bibliographic Review. New Haven, Hillhouse Press, 1948.
2. Floeckinger, E. C.: An experimental study of aspirin, a new salicylic-acid preparation. Med. News (N.Y.) *75*:645, 1899.
3. Leist, E. R., and Banwell, J. G.: Products containing aspirin. N. Engl. J. Med. *291*:710, 1974.
4. Vane, J. R.: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol. *231*:232, 1971.
5. Martin, B. K.: The formulation of aspirin. Adv. Pharm. Sci. *3*:107, 1971.
6. Leonards, J. R.: Presence of acetylsalicylic acid in plasma following oral ingestion of aspirin. Proc. Soc. Exp. Biol. Med. *110*:304, 1962.
7. Leonards, J. R.: The influence of solubility on the rate of gastrointestinal absorption of aspirin. Clin. Pharmacol. Ther. *4*:476, 1963.
8. Levy, G., and Yacobi, A.: Assessment of aspirin absorption rate from urinary excretion rate measurements. J. Clin. Pharmacol. *15*:525, 1975.
9. Davison, C., Smith, B. W., and Smith, P. K.: Effects of buffered and unbuffered acetylsalicylic acid upon the gastric acidity of normal human subjects. J. Pharm. Sci. *51*:759, 1962.
10. Nayak, R. K., Smyth, R. D., Polk, A., Herczeg, T., Carter, V., Visalli, A. J., and Reavey-Cantwell, N. H.: Effect of antacids on aspirin dissolution and bioavailability. J. Pharmacokinet. Biopharm. *5*:597, 1977.
11. Douthwaite, A. H., and Lintott, G. A. M.: Gastroscopic observation of the effect of aspirin and certain other substances on the stomach. Br. Med. J. *2*:1222, 1938.
12. Hogben, C. A. M., Schanker, L. S., Tocco, D. J., and Brodie, B. B.: Absorption of drugs from the stomach. II. The human. J. Pharmacol. Exp. Ther. *120*:540, 1957.
13. Truitt, E. B., and Morgan, A. M.: Absorption of aspirin from the stomach in man. Toxicol. Appl. Pharmacol. *2*:237, 1960.
14. Dotevall, G., and Ekenved, G.: The absorption of acetylsalicylic acid from the stomach in relation to intragastric pH. Scand. J. Gastroenterol. *11*:801, 1976.
15. Hogben, C. A. M., Tocco, D. J., Brodie, B. B., and Schanker, L. S.: On the mechanism of intestinal absorption of drugs. J. Pharmacol. Exp. Ther. *125*:275, 1959.
16. Nogami, H., and Matsuzawa, T.: Studies on absorption and excretion of drugs. I. Kinetics of penetration of acidic drug, salicylic acid, through the intestinal barrier in vitro. Chem. Pharm. Bull. *9*:532, 1961.
17. Davenport, H. W.: Damage to the gastric mucosa: Effects of salicylates and stimulation. Gastroenterology *49*:189, 1965.
18. Flower, R. J., and Vane, J. R.: Some pharmacologic and biochemical aspects of prostaglandin biosynthesis and its inhibition. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthesis Inhibitors. New York, Raven Press, 1974.
19. Lester, D., Lolli, G., and Greenberg, L. A.: The fate of acetylsalicylic acid. J. Pharmacol. Exp. Ther. *87*:329, 1946.
20. Mandel, H. G., Cambosos, N. M., and Smith, P. K.: The presence of aspirin in human plasma after oral administration. J. Pharmacol. Exp. Ther. *112*:495, 1954.
21. Soren, A.: Dissociation of acetylsalicylic acid in blood and joint fluid. Scand. J. Rheumatol. *6*:17, 1977.
22. Roth, G. J., and Majerus, P. W.: The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. J. Clin. Invest. *56*:624, 1975.
23. Bridges, K. R., Schmidt, G. J., Jensen, M., Cerami, M., and Bunn, H. F.: The acetylation of hemoglobin by aspirin. In vitro and in vivo. J. Clin. Invest. *56*:201, 1975.
24. Walker, J. E.: Lysine residue 199 of human serum albumin is modified by acetylsalicylic acid. FEBS Letters *66*:173, 1976.
25. Mulinos, M. G., and Ardam, I.: An aspirin splitting enzyme in blood (abstract). J. Pharmacol. Exp. Ther. *98*:23, 1950.
26. Lowenthal, D. T., Briggs, W. A., and Levy, G.: Kinetics of salicylate elimination by anephric patients. J. Clin. Invest. *54*:1221, 1974.
27. Levy, G., Procknal, J. A., and Garrettson, L. K.: Distribution of salicylate between neonatal and maternal serum at diffusion equilibrium. Clin. Pharmacol. Ther. *18*:210, 1975.
28. Reed, J. R., and Palmisano, P. A.: Central nervous system salicylate. Clin. Toxicol. *8*:623, 1975.
29. Hill, J. B.: Salicylate intoxication. N. Engl. J. Med. *288*:1110, 1973.
30. Schachter, D., and Manis, J. G.: Salicylate and salicyl conjugates: Fluorimetric estimation, biosynthesis and renal excretion in man. J. Clin. Invest. *37*:800, 1958.
31. Flower, R. J., and Vane, J. R.: Some pharmacologic and biochemical aspects of prostaglandin biosynthesis and its inhibition. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthesis Inhibitors. New York, Raven Press, 1974.
32. Paulus, H. E., Siegel, M., Mongan, E., Okun, R., and Calabro, J. J.: Variations of serum concentrations and half-life of salicylates in patients with rheumatoid arthritis. Arthritis Rheum. *14*:527, 1971.
33. Smith, P. K., Gleason, H. L., Stoll, C. G., and Ogorzalek, S.: Studies on the pharmacology of salicylates. J. Pharmacol. Exp. Ther. *87*:237, 1946.
34. Levy, G., and Leonards, J. R.: Urine pH and salicylate therapy (letter). JAMA *217*:81, 1971.
35. Levy, G., Lampman, T., Kamath, B. L., and Garrettson, L. K.: Decreased serum salicylate concentration in children with rheumatic fever treated with antacid. N. Engl. J. Med. *293*:323, 1975.
36. Levy, G., Tsuchiya, T., and Amsel, L. P.: Limited capacity for salicyl phenolic glucoronide formation and its effect on the kinetics of salicylate elimination in man. Clin. Pharmacol. Ther. *13*:258, 1972.
37. Tsuchiya, T., and Levy, G.: Biotransformation of salicylic acid to its acyl and phenolic glucoronides in man. J. Pharm. Sci. *61*:800, 1972.

3. Gupta, N., Sarkissian, E., and Paulus, H. E.: Correlation of plateau serum salicylate level with rate of salicylate metabolism. Clin. Pharmacol. Ther. *18*:350, 1975.
3. Furst, D. E., Gupta, N., and Paulus, H. E.: Salicylate metabolism in twins. Evidence suggesting a genetic influence and induction of salicylurate formation. J. Clin. Invest. *60*:32, 1977.
4. Ayres, J. W., Weidler, D. J., Mackichan, J., and Wagner, J. G.: Circadian rhythm of urinary pH in man with and without chronic antacid administration. Eur. J. Clin. Pharmacol. *12*:415, 1977.
41. Aarons, L. J., Bochner, F., and Rowland, M.: A chronic dose-ranging kinetic study of salicylate in man (abstract). Br. J. Pharmacol. *61*:456P, 1977.
42. Bernheim, H. A., and Kluger, M. J.: Fever: Effect of drug-induced antipyresis on survival. Science *193*:237, 1976.
43. Jackson, D. L.: A hypothalamic region responsive to localized injection of pyrogens. J. Neurophysiol. *30*:586, 1967.
44. Cooper, K. E., Cranston, W. I., and Honour, A. J.: Observations on the site and mode of action of pyrogens in the rabbit brain. J. Physiol. *191*:325, 1967.
45. Milton, A. S., and Wendlandt, S.: A possible role for prostaglandin E_1 as a modulator for temperature regulation in the central nervous system of the cat (abstract). J. Physiol. *207*:76P, 1970.
46. Chai, C. Y., Lin, M. T., Chen, H. I., and Wang, S. C.: The site of action of leukocytic pyrogen and antipyresis of sodium acetylsalicylate in monkeys. Neuropharmacology *10*:715, 1971.
47. Lin, M. T., and Chai, C. Y.: The antipyretic effect of sodium acetylsalicylate on pyrogen-induced fever in rabbits. J. Pharmacol. Exp. Ther. *180*:603, 1972.
48. Flower, R. J., and Vane, J. R.: Inhibition of prostaglandin synthetase in brain explains the antipyretic activity of paracetamol (4-acetamidophenol). Nature *240*:410, 1972.
49. Seed, J. C.: A clinical comparison of the antipyretic potency of aspirin and sodium salicylate. Clin. Pharmacol. Ther. *6*:354, 1965.
50. Feldberg, W., and Gupta, K. P.: Pyrogen fever and prostaglandin-like activity in cerebrospinal fluid. J. Physiol. *228*:41, 1973.
51. Schoener, E. P., and Wang, S. C.: Sodium acetylsalicylate effectiveness against fever induced by leukocyte pyrogen and prostaglandin E_1 in the cat. Experientia *30*:383, 1974.
52. Woolf, C. J., Willies, G. H., Laburn, H., and Rosendorff, C.: Pyrogen and prostaglandin fever in the rabbit. I. Effects of salicylate and the role of cyclic AMP. Neuropharmacology *14*:397, 1975.
53. Bodel, P., Reynolds, C. F., and Atkins, E.: Lack of effect of salicylate on pyrogen release from human blood leucocytes in vitro. Yale J. Biol. Med. *46*:190, 1973.
54. Schoener, E. P., and Wang, S. C.: Observations on the central mechanism of acetylsalicylate antipyresis. Life Sci. *17*:1063, 1975.
55. Avery, D. D., and Penn, P. E.: Blockade of pyrogen induced fever by intrahypothalamic injections of salicylate in the rat. Neuropharmacology *13*:1179, 1974.
56. Satinoff, E.: Salicylate: Action on normal body temperature in rats. Science *176*:532, 1972.
57. Pittman, Q. J., Veale, W. L., and Cooper, K. E.: Observations on the effect of salicylate in fever and the regulation of body temperature against cold. Can. J. Physiol. Pharmacol. *54*:101, 1976.
58. Lim, R. K. S.: Salicylate analgesia. *In* Smith, M. J. H., and Smith, P. K. (eds.): The Salicylates. A Critical Bibliographic Review. New York, Wiley, 1966.
59. Wallenstein, S. L., and Houde, R. W.: Clinical comparison of analgetic effectiveness of N-acetyl-p-aminophenol, salicylamide and aspirin (abstract). Fed. Proc. *13*:414, 1954.
60. Houde, R. W., Wallenstein, S. L., and Rogers, A.: Clinical pharmacology of analgesics. I. A method of assaying analgesic effect. Clin. Pharmacol. Ther. *1*:163, 1960.
61. Fremont-Smith, K., and Bayles, T. B.: Salicylate therapy in rheumatoid arthritis. A scientific exhibit. JAMA *190*:383, 1964. (Cited in Reference 58.)
62. Lasagna, L.: Anaglesic drugs. Am. J. Med. Sci. *242*:620, 1960.
63. Guzman, F., Braun, C., Lim, R. K. S., Potter, G. D., and Rodgers, D. W.: Narcotic and non-narcotic analgesics which block visceral pain evoked by intra-arterial injection of bradykinin and other algesic agents. Arch. Int. Pharmacodyn. Ther. *149*:571, 1964.
64. Lim, R. K. S., Guzman, F., Rodgers, D. W., Goto, K., Braun, C., Dickerson, G. D., and Engle, R. J.: Site of action of narcotic and non-narcotic analgesics determined by blocking bradykinin-evoked visceral pain. Arch. Int. Pharmacodyn. Ther. *152*:25, 1964.
65. Winder, C. V.: Aspirin and algesimetry. Nature *184*:494, 1959.
66. Hashimoto, K., Kumakura, S., and Taira, N.: Vascular reflex responses induced by an intra-arterial injection of azaazepinophenothiazine, andromedotoxin, veratridine, bradykinin and kallikrein and blocking action of sodium salicylate. Jap. J. Physiol. *14*:299, 1964.
67. Thompkins, L., and Lee, K. H.: Comparison of analgesic effects of isosteric variations of salicylic acid and aspirin (acetylsalicylic acid). J. Pharm. Sci. *64*:760, 1975.
68. Ferreira, S. H., Moncada, S., and Vane J. R.: Further experiments to establish that the analgesic action of aspirin-like drugs depends on the inhibition of prostaglandin biosynthesis (abstract). Br. J. Pharmacol. *47*:629P, 1973.
69. Willis, A. L., and Cornelsen, M.: Repeated injection of prostaglandin E_2 in rat paws induces chronic swelling and a marked decrease in pain threshold. Prostaglandins *3*:353, 1973.
70. Ferreira, S. H.: Prostaglandins, aspirin-like drugs and analgesia. Nature New Biol. *240*:200, 1972.
71. Rosenthale, M. E., Dervinis, A., Kassarich, J., and Singer, S.: Prostaglandins and anti-inflammatory drugs in the dog knee joint. J. Pharm. Pharmacol. *24*:149, 1972.
72. Levitan, H., and Barker, J. L.: Effect of non-narcotic analgesics on membrane permeability of molluscan neurones. Nature New Biol. *239*:55, 1972.
73. Beaven, M. A., Horakova, Z., and Keiser, H. R.: Interference with histamine and imidazole acetic acid metabolism by salicylates: A possible contribution to salicylate analgesic activity? Experientia *32*:1180, 1976.
74. Moss, J., De Mello, M. C., Vaughn, M., and Beaven, M. A.: Effect of salicylates on histamine and L-histidine metabolism. Inhibition of imidazoleacetate phosphoribosyl transferase. J. Clin. Invest. *58*:137, 1976.
75. Boardman, P. L., and Hart, F. D.: Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis. Br. Med. J. *2*:264, 1967.
76. Robinson, D. R., and Levine, L.: Prostaglandin concentrations in synovial fluid in rheumatic diseases: Action of indomethacin and aspirin. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthetase Inhibitors. New York, Raven Press, 1974.
77. Winter, C. A., Risley, E. A., and Nuss, G. W.: Carrageenin-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Proc. Soc. Exp. Biol. Med. *111*:544, 1962.
78. Mielens, Z. E., Drobeck, H. P., Rozitis, J., and Sansone, V. J.: Interaction of aspirin with non-steroidal anti-inflammatory drugs in rats (letter). J. Pharm. Pharmacol. *20*:567, 1968.
79. Swingle, K. F., Grant, T. J., Jaques, L. W., and Kvam, D. C.: Interactions of anti-inflammatory drugs in carrageenan-induced foot edema of the rat. J. Pharmacol. Exp. Ther. *172*:423, 1970.
80. Willis, A. L., Davison, P., Ramwell, P. W., Brocklehurst, W. E., and Smith, B.: Release and actions of prostaglandins in inflammation and fever: Inhibition by anti-inflammatory and antipyretic drugs. *In* Ramwell, P. W., and Pharriss, B. B. (eds.): Prostaglandins in Cellular Biology. New York, Plenum Press, 1972.

81. Vinegar, R., Truax, J. F., and Selph, J. L.: Some quantitative temporal characteristics of carrageenin-induced pleurisy in the rat. Proc. Soc. Exp. Biol. Med. *143*:711, 1973.
82. Randall, L. O., Selitto, J. J., and Valdes, J.: Anti-inflammatory effects of xylopropamine. Arch. Int. Pharmacodyn. Ther. *113*:233, 1957.
83. Gilfoil, T. M., Klavins, I., and Grumbach, L.: Effects of acetylsalicylic acid on the edema and hyperesthesia of the experimentally inflamed rat's paw. J. Pharmacol. Exp. Ther. *142*:1, 1963.
84. Van Arman, C. G., Carlson, R. P., Risley, E. A., Thomas, R. H., and Nuss, G. W.: Inhibitory effects of indomethacin, aspirin and certain other drugs on inflammations induced in rat and dog by carrageenan, sodium urate and ellagic acid. J. Pharmacol. Exp. Ther. *175*:459, 1970.
85. Smith, M. J. H.: Anti-inflammatory activity of salicylates. *In* Smith, M. J. H., and Smith, P. K. (eds.): The Salicylates. A Critical Bibliographic Review. New York, Wiley, 1966.
86. Winter, C. A., and Nuss, G. W.: Treatment of adjuvant arthritis in rats with anti-inflammatory drugs. Arthritis Rheum. *9*:394, 1966.
87. Van Arman, C. G., Nuss, G. W., and Risley, E. A.: Interactions of aspirin, indomethacin and other drugs in adjuvant-induced arthritis in the rat. J. Pharmacol. Exp. Ther. *187*:400, 1973.
88. Sofia, R. D., Knobloch, L. C., and Douglas, J. F.: Effect of concurrent administration of aspirin, indomethacin or hydrocortisone with gold sodium thiomalate against adjuvant-induced arthritis in the rat. Agents Actions *6*:728, 1976.
89. Gold, E. W., Anderson, L. B., Schwartz, E. R., and Miller, C. W.: The effect of salicylate on prostaglandin levels in rabbit knees following inducement of osteoarthritic changes. Prostaglandins *12*:837, 1976.
90. Goldlust, M. B., Rich, L. C., and Harrity, T. W.: Effects of anti-inflammatory agents on the acute response of immune synovitis in rabbits. Arthritis Rheum. *20*:937, 1977.
91. Robinson, D. R., Tashjian, A. H., and Levine, L.: Prostaglandin-induced bone resorption by rheumatoid synovia. Trans. Assoc. Am. Physicians *88*:146, 1975.
92. Dayer, J-M., Robinson, D. R., and Krane, S. M.: Prostaglandin production by rheumatoid synovial cells. J. Exp. Med. *145*:1399, 1977.
93. Kaley, G., and Weiner, R.: Prostaglandin E_1: A potential mediator of the inflammatory response. Ann. N.Y. Acad. Sci. *180*:338, 1971.
94. Higgs, G. A., McCall, E., and Youlten, L. J. F.: A chemotactic role for prostaglandins released from polymorphonuclear leukocytes during phagocytosis. Br. J. Pharmacol. *53*:539, 1975.
95. MacGregor, R. R., Spagnuolo, P. J., and Lentnek, A. L.: Inhibition of granulocyte adherence by ethanol, prednisone, and aspirin, measured with an assay system. N. Engl. J. Med. *291*:642, 1974.
96. Robinson, H. J., Phares, H. F., and Graessle, O. E.: Prostaglandin synthetase inhibitors and infection. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthetase Inhibitors. New York, Raven Press, 1974.
97. Stone, C. A., Van Arman, C. G., Peck, H. M., Minsker, D. H., and Ham, E. A.: Pharmacologic and toxicologic action of prostaglandin synthetase inhibitors: Potential role of prostaglandin synthesis blockade. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthetase Inhibitors. New York, Raven Press, 1974.
98. Ferreira, S. H., Moncada, S., and Vane, J. R.: Prostaglandins and signs and symptoms of inflammation. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthetase Inhibitors. New York, Raven Press, 1974.
99. Stefanovich, V.: Inhibition of 3', 5'-cyclic AMP phosphodiesterase with anti-inflammatory agents. Res. Commun. Chem. Pathol. Pharmacol. *7*:573, 1974.
100. Athreya, B. H., Moser, G., Cecil, H. S., and Myers, A. R.: Aspirin-induced hepatotoxicity in juvenile rheumatoid arthritis. Arthritis Rheum. *18*:347, 1975.
101. Ropes, M. W.: Systemic Lupus Erythematosus. Cambridge, Mass., Harvard University Press, 1976.
102. Kimberly, R. P., and Plotz, P. H.: Aspirin-induced depression of renal function. N. Engl. J. Med. *296*:418, 1977.
103. Buckingham, R. B.: Interactions involving anti-rheumatic drugs. I and II. Bull. Rheum. Dis. *28*:960, 1978.
104. Mason, R. W., and McQueen, E. G.: Protein binding of indomethacin: Binding of indomethacin to human plasma albumin and its displacement from binding by ibuprofen, phenylbutazone and salicylate, in vitro. Pharmacology *12*:12, 1974.
105. Jeremy, R., and Towson, J.: Interaction between aspirin and indomethacin in the treatment of rheumatoid arthritis. Med. J. Aust. *2*:127, 1970.
106. Champion, G. D., Paulus, H. E., Mongan, E., Okun, R., and Pearson, C. M.: The effect of aspirin on serum indomethacin. Clin. Pharmacol. Ther. *13*:239, 1972.
107. Garnham, J. C., Raymond, K., Shotton, E., and Turner, P.: The effect of buffered aspirin on plasma indomethacin. Eur. J. Clin. Pharmacol. *8*:107, 1975.
108. Kaldestad, E., Hansen, T., and Brath, H. K.: Interaction of indomethacin and acetylsalicylic acid as shown by the serum concentrations of indomethacin and salicylate. Eur. J. Clin. Pharmacol. *9*:199, 1975.
109. Barraclough, D. R., Muirden, K. D., and Laby, B.: Salicylate therapy and drug interaction in rheumatoid arthritis. Aust. N.Z. J. Med. *5*:518, 1975.
110. Rome, L. H., Lands, W. E., Roth, G. J., and Majerus, P. W.: Aspirin as a quantitative acetylating reagent for the fatty acid oxygenase that forms prostaglandins. Prostaglandins *11*:23, 1976.
111. Thomas, B. H., Zeitz, W., and Coldwell, B. B.: Effect of aspirin on biotransformation of 14C-acetaminophen in rats. J. Pharm. Sci. *63*:1367, 1974.
112. Whitehouse, L. W., Paul, C. J., and Thomas, B. H.: Effect of aspirin on fate of 14C-acetaminophen in guinea pigs. J. Pharm. Sci. *64*:819, 1975.
113. Whitehouse, L. W., Paul, C. J., and Thomas, B. H.: Effect of acetylsalicylic acid on a toxic dose of acetaminophen in the mouse. Toxicol. Appl. Pharmacol. *38*:571, 1976.
114. Cotty, V. F., Sterbenz, F. J., Mueller, F., Melman, K., Ederma, H., Skerpac, J., Hunter, D., and Lehr, M.: Augmentation of human blood acetylsalicylate concentration by the simultaneous administration of acetaminophen with aspirin. Toxicol. Appl. Pharmacol. *41*:7, 1977.
115. Muirden, K. D., Deutschman, P., and Phillips, M.: Competition between salicylate and other drugs in binding to human serum protein in vitro. Aust. N.Z. J. Med. *4*:149, 1974.
116. Segre, E., Chaplin, M., Forchelli, E., Runkel, R., and Sevelius, H.: Naproxen-aspirin interactions in man. Clin. Pharmacol. Ther. *15*:374, 1974.
117. Rubin, A., Rodda, B. E., Warrick, P., Gruber, C. M., and Ridolfo, A. S.: Interactions of aspirin with non-steroidal anti-inflammatory drugs in man. Arthritis Rheum. *16*:635, 1973.
118. Quick, A. J., and Clesceri, L.: Influence of acetylsalicylic acid and salicylamide on the coagulation of blood. J. Pharmacol. Exp. Ther. *128*:95, 1960.
119. Loew, D., and Vinazzer, H.: Dose dependent influence of acetylsalicylic acid on platelet functions and plasmatic coagulation factors. Haemostasis *5*:239, 1976.
120. Kelley, W. N.: Effects of drugs on uric acid in man. Ann. Rev. Pharmacol. Toxicol. *15*:327, 1975.
121. Sorensen, L. B., and Levinson, D. J.: Clinical evaluation of benzbromarone. A new uricosuric drug. Arthritis Rheum. *19*:183, 1976.
122. Jaffe, R. M., Kasten, B., Young, D. S., and MacLowry, J. D.: False-negative stool occult blood tests caused by inges-

tion of ascorbic acid (vitamin C). Ann. Intern. Med. *83*:824, 1975.
123. Klinenberg, J. R., and Miller, F.: Effect of corticosteroids on blood salicylate concentration. JAMA *194*:601, 1965.
124. Mandel, M. A.: The synergistic effect of salicylate on methotrexate toxicity. Plast. Reconstr. Surg. *57*:733, 1976.
125. Zuik, M., and Mandel, M. A.: Methotrexate-salicylate interaction: A clinical and experimental study. Surg. Forum *26*:567, 1975.
126. Slone, D., Siskind, V., Heinonen, O. P., Monson, R. P., Kaufman, D. W., and Shapiro, S.: Aspirin and congenital malformations. Lancet *1*:1373, 1976.
127. Turner, G., and Collins, E.: Fetal effects of regular salicylate ingestion in pregnancy. Lancet *2*:338, 1975.
128. Shapiro, S., Siskind, V., Monson, R. P., Heinonen, O. P., Kaufman, D. W., and Slone, D.: Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. Lancet *1*:1375, 1976.
129. Collins, E., and Turner, G.: Maternal effects of regular salicylate ingestion in pregnancy. Lancet *2*:335, 1975.
130. Lewis, R. B., and Schulman, J. D.: Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. Lancet *2*:1159, 1973.
131. Lamson, R. W., and Thomas, R.: Some untoward effects of acetylsalicylic acid. JAMA *99*:107, 1932.
132. Samter, M., and Beers, R. F.: Concerning the nature of intolerance to aspirin. J. Allergy *40*:281, 1967.
133. Friedlaender, S., and Feinberg, S. M.: Aspirin allergy: Its relationship to chronic intractable asthma. Ann. Intern. Med. *26*:734, 1947.
134. Feinberg, A. R., and Malkiel, S.: Aspirin sensitivity — experimental studies. J. Allergy *22*:74, 1951.
135. Schlumberger, H. D., Lobbecke, E. A., and Kallos, P.: Acetylsalicylic acid intolerance. Acta Med. Scand. *196*:451, 1974.
136. Delaney, J. C.: The diagnosis of aspirin idiosyncrasy by analgesic challenge. Clin. Allergy *6*:177, 1976.
137. Szczeklik, A., Gryglewski, R. J., and Czerniawska-Mysik, G.: Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. Br. Med. J. *1*:67, 1975.
138. Szczeklik, A., Gryglewski, R. J., Czerniawska-Mysik, G., and Zmuda, A.: Aspirin-induced asthma. Hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action on prostaglandin generation by different microsomal enzymic preparations. J. Allergy Clin. Immunol. *58*:10, 1976.
139. Settipane, G. A., and Pudupakkam, R. K.: Aspirin intolerance. III. Subtypes, familial occurrence, and cross-reactivity with tartrazine. J. Allergy Clin. Immunol. *56*:215, 1975.
140. Settipane, G. A., Chafee, F. H., and Klein, D. E.: Aspirin intolerance. II. A prospective study in an atopic and normal population. J. Allergy Clin. Immunol. *53*:200, 1974.
141. Myers, E. N., and Bernstein, J. M.: Salicylate ototoxicity. A clinical and experimental study. Arch. Otolaryngol. *82*:483, 1965.
142. Silverstein, H., Bernstein, J. M., and Davies, D. G.: Salicylate ototoxicity. A biochemical and electrophysiological study. Ann. Otol. *76*:118, 1967.
143. Aly, S., Mousa, S., el-Kahky, M., Saleh, A., and el-Mofty, A.: Toxic deafness. I. J. Egypt. Med. Assoc. *58*:144, 1975.
144. Aly, S., el-Kahky, M., Eid, S., Mousa, S., Ramandan, M., Saleh, A., and el-Mofty, A.: Toxic deafness. II. J. Egypt. Med. Assoc. *58*:158, 1975.
145. Crifo, S.: Aspirin ototoxicity in the guinea pig. ORL *37*:27, 1975.
146. Krzanowski, J. J., Jr., and Matschinsky, F. M.: Adenosine triphosphate and phosphocreatine levels in cochlear structures. Use rate and effect of salicylates. J. Histochem. Cytochem. *23*:766, 1975.
147. Bernstein, J. M., and Weiss, A. D.: Further observations on salicylate ototoxicity. J. Laryngol. Otol. *81*:915, 1967.
148. Mongan, E., Kelly, P., Nies, K., Porter, W. W., and Paulus, H. E.: Tinnitus as an indication of therapeutic serum salicylate levels. JAMA *226*:142, 1973.
149. Muir, A., and Cossar, I. A.: Aspirin and ulcer. Br. Med. J. *2*:7, 1955.
150. Batterman, R. C.: Comparison of buffered and unbuffered acetylsalicylic acid. N. Engl. J. Med. *258*:213, 1958.
151. Cronk, G. A.: Laboratory and clinical studies with buffered and non-buffered acetylsalicylic acid. N. Engl. J. Med. *258*:219, 1958.
152. Sadove, M. S., and Schwartz, L.: An evaluation of buffered versus non-buffered acetylsalicylic acid. Postgrad. Med. *24*:183, 1958.
153. Miller, R. R.: Analgesics. *In* Miller, R. R., and Greenblatt, D. J. (eds.): Drug Effects in Hospitalized Patients. New York, Wiley, 1976.
154. Linnoila, M., and Lehtola, J.: Absorption, and effect on gastric mucosa, of buffered and non-buffered tablets of acetylsalicylic acid. Int. J. Clin. Pharmacol. Biopharm. *15*:61, 1977.
155. Stubbe, L.: Occult blood in faeces after administration of aspirin. Br. Med. J. *2*:1061, 1958.
156. Weiss, A., Pitman, E. R., and Graham, E. C.: Aspirin and gastric bleeding. Am. J. Med. *31*:266, 1961.
157. Wood, P. H. N., Harvey-Smith, E. A., and Dixon, A. St. J.: Salicylates and gastrointestinal blooding. Acetylsalicylic acid and aspirin derivatives. Br. Med. J. *1*:669, 1962.
158. Metzger, W. H., McAdam, L., Bluestone, R., and Guth, P. H.: Acute gastric mucosal injury during continuous or interrupted aspirin ingestion in humans. Am. J. Dig. Dis. *21*:963, 1976.
159. Caravati, C. M., and Cosgrove, E. F.: Salicylate toxicity: The probable mechanism of its action. Ann. Intern. Med. *24*:638, 1946.
160. Pierson, R. N., Holt, P. R., Watson, R. M., and Keating, R. P.: Aspirin and gastrointestinal bleeding. Am. J. Med. *31*:259, 1961.
161. Leonards, J. R.: Aspirin and gastrointestinal blood loss. Gastroenterology *44*:617, 1963.
162. Croft, D. N., and Wood, P. H. N.: Gastric mucosa and susceptibility to occult gastrointestinal bleeding caused by aspirin. Br. Med. J. *1*:137, 1967.
163. Goulston, K., and Cooke, A. R.: Alcohol, aspirin, and gastrointestinal bleeding. Br. Med. J. *4*:664, 1968.
164. Leonards, J. R., and Levy, G.: Aspirin-induced occult gastrointestinal blood loss: Local versus systemic effects. J. Pharm. Sci. *59*:1511, 1970.
165. Jabbari, M., and Valberg, L. S.: Role of acid secretion in aspirin-induced gastric mucosal injury. Can. Med. Assoc. J. *102*:178, 1970.
166. St. John, D. J. B., and McDermott, F. T.: Influence of achlorhydria on aspirin-induced occult gastrointestinal blood loss: Studies in Addisonian pernicious anemia. Br. Med. J. *2*:450, 1970.
167. Scott, J. T., Porter, I. H., Lewis, S. M., and Dixon, A. St. J.: Study of gastrointestinal bleeding caused by corticosteroids, salicylates and other analgesics. Quart. J. Med. *30*:167, 1961.
168. Grossman, M. I., Matsumoto, K. K., and Lichter, R. J.: Fecal blood loss produced by oral and intravenous administration of various salicylates. Gastroenterology *40*:383, 1961.
169. Stubbe, L., Pietersen, J. H., and van Heulen, C.: Aspirin preparations and their noxious effect on the gastrointestinal tract. Br. Med. J. *1*:675, 1962.
170. Beeken, W. L.: Effect of five salicylate-containing compounds upon loss of ^{51}chromium-labeled erythrocytes from the gastrointestinal tract of normal man. Gut *9*:475, 1968.
171. Leonards, J. R., and Levy, G.: Reduction or prevention of aspirin-induced occult gastrointestinal blood loss in man. Clin. Pharmacol. Ther. *10*:571, 1969.
172. Leonards, J. R., and Levy, G.: Effect of pharmaceutical for-

mulation on gastrointestinal bleeding from aspirin tablets. Arch. Intern. Med. *129*:457, 1972.
173. Leonards, J. R., and Levy, G.: Gastrointestinal blood loss from aspirin and sodium salicylate tablets in man. Clin. Pharmacol. Ther. *14*:62, 1973.
174. Parry, D. J., and Wood, P. H. N.: Relationship between aspirin taking and gastroduodenal hemorrhage. Gut *8*:301, 1967.
175. Bouchier, I. A. D., and Williams, H. S.: Determination of faecal blood loss after combined alcohol and sodium acetylsalicylate. Lancet *1*:178, 1969.
176. Leonards, J. R., Levy, G., and Niemczura, R.: Gastrointestinal blood loss during prolonged aspirin administration. N. Engl. J. Med. *289*:1020, 1973.
177. Schmid, F. R., and Culic, D. D.: Anti-inflammatory drugs and gastrointestinal bleeding: A comparison of aspirin and ibuprofen. J. Clin. Pharmacol. *16*:418, 1976.
178. Cooke, A. R., and Goulston, K.: Failure of intravenous aspirin to increase gastrointestinal blood loss. Br. Med. J. *3*:330, 1969.
179. Watson, R. M., and Pierson, R. N.: Effect of anticoagulant therapy upon aspirin-induced gastrointestinal bleeding. Circulation *24*:613, 1961.
180. Baragar, F. D., and Duthie, J. J. R.: Importance of aspirin as a cause of anaemia and peptic ulcer in rheumatoid arthritis. Br. Med. J. *1*:1106, 1960.
181. Muir, A., and Cossar, I. A.: Aspirin and gastric bleeding: Further studies of calcium aspirin. Am. J. Dig. Dis. *6*:1115, 1961.
182. Paul, W. D.: The effect of acetylsalicylic acid (aspirin) on the gastric mucosa, a gastroscopic study. J. Iowa Med. Soc. *33*:155, 1943.
183. Thorsen, W. B., Western, D., Tanaka, Y., and Morrissey, J. F.: Aspirin injury to gastric mucosa. Gastrocamera observations of the effect of pH. Arch. Intern. Med. *121*:499, 1968.
184. Kuiper, D. H., Fall, D. S., Overholt, B. F., and Pollard, H. M.: The effect of aspirin on fecal blood loss with gastroscopic correlation in healthy volunteers (abstract). Ann. Intern. Med. *70*:1069, 1969.
185. Edmar, D.: The effects of acetylsalicylic acid on the human gastric mucosa as revealed by gastrocamera. Scand. J. Gastroenterol. *10*:495, 1975.
186. Baskin, W. N., Ivey, K. J., Krause, W. J., Jeffrey, G. E., and Gemmell, R. T.: Aspirin-induced ultrastructural changes in human gastric mucosa: Correlation with potential difference. Ann. Intern. Med. *85*:299, 1976.
187. Rahbek, I.: Gastroscopic evaluation of the effect of a new anti-rheumatic compound Ketoprofen (19.583 R.P.) on the human gastric mucosa. A double-blind cross-over trial against acetylsalicylic acid. Scand. J. Rheumatol. (Suppl.) 63, 1976.
188. Loebl, D. H., Craig, R. M., Culic, D. D., Ridolfo, A. S., Falk, J., and Schmid. F. R.: Gastrointestinal blood loss. Effect of aspirin, fenoprofen, and acetaminophen in rheumatoid arthritis as determined by sequential gastroscopy and radioactive fecal markers. JAMA *237*:976, 1977.
189. Croft, D. N.: Cell turnover and loss and the gastric mucosal barrier. Am. J. Dig. Dis. *22*:383, 1977.
190. Davenport, H. W.: Salicylate damage to the gastric mucosal barrier. N. Engl. J. Med. *276*:1307, 1967.
191. Silen, W.: New concepts of the gastric mucosal barrier. Am. J. Surg. *133*:8, 1977.
192. Brown, R. K., and Mitchell, N.: The influence of some of the salicyl compounds (and alcoholic beverages) on the natural history of peptic ulcer. Gastroenterology *31*:198, 1956.
193. Alvarez, A., and Summerskill, W. H. J.: Gastrointestinal haemorrhage and salicylates. Lancet *2*:920, 1958.
194. Jennings, G. H.: Causal influences in haematemesis and melena. Gut *6*:1, 1965.
195. Muir, A., and Cossar, I. A.: Aspirin and gastric haemorrhage. Lancet *1*:539, 1959.
196. Needham, C. D., Kyle, J., Jones, P. F., Johnston, S. J., and Kerridge, D. F.: Aspirin and alcohol in gastrointestinal haemorrhage. Gut *12*:819, 1971.
197. Dagradi, A. E., Lee, E. R., Bosco, D. L., and Stempien, S. J.: The clinical spectrum of hemorrhagic erosive gastritis. Am. J. Gastroenterol. *60*:30, 1973.
198. Cameron, A. J.: Aspirin and gastric ulcer. Mayo Clin. Proc. *50*:565, 1975.
199. Jorgensen, T. G.: Drug consumption before perforation of peptic ulcer. Br. J. Surg. *64*:247, 1977.
200. Langman, M. J. S.: Aspirin is not a major cause of acute gastrointestinal bleeding. *In* Inglefinger, F. J., Ebert, R. V., Finland, M., and Relman, A. S. (eds.): Controversy in Internal Medicine II. Philadelphia, W. B. Saunders Company, 1974.
201. Spiro, H. M.: Aspirin is dangerous for the peptic ulcer patient. *In* Inglefinger, F. J., Ebert, R. V., Finland, M., and Relman, A. S. (eds.): Controversy in Internal Medicine II. Philadelphia, W. B. Saunders Company, 1974.
202. Levy, M.: Aspirin use in patients with major upper gastrointestinal bleeding and peptic ulcer disease. N. Engl. J. Med. *290*:1158, 1974.
203. Duggan, J. M.: Progress report. Aspirin in chronic gastric ulcer: An Australian experience. Gut *17*:378, 1976.
204. Gault, M. H., Rudwal, T. C., Engles, W. D., and Dossetor, J. B.: Syndrome associated with the abuse of analgesics. Ann. Intern. Med. *68*:906, 1968.
205. Winawer, S. J., Bejar, J., and Zamcheck, N.: Recurrent massive hemorrhage in patients with achlorhydria and atrophic gastritis. Arch. Intern. Med. *120*:327, 1967.
206. Rafoth, R. J., and Silvis, S. E.: Gastric ulceration associated with aspirin ingestion in an achlorhydric patient: A case report. Am. J. Dig. Dis. *21*:279, 1976.
207. Bergman, G. E., Philippidis, P., and Naiman, J. L.: Severe gastrointestinal hemorrhage and anemia after therapeutic doses of aspirin in normal children. J. Pediat. *88*:501, 1976.
208. MacKercher, P. A., Ivey, K. J., Baskin, W. N., and Krause, W. J.: Protective effect of cimethidine on aspirin-induced gastric mucosal damage. Ann. Intern. Med. *87*:676, 1977.
209. Okabe, S., Takeuchi, K., Urushidani, T., and Takagi, K.: Effects of cimetidine, a histamine H2-receptor antagonist, on various experimental gastric and duodenal ulcers. Am. J. Dig. Dis. *22*:677, 1977.
210. Tarnawski, A., Krause, W. J., and Ivey, K. J.: Effect of glucagon on aspirin-induced gastric mucosal damage in man. Gastroenterology *74*:240, 1978.
211. Welch, R. W., Bentch, H. L., and Harris, S. C.: Reduction of aspirin-induced gastrointestinal bleeding with cimethidine. Gastroenterology *74*:459, 1978.
212. Geall, M. G., Phillips, S. F., and Summerskill, W. H. J.: Profile of gastric potential difference in man. Effects of aspirin, alcohol, bile, and endogenous acid. Gastroenterology *58*:437, 1970.
213. Ivey, K. J., Morrison, S., and Gray, C.: Effect of salicylates on the gastric mucosal barrier in man. J. Appl. Physiol. *33*:81, 1972.
214. Davenport, H. W., Warner, H. A., and Code, C. F.: Functional significance of gastric mucosal barrier to sodium. Gastroenterology *47*:142, 1964.
215. Chvasta, T. E., and Cooke, A. R.: The effect of several ulcerogenic drugs on the canine gastric mucosal barrier. J. Lab. Clin. Med. *79*:302, 1972.
216. Caspary, W. F.: The effect of aspirin, antacids, alcohol and bile acids on transmural potential difference of the human stomach. Dtsch. Med. Wochenschr. *100*:1263, 1975.
217. Bowen, B. K., Krause, W. J., and Ivey, K. J.: Effect of sodium bicarbonate on aspirin-induced damage and potential difference changes in human gastric mucosa. Br. Med. J. *2*:1052, 1977.
218. Murray, H. S., Strottman, M. P., and Cooke, A. R.: Effect of several drugs on gastric potential difference in man. Br. Med. J. *1*:19, 1974.
219. Cohen, M. M., and Pollett, J. M.: Prostaglandin E_2 prevents

aspirin and indomethacin damage to human gastric mucosa. Surg. Forum *27*:400, 1976.
220. Davenport, H. W.: Gastric mucosal hemorrhage in dogs. Effects of acid, aspirin, and alcohol. Gastroenterology *56*:439, 1969.
221. Brown, P. A., Sawrey, J. M., and Vernikos-Danillis, J.: Attenuation of salicylate and stress-produced gastric ulceration by metiamide. Proc. West. Pharmacol. Soc. *18*:123, 1975.
222. Rainsford, K. D.: Aspirin and gastric ulceration: Light and electron microscopic observations in a model of aspirin plus stress-induced ulcerogenesis. Br. J. Exp. Pathol. *58*:215, 1977.
223. MacDonald, A., Dekanski, J. B., Gottfried, S., Parke, D. V., and Sacra, P.: Effects of blood glucose levels on aspirin-induced gastric mucosal damage. Am. J. Dig. Dis. *22*:909, 1977.
224. Semple, P. F., and Russell, R. I.: Role of bile acids in the pathogenesis of aspirin-induced mucosal hemorrhage in rats. Gastroenterology *68*:67, 1975.
225. Guth, P. H., Paulsen, G., Lynn, D., and Aures, D.: Mechanism of prevention of aspirin-induced gastric lesions by bile duct ligation in the rat. Gastroenterology *71*:750, 1976.
226. Brodie, D. A., and Chase, B. J.: Role of gastric acid in aspirin-induced gastric irritation in the rat. Gastroenterology *53*:604, 1967.
227. Dagle, G. E., Brodie, D. A., and Bauer, B. G.: Comparison of gross and microscopic gastric lesions produced in rats after single doses of aspirin and 2-deoxyglucose. Toxicol. Appl. Pharmacol. *16*:638, 1970.
228. Okabe, S., Honda, K., Takeuchi, K., and Takagi, K.: Inhibitory effect of L-glutamine on gastric irritation and back diffusion of gastric acid in response to aspirin in the rat. Am. J. Dig. Dis. *20*:626, 1975.
229. Boyle, E., Freeman, P. C., Goudie, A. C., Mangan, F. R., and Thomson, M.: The role of copper in preventing gastrointestinal damage by acidic anti-inflamamtory drugs. J. Pharm. Pharmacol. *28*:865, 1976.
230. Rainsford, K. D., and Whitehouse, M. W.: Gastric irritancy of aspirin and its congeners: Anti-inflammatory activity without this side-effect. J. Pharm. Pharmacol. *28*:599, 1976.
231. Cheung, L. Y., Jubiz, W., Torma, M. J., and Frailey, J.: Effects of aspirin on canine gastric prostaglandin output and mucosal permeability. Surg. Forum *25*:407, 1974.
232. Child, C., Jubiz, W., and Moore, J. G.: Effects of aspirin on gastric prostaglandin E (PGE) and acid output in normal subjects. Gut *17*:54, 1976.
233. Cheung, L. Y., Moody, F. G., and Reese, R. S.: Effect of aspirin, bile salt, and ethanol on canine gastric mucosal blood flow. Surgery *77*:786, 1975.
234. Gerkens, J. F., Shand, D. G., Flexner, C., Nies, A. S., Oates, J. A., and Data, J. L.: Effect of indomethacin and aspirin on gastric blood flow and acid secretion. J. Pharmacol. Exp. Ther. *203*:646, 1977.
235. Farris, R. K., Tapper, E. J., Powell, D. W., and Morris, S. M.: Effect of aspirin on normal and cholera toxin-stimulated intestinal electrolyte transport. J. Clin. Invest. *57*:916, 1976.
236. Kingham, J. G., Whorwell, P. J. and Loehry, C. A.: Small intestinal permeability I. Effects of ischaemia and exposure to acetyl salicylate. Gut *17*:354, 1976.
237. Arvanitakis, C., Chen, G-H., Folscroft, J., and Greenberger, N. J.: Effect of aspirin on intestinal absorption of glucose, sodium, and water in man. Gut *18*:187, 1977.
238. Beaumont, J. L., and Willie, A.: Influence sur l'hémostase, de l'hypertension artérielle, des antivitamines K, de l'héparine et de l'acide acétyl salicylique. Sang *26*:880, 1955.
239. Beaumont, J. L., Caen, J., and Bernard, J.: Influence de l'acide acétyl salicylique dans les maladies hémorragiques. Sang *27*:243, 1956.
240. Gast, L. F.: Influence of aspirin on hemostatic parameters. Ann. Rheum. Dis. *23*:500, 1964.
241. Weiss, H. J., Aledort, L. M., and Kochwa, S.: The effect of salicylates on the hemostatic properties of platelets in man. J. Clin. Invest. *47*:2169, 1968.
242. Mielke, C. H., Kaneshiro, M. M., Maher, I. A., Weiner, J. M., and Rapaport, S. I.: The standardized normal Ivy bleeding time and its prolongation by aspirin. Blood *34*:204, 1969.
243. Bick, R. L., Adams, T., and Schmalhorst, W. R.: Bleeding times, platelet adhesion, and aspirin. Am. J. Clin. Pathol. *65*:69, 1976.
244. Evans, G., Mustard, J. F., and Packham, M. A.: Spontaneous bruising (letter). Lancet *2*:724, 1967.
245. Weiss, H. J., and Aledort, L. M.: Impaired platelet/connective tissue reaction in man after aspirin ingestion. Lancet *2*:495, 1967.
246. O'Brien, J. R.: Effects of salicylates on human platelets. Lancet *1*:779, 1968.
247. Zucker, M. B., and Peterson, J.: Inhibition of adenosine diphosphate-induced secondary aggregation and other platelet functions by acetylsalicylic acid ingestion. Proc. Soc. Exp. Biol. Med. *127*:547, 1968.
248. Zucker, M. B., and Peterson, J.: Effect of acetylsalicylic acid, other nonsteroidal anti-inflammatory agents, and dipyridamole on human blood platelets. J. Lab. Clin. Med. *76*:66, 1970.
249. Weiss, H. J., Tschopp, T. B., and Baumgartner, H. R.: Impaired interaction (adhesion-aggregation) of platelets with the subendothelium in storage-pool disease and after aspirin ingestion. A comparison with von Willebrand's disease. N. Engl. J. Med. *293*:619, 1975.
250. Cazenave, J. P., Packham, M. A., Guccione, M. A., and Mustard, J. F.: Inhibition of platelet adherence to damaged surface of rabbit aorta. J. Lab. Clin. Med. *86*:551, 1975.
251. Tschopp, T. B.: Aspirin inhibits platelet aggregation on, but not adhesion to, collagen fibrils: An assessment of platelet adhesion and deposited platelet mass by morphometry and ^{51}Cr-labeling. Thromb. Res. *11*:619, 1977.
252. Baumgartner, H. R., Tschopp, T. B., and Weiss, H. J.: Platelet interaction with collagen fibrils in flowing blood. II. Impaired adhesion-aggregation in bleeding disorders. A comparison with subendothelium. Thromb. Haemostas. *37*:17, 1977.
253. Stuart, R. K.: Platelet function studies in human beings receiving 300 mg of aspirin per day. J. Lab. Clin. Med. *75*:463, 1970.
254. Rowan, R. M., McDonald, G. A., Renton, R. L., Corne, S. J., and Brown, D. F.: Inhibition of platelet release reaction by acetylsalicylic acid. Postgrad. Med. J. *52*:71, 1976.
255. Seuter, F.: Inhibition of platelet aggregation by acetylsalicylic acid and other inhibitors. Haemostasis *5*:85, 1976.
256. Malmsten, C., Hamberg, M., Svensson, J., and Samuelsson, B.: Physiological role of an endoperoxide in human platelets: Hemostatic defect due to platelet cyclo-oxygenase deficiency. Proc. Natl. Acad. Sci. *72*:1446, 1975.
257. Weiss, H. J., Willis, A. L., Kuhn, D., and Brand, H.: Prostaglandin E_2 potentiation of platelet aggregation induced by LASS endoperoxide: Absent in storage pool disease, normal after aspirin ingestion. Br. J. Haematol. *32*:257, 1976.
258. Burch, J. W., Stanford, N., and Majerus, P. W.: Inhibition of platelet prostaglandin synthetase by oral aspirin. J. Clin. Invest. *61*:314, 1978.
259. Gerrard, J. M., White, J. G., Rao, G. H. R., Krivit, W., and Witkop, C. J.: Labile aggregation stimulating substance (LASS): The factor from storage pool deficient platelets correcting defective aggregation and release of aspirin treated normal platelets. Br. J. Haematol. *29*:657, 1975.
260. Gerrard, J. M., and White, J. G.: The influence of aspirin and indomethacin on the platelet contractile wave. Am. J. Pathol. *82*:513, 1976.
261. Glass, D. B., Gerrard, J. M., Townsend, D., Carr, D. W., White, J. G., and Goldberg, N. D.: The involvement of prostaglandin endoperoxide formation in the elevation of cyclic GMP levels during platelet aggregation. J. Cyclic Nucleotide Res. *3*:37, 1977.
262. Smith, J. B., and Willis, A. L.: Aspirin selectivity inhibits

prostaglandin production in human platelets. Nature New Biol. *231*:235, 1971.
263. Roth, G. J., Stanford, N., and Majerus, P. W.: Acetylation of prostaglandin synthetase by aspirin. Proc. Natl. Acad. Sci. *72*:3073, 1975.
264. Lands, W. E. M., and Rome, L. H.: Inhibition of prostaglandin biosynthesis. *In* Karim, S. M. M. (ed.): Prostaglandins: Chemical and Biochemical Aspects. Lancaster, England, MTP Press, 1976.
265. Fajardo, L. F., Platelet morphology after aspirin. Am. J. Clin.. Pathol. *63*:554, 1975.
266. Lewis, J. C., and Hagedorn, A. B.: Aspirin effects on human platelets: A scanning electron microscope study. Thromb. Res. *9*:647, 1976.
267. Crook, D., and Collins, A. J.: Comparison of effects of aspirin and indomethacin on human platelet prostaglandin synthetase. Ann. Rheum. Dis. *36*:459, 1977.
268. Loew, D., and Vinazzer, H.: Dose-dependent influence of acetylsalicylic acid on platelet function and plasmatic coagulation factors. Haemostasis *5*:239, 1976.
269. Goldsweig, H. G., Kapusta, M., and Schwartz, J.: Bleeding, salicylates, and prolonged prothrombin time: Three case reports and a review of the literature. J. Rheumatol. *3*:37, 1976.
270. Pinedo, H. M., van de Putte, L. B. A., and Loeliger, E. A.: Salicylate-induced consumption coagulopathy. Ann. Rheum. Dis. *32*:66, 1973.
271. Sbarbaro, J. A., and Bennett, R. M.: Aspirin hepatotoxicity and disseminated intravascular coagulation. Ann. Intern. Med. *86*:183, 1977.
272. Verstraete, M.: Are agents affecting platelet function clinically useful? Am. J. Med. *61*:897, 1976.
273. Opelz, G., Terasaki, P. I., and Hirata, A. A.: Suppression of lymphocyte transformation by aspirin. Lancet *2*:478, 1973.
274. Panush, R. S., and Anthony, C. R.: Effects of acetylsalicylic acid on normal human peripheral blood lymphocytes. Inhibition of mitogen- and antigen-stimulated incorporation of tritiated thymidine. Clin. Exp. Immunol. *23*:114, 1976.
275. Coeugniet, E., Bendtzen, K., and Bendixen, G.: Leukocyte migration inhibitory activity of concanavalin-A-stimulated human lymphocytes. Modification by dipyridamole, lysine-acetylsalicylate and heparin. Acta Med. Scand. *199*:99, 1976.
276. Brown, K. A., and Collins, A. J.: Action of non-steroidal anti-inflammatory drugs on human and rat peripheral leucocyte migration in vitro. Ann. Rheum. Dis. *36*:239, 1977.
277. Crout, J. E., Hepburn, B., and Ritts, R. E., Jr.: Suppression of lymphocyte transformation after aspirin ingestion. N. Engl. J. Med. *292*:221, 1975.
278. Smith, M. J., Hoth, M., and Davis, K.: Aspirin and lymphocyte transformation. Ann. Intern. Med. *83*:509, 1975.
279. Snider, D. E., and Parker, C. W.: Aspirin effects on lymphocyte cyclic AMP levels in normal human subjects. J. Clin. Invest. *58*:524, 1976.
280. Duncan, M. W., Person, D. A., Rich, A. A., and Sharp, J. T.: Aspirin and delayed type hypersensitivity. Arthritis Rheum. *20*:1174, 1977.
281. Austen, K. F.: Immunologic aspects of salicylate action. *In* Dixon, A. St. J., Martin, B. K., Smith, M. J. H., and Wood, P. N. H. (eds.): Salicylates. Boston, Little, Brown & Company, 1963.
282. MacGregor, R. R., Spagnuolo, P. J., and Lentnek, A. L.: Inhibition of granulocyte adherence by ethanol, prednisone, and aspirin measured with an assay system. N. Engl. J. Med. *291*:642, 1974.
283. Glader, B. E.: Evaluation of the hemolytic role of aspirin in glucose-6-phosphate dehydrogenase deficiency. J. Pediat. *89*:1027, 1976.
284. Chan, T. K., Todd, D., and Tso, S. C.: Drug-induced hemolysis in glucose-6-phosphate dehydrogenase deficiency. Br. Med. J. *2*:1227, 1976.
285. Glader, B. E.: Salicylate-induced injury of pyruvate-kinase deficient erythrocytes. N. Engl. J. Med. *294*:916, 1976.
286. Wijnja, L., Snijder, J. A. M., and Nieweg, H. O.: Acetylsalicylic acid as a cause of pancytopenia from bone marrow damage. Lancet *2*:768, 1966.
287. Reid, J., Watson, R. D., and Sproull, D. H.: The mode of action of salicylate in acute rheumatic fever. Quart. J. Med. *19*:1, 1950.
288. Bywaters, E. G. L., and Thomas, G. T.: Bed rest, salicylates, and steroid in rheumatic fever. Br. Med. J. *1*:1628, 1961.
289. Alexander, W. D., and Smith, G.: Disadvantageous circulating effects of salicylate in rheumatic fever. Lancet *1*:768, 1962.
290. Sutcliffe, J.: Pulmonary oedema due to salicylates with report of a case. Br. J. Radiol. *28*:314, 1955.
291. Granville-Grossman, K. L., and Sergeant, H. G. S.: Pulmonary oedema due to salicylate intoxication. Lancet *1*:575, 1960.
292. Hrnicek, G., Skelton, J., and Miller, W. C.: Pulmonary edema and salicylate intoxication. JAMA *230*:866, 1974.
293. Tashima, C. K., and Rose, M.: Pulmonary edema and salicylates. Ann. Intern. Med. *81*:274, 1974.
294. Davis, P. R., and Burch, R. E.: Pulmonary edema and salicylate intoxication (letter). Ann. Intern. Med. *80*:553, 1974.
295. Karliner, J. S.: Noncardiogenic forms of pulmonary edema. Circulation *46*:212, 1972.
296. Bowers, R. E., Brigham, K. L., and Owen, P. J.: Salicylate pulmonary edema: The mechanism in sheep and review of the clinical literature. Am. Rev. Respir. Dis. *115*:261, 1977.
297. Anderson, R. J., Potts, D. E., Gabow, P. A., Rumack, B. H., and Schrier, R. W.: Unrecognized adult salicylate intoxication. Ann. Intern. Med. *85*:745, 1976.
298. Tenney, S. M., and Miller, R. M.: The respiratory and circulating actions of salicylate. Am. J. Med. *19*:498, 1955.
299. Starling, M. B., and Elliott, R. B.: The effects of prostaglandins, prostaglandin inhibition, and oxygen on the closure of the ductus arteriosus, pulmonary arteries and umbilical vessels in vitro. Prostaglandins *8*:187, 1974.
300. Elliott, R. B., Starling, M. B., and Neutze, J. M.: Medical manipulation of the ductus arteriosus. Lancet *1*:140, 1975.
301. Friedman, W. F., Hirschklau, M. J., Printz, M. P., Pitlick, P. T., and Kirkpatrick, S. E.: Pharmacologic closure of patient ductus arteriosus in the premature infant. N. Engl. J. Med. *295*:526, 1976.
302. Heymann, M. A., Rudolph, A. M., and Silverman, N. H.: Closure of ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N. Engl. J. Med. *295*:530, 1976.
303. Eisner, D. A., Ohba, M., and Ojeda, C.: The effect of salicylate in Purkinje fibre pace-maker activity. J. Physiol. *269*:84P, 1977.
304. Jackson, H. R., Johnson, S. M., Ng, K. H., Pye, W., and Hall, R. C.: The effect of acetylsalicylic acid on the response of the cardiovascular system to catecholamines. Eur. J. Pharmacol. *28*:119, 1974.
305. Nydick, I., Tang, J., Stollerman, G. H., Wroblewski, F., and LaDue, J. S.: The influence of rheumatic fever on serum concentrations of the enzyme, glutamic oxalacetic transaminase. Circulation *12*:795, 1955.
306. Manso, C., Taranta, A., and Nydick, I.: Effect of aspirin administration on serum glutamic oxalacetic and glutamic pyruvic transaminases in children. Proc. Soc. Exp. Biol. Med. *93*:84, 1956.
307. Russell, A. S., Sturge, R. A., and Smith, M. A.: Serum transaminases during salicylate therapy. Br. Med. J. *2*:428, 1971.

308. Rich, R. R., and Johnson, J. S.: Salicylate hepatotoxicity in patients with juvenile rheumatoid arthritis. Arthritis Rheum. *16*:1, 1973.
309. Seaman, W. E., and Plotz, P. H.: Effect of aspirin on liver tests in patients with RA or SLE and in normal volunteers. Arthritis Rheum. *19*:155, 1976.
310. Okumura, H., Ichikawa, T., Aramaki, T., and Oobayaski, K.: Liver disorder caused by aspirin. Naika *17*:749, 1966.
311. Saltzman, D. A., Gall, E. P., and Robinson, S. F.: Aspirin-induced hepatic dysfunction in a patient with adult rheumatoid arthritis. Am. J. Dig. Dis. *21*:815, 1976.
312. Wilson, J. R.: Aspirin hepatotoxicity in adults with rheumatoid arthritis. Ohio State Med. J. *72*:577, 1976.
313. O'Gorman, T., and Koff, R. S.: Salicylate hepatitis. Gastroenterology *72*:726, 1977.
314. Seaman, W. E., Ishak, K. G., and Plotz, P. H.: Aspirin-induced hepatotoxicity in patients with systemic lupus erythematosus. Ann. Intern. Med. *80*:1, 1974.
315. Wolfe, J. D., Metzger, A. L., and Goldstein, R. C.: Aspirin hepatitis. Ann. Intern. Med. *80*:74, 1974.
316. Bernstein, B. H., Singsen, B. H., King, K. K., and Hanson, V.: Aspirin-induced hepatotoxicity and its effect on juvenile rheumatoid arthritis. Am. J. Dis. Child. *131*:659, 1977.
317. Miller, J. J., and Weissman, D. B.: Correlations between transaminase concentrations and serum salicylate concentration in juvenile rheumatoid arthritis. Arthritis Rheum. *19*:115, 1976.
318. Kalczak, M., Gutowska-Grzegorczyk, G., and Maldyk, E.: The effect of chronic administration of acetylsalicylic acid on the rabbit's liver. Polish Med. J. *IX*:128, 1970.
319. Menguy, R., Desbaillets, L., Okabe, S., and Masters, Y. F.: Abnormal aspirin metabolism in patients with cirrhosis and its possible relationship to bleeding in cirrhotics. Ann. Surg. *176*:412, 1972.
320. Tolman, K. G., Peterson, P., Gray, P., and Hammar, S. P.: Hepatotoxicity of salicylates in monolayer cell cultures. Gastroenterology *74*:205, 1978.
321. Rosenfeld, R. G., and Liebhaber, M. I.: Acute encephalopathy in siblings. Reye syndrome vs salicylate intoxication. Am. J. Dis. Child. *130*:295, 1976.
322. Sillanpaan, M., Makela, A. L., and Koivikko, A.: Acute liver failure and encephalopathy (Reye's syndrome?) during salicylate therapy. Acta Paediat. Scand. *64*:877, 1975.
323. Clausen, E., and Harvald, B.: Nephrotoxicity of different analgesics. Acta Med. Scand. *170*:469, 1961.
324. Scott, J. T.: Renal irritation caused by salicylates. *In* Dixon, A. St. J., Martin, B. K., Smith, M. J. H., and Wood, P. H. N. (eds.): Salicylates. Boston, Little, Brown and Company, 1963.
325. Stewart, J. H., and Gallery, E. D. M.: Analgesic abuse and kidney disease. Aust. N.Z. J. Med. *6*:498, 1976.
326. Murray, T., and Goldberg, M.: Analgestic abuse and renal disease. Ann. Rev. Med. *26*:537, 1975.
327. Robinson, M. J., Nichols, E. A., and Taitz, L.: Nephrotoxic effect of acute sodium salicylate intoxication in the rat. Arch. Pathol. *84*:224, 1967.
328. Axelsen, R. A.: Analgesic-induced renal papillary necrosis in the Gunn rat: The comparative nephrotoxicity of aspirin and phenacetin. J. Pathol. *120*:145, 1976.
329. Salomon, M. I., Gallo, G., Poon, T. P., Goldblat, M. V., and Tchertkoff, V.: The kidney in rheumatoid arthritis. Nephron *12*:297, 1974.
330. New Zealand Rheumatism Association: Aspirin and the kidney. Br. Med. J. *1*:593, 1974.
331. Hanzlik, P. J., Scott, R. W., and Thoburn, T. W.: The salicylates. VII. Further observations on albuminuria and renal functional changes following the administration of full therapeutic doses of salicylate. Arch. Intern. Med. *19*:1029, 1917.
332. Hanzlik, P. J., Scott, R. W., and Reycraft, J. L.: The salicylates. VIII. Salicyl edema. Arch. Intern. Med. *20*:329, 1917.
333. Beeley, L., and Kendall, M. J.: Effect of aspirin on renal clearance of ^{123}I-diatrizoate. Br. Med. J. *1*:707, 1971.
334. Robert, M., Fillastre, J. P., Berger, H., and Malandain, H.: Effect of intravenous infusion of acetylsalicylic acid on renal function. Br. Med. J. *2*:466, 1972.
335. Berg, K. J.: Acute effects of acetylsalicylic acid in patients with chronic renal disease. Eur. J. Clin. Pharmacol. *11*:111, 1977.
336. Berg, K. J.: Acute effects of acetylsalicylic acid on renal function in normal man. Eur. J. Clin. Pharmacol. *11*:117, 1977.
337. Kimberly, R. P., Bowden, R. E., Keiser, H. R., and Plotz, P. H.: Reduction of renal function by newer non-steroidal anti-inflammatory drugs. Am. J. Med. *64*:804, 1978.
338. Kimberly, R. P., Gill, J. R., Bowden, R. E., Keiser, H. R., and Plotz, P. H.: Elevated urinary prostaglandins and the effects of aspirin on renal function in lupus erythematosus. Ann. Intern. Med. *89*:336, 1978.
339. McGiff, J. C., Terragno, N. A., and Itskovitz, H. D.: Role of renal prostaglandins as revealed by inhibition of prostaglandin synthesis. *In* Robinson, H. J., and Vane, J. R. (eds.): Prostaglandin Synthetase Inhibitors. New York, Raven Press, 1974.
340. Norby, L., Flamenbaum, W., Lentz, R., and Ramwell, P.: Prostaglandins and aspirin therapy in Bartter's syndrome. Lancet *2*:604, 1976.
341. Feldman, D., and Couropmitree, C.: Intrinsic mineralocorticoid agonist activity of some non-steroidal anti-inflammatory drugs. J. Clin. Invest. *57*:1, 1976.
342. Tweedale, M. H., and Ogilvie, R. I.: Antagonism of spironolactone-induced natriuresis by aspirin in man. N. Engl. J. Med. *289*:198, 1973.
343. Done, A. K.: Treatment of salicylate poisoning: Review of personal and published experiences. Clin. Toxicol. *1*:451, 1968.
344. Irey, N. S.: Blood and tissue concentrations of drugs associated with fatalities. Med. Clin. North Am. *58*:1093, 1974.
345. Wegria, R., Capeci, N., Kiss, G., Glaviano, V. V., Keating, J. H., and Hilton, J. G.: Effect of salicylate on the acid-base equilibrium of patients with chronic CO_2 retention due to pulmonary emphysema. Am. J. Med. *19*:509, 1955.
346. Smith, M. J. H.: Metabolic effects of salicylates. *In* Smith, M. J. H., and Smith, P. K. (eds.): The Salicylates. A Critical Bibliographic Review. New York, Wiley, 1966.
347. Thurston, J. H., Pollock, P. G., Warren, S. K., and Jones, E. M.: Reduced brain glucose with normal plasma glucose in salicylate poisoning. J. Clin. Invest. *49*:2139, 1970.
348. Mukherjee, A. B., Chan, M., Waite, R., Metzger, M. I., and Yaffee, S. J.: Inhibition of RNA synthesis by acetyl salicylate and actinomycin D during early development in the mouse. Pediat. Res. *9*:652, 1975.
349. Hial, V., Horakova, Z., Shaff, F. E., and Beaven, M. A.: Alteration of tumor growth by aspirin and indomethacin: Studies with two transplantable tumors in mouse. Eur. J. Pharmacol. *37*:367, 1976.
350. Seifter, E., Rettura, G., Levenson, S. M., Appleman, M., and Seifter, J.: Aspirin inhibits a murine viral infection. Life Sci. *16*:629, 1975.