and K. Kareng. Hematologists and physicians in the participating hospitals were V. Suvatte, T. Intaragumthornchai, S. Chancharunee, V. Prayoonwiwat, P. Seksan, A. Chuansumrit, V. Chinarat, S. Angkuravorakul, V. Atichartkarn, S. Chutipong, S. Fucharoen, P. Hathirat, P. Isarankura, A. Jetsrisuparb, S. Jootar, N. Kiatkachorntada, S. Kitkornpan, S. Laohavinij, V. Laosombat, A. Lekhakul, C. Mahasandana, V. Makornkaewkayoon, P. Nitiyanont, P. Pootrakul, K. Singhapan, N. Siritanaratanakul, D. Sonakul, T. Srichaikul, T. Sripaisal, P. Sucharitchan, S. Sukpanichnand, S. Y. Sukpanichnand, P. Supradit, N. Suwanwela, V. S. Tanphaichitr, C. Tantechanurak, K. Tanyavudh, S. Vatanavicharn, S. Visudhiphan, W. Wanachiwanawin, and P. Watananukul.

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Could Salicylates in Food Have Contributed to the Decline in Cardiovascular Disease Mortality? A New Hypothesis

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ABSTRACT

Objectives. The prophylactic effect of aspirin (at 80 mg/day) for the prevention of cardiovascular disease mortality has long been recognized. This study examined whether other salicylates are present in comparable quantities in the US food supply.

Methods. To estimate the order of magnitude for salicylates in the food supply, annual production data for selected synthetic salicylates were analyzed.

Results. Production figures for 1960 indicate exposure to salicylates of 259 mg/day per person, or 95 mg/day per person excluding aspirin. Trend data indicate a rise in the production of salicylates over time, reaching 341 mg/day per person, or 126 mg/day per person excluding aspirin, in 1970.

Conclusions. The US ingestion of salicylates with aspirinlike properties may have increased to the point that many susceptible individuals have received a beneficial effect that has contributed to the decline in cardiovascular disease mortality. (*Am J Public Health.* 1997;87:1554–1557)

Introduction

Although the decline in cardiovascular disease mortality is well documented,[1] the beginning of this decline in the mid-1960s has not been satisfactorily explained. The decline began before changes had occurred in the lifestyle of the general population, such as reduced consumption of fats and cholesterol, reduced cigarette smoking, and widespread use of hypertensive medications and cholesterol-lowering agents. Researchers have not been able to demonstrate whether any or all of these changes have influenced the incidence of cardiovascular disease, although the decline in mortality continues.[2]

In the past 15 years, aspirin (acetylsalicylic acid) has been accepted as an effective agent for the prevention of cardiac death in patients with previous myocardial infarctions.[3] But other salicylates, which have similar pharmacologic properties (albeit with lower potencies), have been ignored in the cardiovascular literature. Although fiber and various natural antioxidants such as vitamin E[4] have received much attention from nutritionists and cardiovascular researchers, the salicylates, synthetic antioxidants,[5] and other synthetic organic additives have not. Yet the volumes of salicylates and these other additives in the food, drug, and cosmetic chain have reached levels that may have therapeutic benefits.

The analgesic, antipyretic, antiinflammatory, and antirheumatic effects of salicylates are well recognized,[6] but the pharmacological literature on salicylates other than aspirin as related to heart disease and coagulation is scant. Like aspirin, other salicylates[7] inhibit the enzyme cyclo-oxygenase, which enters into the production of prostaglandins and their derivatives.[8] These enzymes play rather complicated roles in platelet release and aggregation[9] and in vasoconstriction and vasodilation, which are concentration dependent.[10,11] By blocking cyclo-oxygenase, salicylates inhibit the aggregation of

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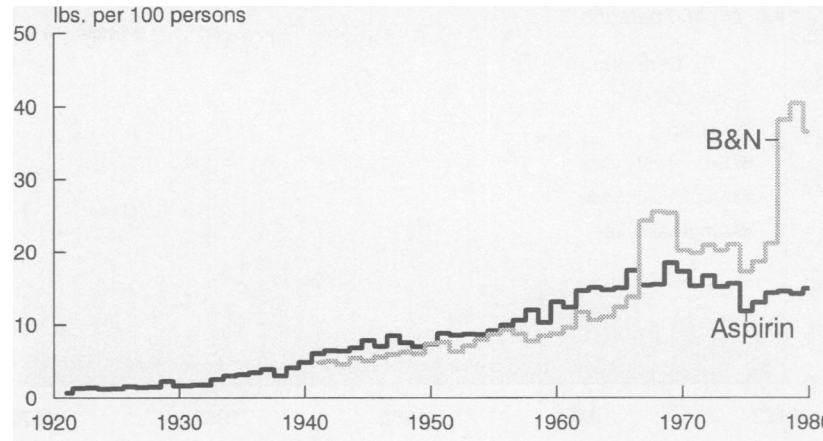
platelets[12] and presumably prevent the adherence of platelets on atherosclerotic plaques and the resulting thromboembolic process. Unlike that of aspirin, the inhibiting effect of other salicylates is reversible. Thus whereas a single dose of aspirin will affect platelets throughout their life span (10 days),[7] the effects of other salicylates are temporary.

Aspirin has shown great potency in its inhibitory effects, so that quite small doses are therapeutically effective. Currently, dosages as low as 80 mg per day,[13] equivalent to one baby aspirin, are commonly prescribed. The potency of other salicylates is probably less than this, for they do not possess the acetyl group believed responsible for the irreversible effect on platelets.[6] However, the salicylates used in the food supply have not been studied for their effects on the cyclo-oxygenase–prostaglandin process. In addition, Williams et al.[14] have demonstrated salicylatelike properties for other food additives that are not salicylates and that display additive interactions with the salicylates.

Salicylates are found in many naturally occurring foods[15,16] and in a great variety of food additives.[15,17] Many herbs and spices are rich in salicylates, as are fruits such as berries, cherries, oranges, raisins, and tomatoes. A variety of plants and flowers containing salicylates are commonly used as flavoring agents in the food industry, and many are also used as flavorings and aromatics in the drug and cosmetic industries.[18] Individual portions contribute relatively small amounts of salicylates, but their combined totals may be significant. Swain et al.[19] estimated the salicylate content of 300 foodstuffs. They concluded that the average amount of natural salicylates in the Western diet may be on the order of 10 to 200 mg per person per day. This wide range in the estimated average daily intake is likely to reflect an even wider range in individual daily intakes. As a result of improvements in the transportation, storage, and distribution of food products in the United States during the 1950s and 1960s, many of these food products became available to the consumer on a year-round basis, providing continual dietary exposure to the salicylates.

Synthetic salicylates are used as food additives, primarily for flavoring and aromatic purposes. The most commonly used synthetic salicylates include benzyl-, ethyl-, isoamyl-, isobutyl-, methyl-, and phenethylsalicylate and salicylaldehyde.[17] Some of their uses are given in Table 1.



Source. Based on data from the International Trade Commission.[23]
Note. B&N = benzenoid and naphthalenoid compounds.

FIGURE 1—Annual production of selected synthetic organic chemicals, United States, 1920 through 1980.

The specific nature and salicylate content of the flavorings and aromatics purchased by the food industry from the flavor manufacturers are closely guarded trade secrets.[20,21] Many salicylates other than aspirin are used for medicinal purposes.[7] Some, such as methyl salicylate and salicylic acid, are used externally but are readily absorbed through the skin.[22]

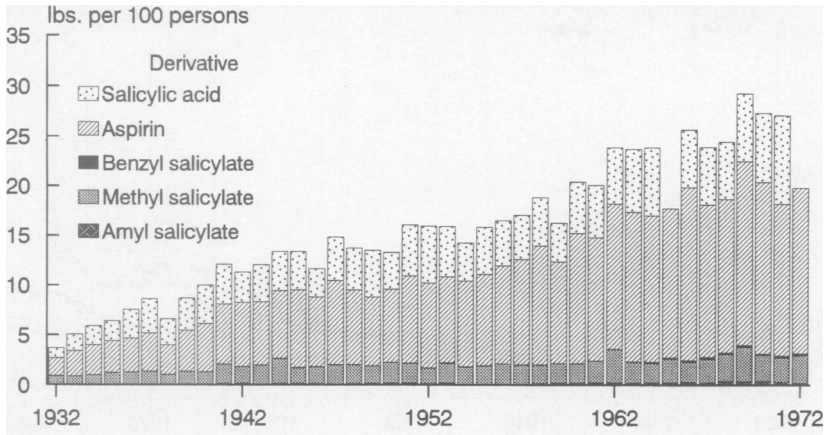
The hypothesis presented here is that during the last 30 years the ingestion of salicylates and other additives with salicylatelike properties in the American diet has increased to the point that many susceptible individuals have received a beneficial effect that has contributed to the observed decline in cardiovascular disease mortality in every demographic subgroup of the population.

Methods

To begin ascertaining the plausibility of this hypothesis, we gathered data from 1920 through 1980 from the International Trade Commission publications on the annual production sales of synthetic organic chemicals.[23] Although these data reflect mandated reporting requirements, data on individual compounds were often not available or not published for some years. One reason lies in nondisclosure rules, which hold that compounds produced by three or fewer manufacturers or by a dominant manufacturer may not be reported due to the risk of inadvertent disclosure. The data for aspirin were taken from the category of synthetic organic compounds used for medicinal purposes. The data for other salicylates were taken from the category benzenoid and naphthalenoid flavorings and aromatics, which is an umbrella category that includes the nonmedicinal salicylates, other food additives with salicylatelike properties, and a variety of unrelated compounds. The benzenoid and naphthalenoid category

TABLE 1—Common Uses of Synthetic Salicylates

Foods
Baked goods
Beverages
Candy
Chewing gum
Condiments
Gelatins and puddings
Ice cream, ices
Syrup
Flavorings
Apricot, grape, peach, strawberry, other fruit
Butter, vanilla
Birch beer, root beer, sarsaparilla
Caramel, cassia
Cinnamon, sassafras, other spices
Liqueurs, muscatel
Mint, wintergreen
Violet, other floral
Walnut, other nut
Other
Drugs
Antiseptics
Cosmetics
Lozenges, mouthwash, toothpaste
Perfumes
Suntan lotion



Source. Based on data from the International Trade Commission.[23]

FIGURE 2—Cumulative production totals for selected salicylates, United States, 1932 through 1972.

TABLE 2—Production Figures for Selected Salicylates and Estimated Daily Exposure per Person

	1960	1970
Production, lb		
Aspirin	23 553 000	35 170 000
Salicylic acid	9 282 000	14 126 000
Salicylic acid salts	595 000	. . .[a]
Amyl salicylate	343 000	767 000
Benzyl salicylate	84 000	241 000
Isobutyl salicylate	52 000	. . .[a]
Methyl salicylate	3 408 000	5 396 000
Total	37 317 000	55 700 000
Total, excluding aspirin	13 764 000	20 530 000
Exposure		
US population	179 323 200	203 211 904
Salicylates, mg/day/person	259	341
Salicylates, excluding aspirin, mg/day/person	95	126

[a]Data not available.

also lists a selected array of individual additives subsumed under it, from which we collected the estimates for all the salicylates the International Trade Commission will permit to be published. These are production data and as such are approximate measures of exposure, since they do not reflect quantities imported or exported and some uses of these compounds are not included in foods, drugs, or cosmetics.

Total US resident population statistics were collected from US Census Bureau reports.[24] These data were used to calculate milligrams per person per day of estimated exposure to synthetic salicylates.

Results

Figure 1 on p 1555 illustrates the annual production sales of aspirin and benzenoid and naphthalenoid compounds, adjusted for population size. Aspirin production rose steadily until about 1970. Sharp increases in production of benzenoid and naphthalenoid compounds in the mid-1960s and mid-1970s are especially evident: in 1966, total production was 13.8 pounds per 100 people; by 1980, total production was 36.6 pounds per 100 people.

Figure 2 illustrates cumulative production sales totals for the synthetic salicylates for which data were available. Aspirin and salicylic acid dominate the exposure pattern for the US population. However, the other salicylates have played an increasing role and perhaps constitute a broader exposure category.

Table 2 shows production sales data for 1960 and 1970, the time frame that spans the peak and the beginning of the decline in cardiovascular disease mortality. The available data for 1960 indicate that a person in the United States was exposed to as much as 259 mg of salicylates per day including aspirin, or 95 mg per day without aspirin. In 1970, estimated exposure increased to 341 mg per person per day including aspirin, or 126 mg per person per day without aspirin.

Discussion

The hypothesis just presented and the data supporting it can be summarized in the form of a syllogism:

1. Aspirin (acetylsalicylic acid) at a dosage of 80 mg per day has been demonstrated in several clinical trials to have a beneficial effect in reducing mortality among persons with previous myocardial infarctions.

2. Other salicylates have shown aspirinlike properties in vitro, although with lower potencies. These salicylates may require lower concentrations when used in conjunction with certain other synthetic food additives.

3. Salicylates occur naturally in a variety of foods, which during the past 30 years have been more readily available on a year-round basis.

4. Natural and synthetic salicylates have been added to foods as ingredients in flavorings and aromatics for many decades.

5. From the 1960s to 1980, synthetic salicylates (other than aspirin) and other additives with salicylatelike properties have been produced in increasing proportions for use in the United States.

6. It is presumed that most of this increased production is widely distributed in foods, drugs, and cosmetics, amounting to about 126 mg per person per day exposure in 1970.

7. Cardiovascular disease mortality rates have been declining since the mid-1960s nationwide.

8. This suggests that natural and synthetic salicylates in the American diet have contributed to the decline in cardiovascular disease mortality rates.

This hypothesis is attractive because it would go a long way toward explaining some of the puzzling aspects of the decline in cardiovascular disease mortality rates. The increasing use of synthetic salicylates and other additives in the early 1960s could explain the remarkable fact that the decline in cardiovascular disease mortality, which first appeared in California, spread rapidly throughout the United States and appeared in every state, for both sexes, and in all age and racial groups by 1970. The ubiquity of synthetic salicylates in products ranging from toothpaste to soft drinks, from pasta sauce to ice cream, would make them available to all segments of the population. Variations in natural salicylates could explain some of the geographic and ethnic variation in cardiovascular disease, such as the apparently beneficial effect of the Mediterranean diet. The hypothesis might also contribute to an understanding of why the decline in mortality has continued despite a steady increase in the prevalence of obesity in the United States.

There are many gaps in this syllogism, however, which must be addressed before the hypothesis can be considered confirmed. The mechanism of salicylates' effect is believed to involve reduced platelet aggregation and interference with prostaglandin production, vasoconstriction, and inflammation, but a much better definition is required. The distribution of salicylates in American food, drug, and cosmetic products is not well characterized and recent data on synthetic salicylate production are scant. Except for persons with known salicylate sensitivities (and persons taking aspirin for therapeutic purposes), variations in intake of salicylates within the population have not been studied. Associations at the individual level must be studied with case–control studies, prospective observational studies, clinical trials, or all three. (Some existing databases may have sufficiently specific information on food items to allow tentative investigations of these relations to be done now.) International comparisons of salicylate consumption and cardiovascular disease trends would also be enlightening.

To fill some of these gaps, new techniques will be needed in such areas as biochemical assay technology to quantify the amount of salicylates and other additives in various foodstuffs, and in nutrition survey instruments to characterize the amount of these compounds ingested and their physiologic levels. More complete and specific reporting of production, distribution, and use data are needed, and this requirement entails adequate support for such resources as the International Trade Commission's handbook of synthetic organic chemicals (which was discontinued in 1995).

Even if the hypothesis is supported, other important questions must still be addressed. What is the correlation and interaction of salicylate intake with other cardiovascular disease risk factors and with supplemental aspirin intake? What are the potential adverse effects from salicylates in food, drugs, and cosmetics? The clinical allergy literature has documented that individuals with certain types of asthma, urticaria, and behavioral disorders suffer these consequences as a result of their salicylate sensitivities.[15,16,18,25–27] Obviously, a great deal of research remains to be done to establish and clarify this hypothesis. □

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