

In the following sections of the background package, we have included Federal Register documents related to the development of the internal analgesic monograph. This provides a frame of reference for the information available in the public record and the rationale behind past decisions. The table below describes what is included in the documents and in some cases the locations that are most relevant to the issues for discussion on September 19 and 20. This will allow you decide what is important to read and what is not in your assessment of the issues.

The OTC drug monograph process can be divided into 4 steps:

1. Advisory Review Panel – Panel reviews information submitted to the FDA
2. Advanced Notice of Proposed Rulemaking (ANPR) – Published recommendations of Panel
3. Tentative final monograph (TFM) or proposed rule – FDA proposal for monograph
4. Final Rule – Final regulation that describes the conditions of use for ingredients in the drug category

The internal analgesic monograph is at the TFM or Proposed rule stage. The FDA is in the process of writing a final rule. Prior to completion of the final monograph, the FDA can amend and finalize portions of the proposed monograph as evidenced in the table below by the proposed and final rule for alcohol warnings. Based upon your recommendations, FDA can make appropriate revisions to be incorporated into the final monograph.

Section	Federal Register Notice	Information in Notice
I.B	Establishment of a Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products (Panel Report or ANPR) <i>[Entire Federal Register Notice Is Not Included]</i>	The rulemaking summarizes the findings by the advisory panel for the safety and efficacy of OTC internal analgesic ingredients. <ul style="list-style-type: none"> • page 35383: Start discussion of Aspirin safety • page 35413: Start discussion of Acetaminophen safety
I.C	Internal Analgesic, Antipyretic and Antirheumatic Products for Over-the-Counter Human Use; Tentative Final Monograph <i>[Entire Federal Register Notice Is Not Included]</i>	This rulemaking outlines the safety and efficacy data to support the conditions of use for internal analgesic drug ingredients. <ul style="list-style-type: none"> • page 46213: Comment 24 starts discussion of warnings for acetaminophen • page 46219: Comment 29 starts discussion of warnings for aspirin • page 46254: Proposed monograph
I.D	Over-The-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning (Notice of proposed rulemaking)	The rulemaking summarizes the data to support an alcohol warning on all OTC products containing acetaminophen, aspirin, nonaspirin salicylates, ibuprofen, ketoprofen and naproxen sodium.
I.E.	Over-The-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning (Final Rule)	The rulemaking requires the following alcohol warning: <i>For acetaminophen:</i> “Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.” <i>For NSAIDS:</i> “Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert name of product] other pain relievers/fever reducers. [Insert name of product] may cause stomach bleeding.”

Section	Federal Register Notice	Information in Notice
I.F.	Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products	Professional Labeling for aspirin <ul style="list-style-type: none">• page 56810: Comment 7. Discusses adverse events• page 56815: Warnings• page 56816: Precautions
I.G.	Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph, and Related Labeling	Proposal to include ibuprofen into the Internal Analgesic monograph. <ul style="list-style-type: none">• page 54142: safety discussion

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INTERNAL ANALGESIC

ANPR

BOOK 2 OF 2 BOOKS

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PART VII



PANEL REPORT

DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE

Food and Drug Administration



OVER-THE-COUNTER
DRUGS

Establishment of a Monograph for OTC
Internal Analgesic, Antipyretic and
Antirheumatic Products

For example, a small increase in the salicylate dose ingested may cause a disproportionate increase in the salicylate blood level and could result in serious consequences.

Unfortunately, acetaminophen has no similar sign of toxicity or "safety valve" to alert the consumer. Further, some advertising for acetaminophen gives the impression that it is much safer than aspirin and implies that the toxic effects of the drug are less than those encountered with aspirin. Actually, a large overdose of acetaminophen can result in serious liver damage which is not as amenable to therapy as salicylate intoxication. This is discussed later in this document. (See part III, paragraph B.1.b. below—Acetaminophen.)

Therefore, the Panel decided to include the warning, "Stop taking this product if ringing in the ears or other symptoms occur", on all products containing salicylates, and the warning, "Do not exceed recommended dosage because severe liver damage may occur", on all products containing acetaminophen, a nonsalicylate.

Likewise, consumers should be alerted to possible serious side effects from therapeutic doses of these products. Some evidence suggests that aspirin might be contraindicated in pregnancy. (See part III, paragraph B.1.a.(2) (iv) below—Adverse effects during pregnancy.) Therefore, the Panel concludes that it is necessary to include the labeling warning statement on all aspirin-containing products, "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

The labeling of several currently marketed aspirin products contains the advice that the product should be taken with a full glass of water. Baum (Ref. 1) also states that aspirin should be taken with large amounts of fluids. *The Medical Letter* (Ref. 2) also advises that "to minimize gastrointestinal irritation, any aspirin tablet should be taken with a full glass of water."

The Panel could not find any controlled studies to support the contention that the quantity of water used to administer the drug has any effect relative to safety or efficacy. However, it is the opinion of the Panel that this advice is sound, since the water would be expected to facilitate dissolution of the drug and reduce the irritation of the mucosa of the stomach from aspirin particles as discussed elsewhere in this document. (See part III, paragraph B.1.a.(2) (ii) below—Adverse effects on the gastrointestinal tract.) The Panel believes that this recommendation should apply to all salicylates. Therefore, the Panel concludes that the labeling for products containing salicylates intended for oral administration as a solid dosage form, e.g., tablets, state for adults, "Adults: Drink a full glass of water with each dose" and for children under 12 years, "Children under 12 years: Drink water with each dose".

In summary, the Panel concludes that the purpose of OTC preparations is to

provide for the temporary relief of self-limited symptoms and not for the self-treatment of disease entities. If OTC products are used for a long period of time to treat symptoms which indicate a potentially serious problem, a disease requiring medical supervision could be masked until irreparable damage has occurred. This is especially important for those drugs with antirheumatic properties. As previously noted, if such drugs are taken there could be a delay in proper treatment of rheumatic disease which could lead to irreversible joint damage when inadequate dosage is taken intermittently for prolonged periods by patients with some rheumatic diseases such as rheumatoid arthritis. The Panel also decided that if an individual needs to take these products for a long period of time, i.e., more than 10 days in an adult, or more than 5 days in a child, he or she is sufficiently ill to require the consultation of a physician. Therefore, the Panel added the word "temporary" to the general indications statement making it read: "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever", and has added a general warnings statement for adults, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician", and for children under 12 years, "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician". Such warnings or cautions will be included in the proposed labeling for individual preparations presented later in this document.

REFERENCES

- (1) Baum, J., "Rheumatoid Arthritis," in "Current Therapy," Edited by Conn, H. F. and W. B. Saunders, Philadelphia, 1973.
- (2) Anonymous, "Is All Aspirin Alike?," *The Medical Letter*, 16: 57-59, 1974.

D. LABELING WARNINGS, ADVERTISING AND THE MEDIA

Because the consumer needs to be correctly and fully informed, the Panel recommends that the advertising in any medium for these drugs that in any way uses the labeling, package or container not be inconsistent, even on subtle implication through mood, focus or innuendo, with the applicable labeling in the OTC internal analgesic monograph.

The Panel has noted, with concern, certain aspects of commercial advertising of OTC medicines that urge the consumption of these drugs without directing attention to adequate warnings regarding the possible immediate hazards of the use of these products or the potential hazards from their long-term use.

This concern was shared by representatives of consumer and children's advocacy groups, by representatives of pharmaceutical associations and manufacturers, the broadcast media, and researchers from the academic world at a 2-day conference on televised OTC drug advertising that was sponsored by the Federal Communications Commission and the Federal Trade Commission on May 20 and 21, 1976. At the three Panels

comprising the conference the status of research, industry self-regulation, and government regulation was discussed and alternatives suggested; governmental policy decisions were not formulated (Ref. 1).

As was pointed out to the Panel, based upon common sources of advertising information, the advertising expenditures for internal analgesic drugs are greater than for other OTC drug categories (Ref. 2). It was noted that analgesic promotion in this country has reached a new level of sophistication with advertising references to whole new ailments such as "file cabinet backaches" or "camper noise tension." While the National Association of Broadcasters and the Proprietary Association representing many OTC drug manufacturers have been active in developing codes for the advertising of nonprescription or OTC medicines, the Panel believes that government requirements for the inclusion of warnings and cautionary language are inadequate, particularly as to possible effects of this advertising upon children (Ref. 2).

The Panel notes that the Food and Drug Administration does not regulate the advertising of OTC drug products. Therefore, the Panel asks that the proper authority, i.e., the Federal Trade Commission, with the full support and active cooperation of the Food and Drug Administration, more effectively regulate commercial advertising of internal analgesic, antipyretic and antirheumatic preparations on the basis of the labeling recommendations contained in this document. Further, the Panel strongly urges the Federal Trade Commission to require that the cautionary language and warnings developed by the Panel be given emphasis in commercial advertising more so than is currently being done, and that special attention be given to the regulation of OTC drug advertising on those television programs watched most often by children or whose viewing audience includes large numbers of children.

REFERENCES

- (1) Transcript of Proceedings, Federal Communications Commission Federal Trade Commission Conference, May 20 and 21, 1976.
- (2) Choate, Robert B., Presentation before the FDA OTC Review Panel on Internal Analgesics, March 17, 1975, copy of unpublished paper is included in OTC Volume 030150.

E. STANDARD DOSAGE UNIT AND ANALGESIC EQUIVALENCE VALUE

1. *Background.* The Panel recognizes that currently the OTC drug market provides for many different products containing a large variety of analgesic, antipyretic and/or antirheumatic drugs. These products are marketed containing either single ingredients or combinations of active ingredients. A majority of these products contain aspirin with variation from product to product in the amount of aspirin per dosage unit. Likewise, there are many marketed products containing nonaspirin ingredients, e.g., acetaminophen, or derivatives of salicylic acid other than aspirin, e.g., sodium salicylate, which in most cases contain labeling

similar to that found for products containing aspirin. The Panel is concerned with the confusion that may arise when a consumer purchases such products.

To more fully inform the consumer as to the contents and therapeutic capabilities of these products as well as to minimize the hazard of confusion, the Panel recommends for these reasons and for reasons of safety described below, that products containing aspirin be clearly labeled on the principal display panel to indicate the presence of aspirin, that a standard amount of aspirin per dosage unit be established of 325 mg (5 gr) for all marketed products containing aspirin alone, as the single OTC analgesic-antipyretic active ingredient, and that labeling clearly indicate that the product contains the standard or a nonstandard amount of aspirin per dosage unit. The Panel has further determined that a standard dosage unit of 325 mg (5 gr) also be established for acetaminophen and sodium salicylate. It is the Panel's opinion that it is rational to establish standards, not only for aspirin, but for all three commonly used ingredients, thus enabling the consumer to more fully compare marketed OTC products.

2. *Standard dosage unit.* Aspirin is the most commonly used OTC drug in the United States. The majority of products marketed are labeled 325 mg or 5 gr aspirin. However, there are products marketed with less than 325 mg and some with 300 mg aspirin labeled as 5 gr. To most individuals these dosages are assumed to be equivalent but on a weight basis they are actually not equivalent. Confusion arises because there are two systems of weight measurement commonly used. One system, which has been historically used in pharmacy is the apothecary system of weights based on the "grain" (gr) and the other being the more universal metric system based on the "gram" (g). The apothecary weight of 1 gr is equivalent to the metric system measurement of 64.8 mg but is often approximated as equal to 60 mg. Therefore, a 5 gr aspirin dosage unit should actually contain 324 mg aspirin but is sometimes equated to 300 mg of active ingredient, thus making for a difference of 24 mg of aspirin.

A further factor contributing to a wide range in the amount of available aspirin is the provision of the *United States Pharmacopeia XIX* to provide for a variation of ± 5 percent of the labeled amount of aspirin per dosage unit (Ref. 1). The Panel recognizes this as an understandable requirement necessary for manufacturing purposes but is concerned with the potentially wide variation in the currently allowable content of aspirin which, because of different interpretations of the "grain", varies for a labeled "5 gr product" between 285 mg and 340.2 mg aspirin from one marketed brand product to another brand. This could represent a possible difference of 55.2 mg or almost 1 gr aspirin between two different marketed products. To avoid the confusion that presently exists in the conversion between the two systems of weight measurement, i.e., be-

tween the apothecary system (gr) and the metric system (mg), the Panel recommends that the amount of aspirin in a 225 mg (5 gr) standard dosage unit be established on the basis of the apothecary weight of 1 gr being equivalent to the metric system measurement of 65 mg.

The Panel also recommends that this equivalence between the apothecary and metric systems be used for all ingredients. The following table illustrates equivalent values for the two systems as used throughout this document:

EQUIVALENT VALUES FOR APOTHECARY AND METRIC SYSTEMS

Apothecary (gr)	Metric (mg)
1.0	65
1.23	80
5.0	325
10.0	650
61.54	4,000

The Panel has evaluated the amounts of aspirin contained in the submissions for marketed products submitted to the review. (See part I, paragraph A, above—Submissions by Firms.) For example, of the submissions reviewed by the Panel, 32 pertained to dosage forms containing aspirin as a "single" ingredient. In 16 of these single ingredient products (50 percent), the amount of aspirin differed from the standard 325 mg (5 gr). The range was from a low of 227 mg for a chewable gum to a high of 650 mg in a single tablet. This represents a variation of 70 to 200 percent of the standard 325 mg (5 gr) aspirin dosage unit available as a single ingredient in such marketed products.

The Panel has provided the following table to illustrate the variations in the amount of aspirin contained in submitted products:

AMOUNT OF ASPIRIN CONTAINED IN SUBMITTED PRODUCTS WHERE ASPIRIN WAS THE SINGLE ANALGESIC INGREDIENT

Grains of aspirin	Number of submissions
3.5	1
4.5	2
5.0	16
6.0	2
7.5	7
10.0	4
Total	32

The Panel is aware of the widespread and common belief that the usual amount of aspirin an adult should ingest is "two tablets." The Panel believes that this can cause a problem to a person accustomed to buying and properly taking a particular analgesic product containing 325 mg aspirin per tablet changes to another analgesic product such as those currently marketed containing 295 mg or even 650 mg aspirin per tablet. If this same individual follows the usual custom of ingesting "two tablets" every 4 hours, he may receive as little as 590 mg or as much as 1,300 mg aspirin. The Panel is concerned that the 1,300 mg dosage will achieve the desired effect but with the potential hazard of toxic overdose. Since aspirin is the most common drug used in the United States, the latter situation is crit-

ically important. If a person takes 1,300 mg aspirin every 4 hours for several dosing intervals, serious aspirin intoxication may result. This is due to both the absolute quantity of aspirin taken and the kinetics of aspirin metabolism which is discussed later in this document. (See part III, paragraph B 1 a (2) below—Safety.)

As an example, a 20 percent increase in dosage can cause a 40 to 60 percent increase in blood salicylate level over a period of time, which can produce a therapeutic response in patients who had not responded to a lower dose, or more importantly, result in an increase of dose-related systemic toxic effects (Refs. 2 and 3). Even those aspirin tablets commonly marketed in 300 mg or 325 mg dosage units, which usually permit variation of ± 5 percent active ingredient per tablet as described above, when calculated to each extreme (a low of 285 mg for the 300 mg tablet to a high of 349 mg for the 325 mg tablet), represent a 20 percent variation in dosage.

This could be a problem in the area of pediatric overdosing. If a pediatrician instructs a parent to give a child half or quarter of an aspirin tablet, the child could, depending upon the strength of the tablet, be exposed to a potentially serious aspirin overdose. In the case of antipyresis (fever reduction) for an infant or small child this is especially hazardous because the young child cannot complain of tinnitus (ringing of the ears), one of the early symptoms of aspirin overdose. Further, the symptoms could progress to include fever, one of the later signs of salicylate intoxication (Ref. 4). The parent, noting that the fever has not subsided, may continue to give excessive amounts of aspirin, continuing a vicious cycle.

The Panel believes that the current availability of so many different amounts of aspirin per dosage unit is very confusing to the consumer. It is the opinion of the Panel that this availability has encouraged the myriad of claims such as "higher levels of pain reliever" or "arthritis strength" that are currently used. Of even more concern to the Panel is the fact that wide ranges in the amount of aspirin per dosage unit can result in either subtherapeutic or even toxic aspirin blood levels.

The Panel strongly recommends, based upon considerations of safety and effectiveness, that all products containing aspirin, acetaminophen, or sodium salicylate be standardized to contain and labeled to indicate either 325 mg (5 gr) per dosage unit for adults or 80 mg (1.23 gr) per dosage unit for children under 12 years of age.

The Panel recommends an adult oral dosage of 325 mg (5 gr) to 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours. The Panel finds this dosage regimen safe and effective for the treatment of occasional minor aches and pains, headache, and fever indicated later in this document. The Panel believes that

a standardized dosage unit of 325 mg (5 gr) is safe and effective when used as directed. More importantly, the adult dosage of 650 mg (10 gr) is the unit consumers believe they are ingesting, i.e., two 325 mg (5 gr) tablets.

However, the Panel recognizes the current availability of products containing an amount different than 325 mg (5 gr) per dosage unit. If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) aspirin, acetaminophen or sodium salicylate per dosage unit, the Panel recommends that products contain not less than 325 mg (5 gr) per dosage unit since this is the minimum effective dosage for adults. Since a single dosage greater than 650 mg (10 gr) is not commonly required by the general population, the Panel believes it rational to establish 650 mg (10 gr) as the upper limit for the quantity of drug to be included in a single dosage unit. Therefore, the Panel has defined nonstandard dosage units as dosage units containing not less than 325 mg (5 gr) and not greater than 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate. In addition, the Panel concludes that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard unit of 325 mg (5 gr) since the Panel is unaware of any other nonstandard dosage units currently available in marketed adult strength products containing acetaminophen as the single active ingredient.

The Panel recommends that any product containing an amount different from 325 mg (5 gr) per dosage unit be clearly labeled as to the amount of active ingredient the product contains and any product containing more than 325 mg (5 gr) per dosage unit shall be labeled appropriately "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit", "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit", or "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" for the specific product shall be used.

3. *Analgesic-antipyretic recommended dosage.* The Panel has defined the components of a dosage schedule below. The basis of the Panel's recommendation and conclusions are discussed elsewhere in this document. (See part II, paragraph F. below—Statement on Recommended Dosage Schedules.)

a. *Dosage range.* The Panel has examined the data submitted and finds for purposes of clarity that it is necessary to define the components of a dosage schedule which include a minimum effective dosage, a usual single dosage, a usual effective dosage range, a maximum dosage, and a maximum daily (24 hrs) dosage. These components of a

dosage schedule are defined by the Panel in relation to a general OTC target population seeking relief of symptoms, such as occasional minor aches, pains and headache, and the reduction of fever.

(1) *Minimum effective dosage.* The minimum effective dosage is the amount of drug necessary to achieve the intended effect in some individuals in the general OTC target population.

(2) *Usual single dosage.* The usual single dosage is the amount of drug necessary to achieve the intended effect in most individuals in the general OTC target population.

(3) *Usual effective dosage range.* The usual effective dosage range is the range between the minimum effective dosage and the usual single dosage.

(4) *Maximum single dosage.* The Panel finds that there may be circumstances when more than the usual single dosage may be needed to provide an adequate effect. An increase in the usual single dosage may be needed, for example, by individuals who because of their large body size (unusual height) or overweight (obesity) require a higher dosage. To meet this contingency, the Panel defines the maximum single dosage as the maximum amount of drug that is safe and effective for use in a 4-hour period. The Panel has established 1,000 mg as the maximum single safe and effective dosage for the standard drugs (aspirin, acetaminophen and sodium salicylate). The Panel does not believe that this maximum single dosage should be encouraged on OTC labeling, except as an initial dosage, as it may be subsequently used routinely even when it may not be necessary and may potentially lead to toxic side effects.

(5) *Maximum daily dosage.* The maximum daily dosage is the maximum amount of drug that is safe and effective for use in a 24-hour period. The Panel has established 4,000 mg as the maximum daily dosage for the standard drugs (aspirin, acetaminophen and sodium salicylate).

The Panel considers the adherence to a maximum daily dosage of not greater than 4,000 mg necessary in the interest of safety. The clinical evaluation of aspirin clearly shows that higher daily dosages produce more side effects on the central

nervous system, the blood clotting system, the gastrointestinal tract, etc. (See part III, paragraph B.1.a. (2) below—Safety.)

b. *Recommended dosage for products containing standard dosage units.* For products containing the standard dosage unit of 325 mg (5 gr) aspirin, acetaminophen or sodium salicylate, the minimum effective dosage for adults is 325 mg (5 gr), the usual single dosage is 650 mg (10 gr), the usual effective dosage range is 325 mg (5 gr) to 650 mg (10 gr), the maximum single dosage is 1,000 mg (15.38 gr) but should not be provided for in OTC drug labeling, and the maximum daily dosage is 4,000 mg (61.54 gr). The Panel notes that it is convenient to relate the standard dosage unit of 325 mg (5 gr) to a maximum single dosage of 975 mg (15 gr) and to a maximum daily dosage of 3,900 mg (60 gr) rather than to the established maximum single dosage of 1,000 mg and the established maximum daily dosage of 4,000 mg as defined above by the Panel. The recommended dosage schedules are described in section d. below.

c. *Recommended dosage for products containing nonstandard dosage units.* The Panel has defined nonstandard dosage units as dosage units containing not less than 325 mg (5 gr) and not more than 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate. In addition, the Panel concludes that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard unit of 325 mg (5 gr) since the Panel is unaware of any other nonstandard dosage unit currently available in marketed adult strength products containing acetaminophen as the single active ingredient. The recommended dosage schedules are described in section d. below.

d. *Recommended adult dosage schedules.* Besides the establishment of standard and nonstandard dosage units, the Panel has also established standard and nonstandard dosage schedules for their use. The Panel strongly recommends that the standard dosage schedule be utilized but recognizes the current availability of nonstandard schedules. Therefore, the Panel recommends the following dosage schedules:

Recommended adult dosage schedules for standard and nonstandard aspirin, acetaminophen or sodium salicylate dosage units

Dosage unit ¹ (milligram (gram))	Initial dosage units ² (milligram)	Frequency ³ (tablets/hours)	Dosage units/day ⁴ (milligram)
Standard dosage schedule under: 325 (5)	2	2 after 4	12 (3,900)
Nonstandard dosage schedule under:			
325 (5)	2 to 3 (650 to 975)	do	12 (3,900)
400 (6.15) ⁵	1 to 2 (400 to 800)	1 after 3	9 (3,600)
421 (6.48) ⁵	1 to 2 (421 to 842)	do	9 (3,789)
455 (7.46) ⁵	1 to 2 (455 to 910)	1 after 4 or 2 after 6	8 (3,880)
500 (7.69)	1 to 2 (500 to 1,000)	1 after 3 or 2 after 6	8 (3,880)
650 (10) ⁵	1 (650)	1 after 4	8 (4,000)
			6 (3,900)

¹ The amount of drug contained in a single dosage unit.

² The maximum number of dosage units that cannot be exceeded when dosing is initiated.

³ The number of dosage units per time interval.

⁴ The maximum total number of dosage units that cannot be exceeded in 24 hours regardless of the initial number of dosage units taken or the frequency of repeated dosing.

⁵ This nonstandard dosage schedule does not apply to acetaminophen since only the 500 mg (7.69 gr) nonstandard dosage unit is recognized by the panel.

4. *Analgesic equivalence value.* Consumers may be perplexed not only by the variation in the available amounts of an active ingredient per dosage unit, but also by any attempt to compare the relative potency of an active ingredient with other active ingredients. For example, if an individual normally takes a product containing 325 mg sodium salicylate and compares its label with the label of a product containing choline salicylate, the directions may instruct the user to take a total of 650 mg sodium salicylate but 870 mg choline salicylate. This may result in the mistaken notion that because more choline salicylate is taken there will be more of a therapeutic benefit, although 650 mg sodium salicylate is chemically equivalent in salicylate content to 870 mg choline salicylate.

The Panel reviewed the submissions for marketed "combination" products containing aspirin. The Panel found that of the submissions containing "combination" analgesic-antipyretic products, the amount of aspirin contained in the products varied from 194.4 mg to 650 mg per dosage unit with the total amount of analgesic ingredients ranging from 360 mg to 842.4 mg per tablet.

It is most difficult to equate the total amount of analgesic effectiveness for such combination products. While these submissions are not necessarily a representative sample of the dosage variation in all of the currently marketed OTC analgesic products, they represent the major products in this market and do in fact give some concept of the range of aspirin dosages currently available to consumers. This represents a confusing and potentially harmful situation, since consumers may substitute one brand of analgesic product for another containing different active ingredients, ignorant of the fact that there are differences in potency between brands, and inadvertently ingest either too much or too little of the product.

The Panel is concerned that current labeling for some products extols the virtues of different quantities of analgesics for pain relief with such claims as "adult pain formula", "extra added ingredients", or "arthritis formula". The consumer, faced with such different claims has no ready source to consult to determine the validity of these claims. Consequently, an analgesic product may be purchased with the mistaken notion, "if one ingredient is good, two or more are better."

In addition to the current confusion, i.e., variable aspirin dosages, availability of many combinations of ingredients with and without aspirin, and many labeling claims, there is still another area of concern which involves the clinical evaluation of analgesics in general, i.e., increased blood levels of analgesic-antipyretics do not demonstrate an equivalent increase in the desired effect. The problem of trying to correlate analgesia with blood levels is discussed elsewhere in this document. (See part II, paragraph J. below—Effects of Product Formulations on Drug Absorption and Pharmacologic Effectiveness.)

Therefore, the Panel recommends that standard drugs (aspirin, acetaminophen and sodium salicylate) and standard dosage units of 325 mg (5 gr) be established. The analgesic equivalence to other drugs can then be compared as follows:

OTC ANALGESIC EQUIVALENCE DRUGS	
Standard 325 mg (5 gr) / dosage unit drugs:	Comparison drugs
Aspirin -----	Aluminum aspirin. Calcium carbaspirin.
Acetaminophen -----	None (comparisons only to standard dosage unit).
Sodium salicylate -----	Choline salicylate. Magnesium salicylate. Salsalate.

The Panel believes that the current availability of so many different products containing derivatives of salicylic acid other than aspirin or nonsalicylate active ingredients with labeling claims similar to products containing aspirin is confusing and recommends that an analgesic equivalence value be established. This value would inform the purchaser as to the contents and therapeutic capabilities of these products and thereby benefit the consumer. The labeling should clearly describe the strength of the product as compared to the standard applicable dosage unit.

5. *Labeling of products.* Because of the many common side effects observed with the use of aspirin as discussed later in this document, the Panel recommends that all products containing aspirin be clearly labeled as containing aspirin on the principal display panel. Such labeling will not only benefit all consumers but will alert those individuals having a sensitivity to aspirin.

a. *Products containing a standard drug in the standard dosage unit.* (1) *Aspirin.* The Panel recommends that products containing 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of aspirin per dosage unit".

(2) *Acetaminophen.* The Panel recommends that products containing 325 mg (5 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of acetaminophen per dosage unit".

(3) *Sodium salicylate.* The Panel recommends that products containing 325 mg sodium salicylate per dosage unit be

clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of sodium salicylate per dosage unit".

b. *Products containing a standard drug in an amount different from the standard dosage unit.* (1) *Aspirin.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) aspirin per dosage unit, the Panel recommends that products containing an amount of aspirin other than 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength aspirin".

(2) *Acetaminophen.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) acetaminophen per dosage unit, the Panel recommends that products containing 500 mg (7.69 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength acetaminophen".

(3) *Sodium salicylate.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg sodium salicylate per dosage unit, the Panel recommends that products containing an amount of sodium salicylate other than 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength sodium salicylate".

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F. STATEMENT ON RECOMMENDED DOSAGE SCHEDULES

1. *Statement on standard and non-standard salicylate dosage schedules.* The Panel has defined the components of a dosage schedule elsewhere in this document. (See part II, paragraph E.3. above — Analgesic-antipyretic recommended dosage.) The basis of the Panel's conclusions regarding recommended dosage schedules is discussed below.

a. *Factors in selection of optimal dosage schedules.* The Panel recognizes that one of the most important and critical factors in maximizing the safe and effective use of any therapeutic agent is the choice of optimal dosage regimens. The need to carefully define and promote adherence to a safe dosage regimen is particularly important for aspirin and other salicylates for several reasons.

First is the alarming fact that a significant proportion of the serious salicylate toxicities including deaths are caused by inappropriate multiple dosing during therapeutic use rather than accidental or suicidal ingestion of large single dosages of salicylates (Refs. 1 through 4). Toxicities that result from overzealous multiple dosing during therapy are claimed to be more serious (Refs. 3 and 4) and said to occur at lower plasma salicylate levels compared to toxicities resulting from large single doses (Ref. 1).

Secondly, the propensity for serious toxicities during multiple dosing can now be explained by the recent discovery that the salicylates have very unusual and complex pharmacokinetic characteristics. They are metabolized by processes which can be saturated by doses within the usual therapeutic range. As a result relatively small increases in the dose may exceed the capacity of the metabolizing systems and cause inordinate increases in salicylate plasma levels during multiple dosing.

A third problem in defining the dosage regimens is that aspirin is used extensively for several effects which may have different dosage schedules, e.g., antipyretic effect or antirheumatic effect. Furthermore, these schedules must be adapted to several age groups in which the metabolic capacity may vary greatly. Different dosage regimens for each type of therapy will also be required as a function of age, weight and other possible relevant variables.

Finally, the problem is further compounded by the large number of dosage forms and chemical derivatives which vary appreciably in the strength of the dosage form and recommended dosage schedules for different purposes. The multitude of strengths in currently marketed aspirin products presents a critical problem in the case of salicylates which have the potential for serious toxic effects when the wrong dosage is used. This can be partially overcome by designating a standard strength and standard dosage regimen which will provide the basis for assuring that each patient will be better informed.

In addition to the above considerations, the Panel received several opinions and recommendations regarding its proposed dosage schedules in response to the Panel's various public statements. The Panel's response to these opinions and recommendations are incorporated into this document.

b. *Considerations of risk to benefit.* Ideally the evaluation of OTC drugs should be based upon benefit to risk considerations. The Panel finds, however, that there are no generally accepted protocols or procedures for the objective evaluation of the often cited but seldom quantitated given "risk to benefit ratio." Unfortunately this phrase is usually employed to describe a subjective assessment rather than a real value, i.e., a number based on reproducibly quantifiable measurements.

The absence of a reasonable procedure that can be used to objectively compare the relative effectiveness and safety of different dosage forms, tablet strengths, dosage regimens or different therapeutic indications, e.g., headache or rheumatoid arthritis, is particularly disadvantageous in the case of OTC salicylates. This is due partly because of the toxicity potential related to the dose dependent saturation kinetics of the salicylates and partly to the multiplicity of products which contain different amounts of aspirin, at different doses and dosage intervals.

There is also no established procedure to address the fundamental question regarding appropriate criteria to determine if the potential risk exceeds the benefit when a product is used for self-medication, rather than under the supervision of a physician or other health professional. The Panel has attempted to address this question in terms of the need for additional types of specific monitoring of drug therapy that is required for safe use and whether this monitoring must be carried out by an individual with training beyond that which can be conveyed to the average individual through labeling instructions.

The Panel used the following guidelines in an attempt to establish a systematic means for the evaluation of risk to benefit questions. Based upon certain assumptions discussed below semi-quantitative methods were used for benefit to risk considerations in salicylate dosing.

In response to the Panel's various public statements, the Panel received submissions, some of which represented conflicting views on several of the recom-

mendations of the Panel including the need for a standard dosage, the use of aspirin for arthritis, and alternative regimens for pediatric dosing and dosage regimens in which data to support the safety of larger dosages than those recommended by the Panel were presented. The Panel also received submissions supporting the recommendations of the Panel but suggesting that they should be more stringent. These submissions were considered by the Panel in the recommendations given in this document.

c. *Correlation of dose to blood levels.*

(1) *Maximum safe salicylate blood levels.* A maximum salicylate blood concentration, termed the steady state blood level, is reached and maintained after several repeated dosages at periodic intervals (dosage interval during multiple dosing). This steady state or plateau salicylate blood concentration correlates quite well with early signs of dosage related salicylate toxicity. Tinnitus (ringing in the ears) and deafness which are early signs of dose related salicylate toxicity, occur above a salicylate concentration of 20 mg/100 ml of plasma.

The correlation of salicylate blood levels with early signs of salicylism provides the basis for using the steady state plasma levels as a quantifiable means to compare the toxic potential of different dosage regimens. Single dosage and multiple dosage regimens should result in plasma salicylate levels which are below 20 mg/100 ml for 95 percent of the population. The mean steady state blood levels are determined by both the total daily dosage and the hourly dosage rate.

The steady state salicylate blood level is a function of the total daily dosage and the average dosage rate throughout the day. Different dosage schedules, e.g., 650 mg every 4 hours or 975 mg every 6 hours can be adequately characterized and compared in terms of the total daily dosage and average hourly rate which is the usual maintenance dosage divided by the dosage interval.

(2) *Standard dosage.* The standard upper limit of the Panel's recommended dosage regimen for aspirin is 650 mg every 4 hours for six dosages which is within the upper limit of 4,000 mg maximum total daily dosage and 167 mg/hour average hourly dosage rate. The Panel considered this to be the maximum safe dosage for the general population. Dosage regimens exceeding either this total daily dosage or mean hourly rate provide a significantly greater risk without a compensating therapeutic benefit. A single dosage of 975 mg provides greater benefits to a few individuals without significant additional risk. Repeated dosing at this level can lead to plasma concentrations in the range where more than 5 percent of the population probably experiences tinnitus.

(3) *Nonstandard dosage.* Nonstandard single ingredient salicylate products containing nonstandard amounts per dosage unit should provide dosing instructions limiting the number and dosage intervals such that the total daily dosage and mean hourly dosage rate do not exceed the standard.

In the Panel's opinion, single active ingredient salicylate products which contain nonstandard amounts per dosage unit provide a greater potential for confusion and thus deviation from the standard dosage regimen. However, there have been no studies designed to evaluate this contention. The Panel concluded that the additional risk is probably minimal provided that the labeling provides adequate notice that such products contain nonstandard amounts per dosage unit and thus require dosage regimens that are suitably modified so as not to exceed maximum daily and hourly dosage rates specified by the Panel. Since the modified dosage schedules for nonstandard products would be expected to provide blood levels and total body salicylate levels comparable to those obtained with the standard strength products, any claims of greater strength, e.g., adult strength, 15 percent stronger than standard aspirin, would be misleading and incorrect.

d. *Criteria for determining optimal dosage regimens.* Wagner (Ref. 5) has summarized some useful criteria that have been used to evaluate comparative risk to benefit ratios for drugs. Listed below are those formulae that are applicable to the evaluation of an optimal dosage regimen for a given indication or relative risk to benefit ratio for different therapeutic indications, e.g., use for general analgesic effect compared to use for anti-inflammatory effect in rheumatoid arthritis. Equation (1), Ehrlich's Chemotherapeutic Index (ECI), is generally used for a single dosage in animals but it can be applied to multiple dosages in humans with the following definitions:

$$(1) \text{ ECI} = \frac{\text{minimal therapeutic dose}}{\text{maximal tolerated dose}}$$

(2) Jardetzky's therapeutic characteristic (Tc):

$$Tc: \frac{Dt}{DE} = \frac{Qt - 2 S.D.}{QE + 2 S.E.}$$

Dosage rate producing toxicity to 2.5 pct of subjects
 = -----
 Dose effective to 97.5 pct of subjects

Qt and QE are defined as the median dosage rate to produce a toxic and therapeutic effect, respectively, in 50 percent of subjects. Dt and DE could be a single dosage or multiple dosages where different dosages are given for a specific duration at fixed dosage intervals. This concept is extended in this document to include any multiple dosage rate (dosage/time) given for a sufficient time to reach steady state or the steady state salicylate plasma levels which correspond to toxic or therapeutic effects.

$$\frac{Dt}{DE} = \frac{Qt - 2 S'}{QE + 2 S'}$$

Qt and QE are defined as the dosage to produce either a toxic effect or a therapeutic effect, respectively, in 50 percent of the subjects. St and SE represent the standard deviation of the distribution of the toxic or effective dosage respec-

tively, which is usually considered to be log normally distributed. Thus Qt-2 St will represent the dosage that will produce toxic effects in 2.5 percent of the target population, and QE+2 SE represents the dosage to produce a desired therapeutic effect in 97.5 percent of the target population. The addition of the statistical estimates of the range of responses in the target population is a desirable approach to defining a general dosage for the total population. As discussed by Wagner (Ref. 5), the therapeutic indices of Chen and Jardetzky are useful for certain comparisons but do not provide a means of determining the optimal dosage to be used.

Wagner (Ref. 5) suggests the minimum loss function of Schneiderman et al. as a method to define the optimal dosage which minimizes a loss index (L) and is defined in terms of a "loss" due to the toxicity (q₁) and a loss due to failure to cure (q₂) in which q₁ and q₂ are equated using a weighing factor (λ) thus:

$$L = (1 - q_1) \lambda q_2$$

e. *Pharmacokinetic relationships.* (1) *A relationship between dosage and plasma concentrations.* Normally for most drugs there are linear relationships between the plasma concentration and the variables of the dosage regimen, mg. kg⁻¹, hour⁻¹. The complex nonlinear kinetics of the salicylates negate these usual assumptions, however, and care must be taken in extrapolating from one dosage regimen to another or using the same dosage regimen in individuals of different age or size. Because of the complex nonlinear pharmacokinetic characteristics of the salicylates, comparison and adjustment of multiple dosage regimens must be based upon substantial experimental data.

Unfortunately there are relatively few carefully controlled multiple dosage studies providing adequate blood level data at different dosage, dosage intervals or different body weights. In many studies, the dosage regimens are given in different units such as daily dosage/m² or mg/kg/4 hours without sufficient additional data on the patient characteristics to allow exact conversion to comparable units. Differences in the number of days the dosage regimen was administered and the types of patients (rheumatoid arthritis) compared to normal subjects also made some published data difficult to assess.

Nevertheless, there are data from pharmacokinetic and clinical studies which provide a firm basis for establishing a safe and effective dosage regimen recommendation consistent with the unusual pharmacokinetic characteristics of the salicylates.

On the basis of these studies reviewed below, the Panel established standard and nonstandard dosage schedules. The schedules shown below reflect the Panel's recommendations of a minimum initial and maintenance dosage of 325 mg (5 gr), a maximum initial single dosage of 975 mg (15 gr) to be used only once, and a maximum maintenance dosage of 650 mg (10 gr) every 4 hours (standard) or

in the case of nonstandard dosage forms dosage instruction schedules designed so as not to exceed a maximum hourly rate of 167 mg/hour and a total maximum daily dosage of 4,000 mg. The dosage schedules are stated in terms of the initial starting number of dosage units, the number of dosage units per time interval and the maximum total dosage units per day (24 hours).

(i) *Hourly dosage rate.* Because of the unusual nonlinear kinetics of salicylates, some changes in dosage schedules which ordinarily would have little or no effect on steady state blood levels can result in clinically significant changes in the case of salicylates. For example, if salicylates behaved like most other drugs which have linear kinetics, the mean steady state blood level would essentially be the same for a total daily dosage regardless of whether it is given as four dosages taken every 4 hours only during the day (dosage rate is 1,000 mg every 4 hours) or every 6 hours day and night (dosage rate is 1,000 mg every 6 hours). In the case of salicylates, a change of the hourly dosage rate can lead to potentially toxic levels and it is necessary to put limits on the hourly dosage rate as well as the total daily dosage. On the basis of clinical data and pharmacokinetic calculations, the maximum critical hourly rate is 167 mg/hour for an adult.

This consideration is particularly important in the case of some currently marketed salicylate products containing 7½ gr aspirin per dosage unit with a recommended dosage schedule of 15 gr (975 mg) every 4 hours for four dosages during the day. Although the total daily dosage is within recommended limits, the hourly dosage rate is 244 mg/hour which is 50 percent greater than the recommended limit of 167 mg/hour.

The Panel's evaluation of the safety claims for this type of product involved the following considerations:

(a) Evaluation of the assumptions used in the submitted computer simulations to justify the safety of this dosage regimen (Ref. 6).

(b) Evaluation of blood level data from the literature in which the same or similar dosage regimens were used.

(c) Benefit to risk considerations regarding the use of this dosage schedule for analgesic, antipyretic and anti-inflammatory effects.

The Panel concludes that this dosage regimen would not provide any significant improvement in analgesic or antipyretic effectiveness, but may result in increased blood levels at the potentially toxic level. The increased blood levels may enhance the therapeutic effect in rheumatoid arthritis but will be inadequate to suppress inflammation in many arthritic patients in whom adequate plasma levels could have been attained under proper professional supervision.

The significance of small changes in the hourly dosage rate can be illustrated by consideration of a simplified model which assumes that drug elimination proceeds by a constant rate regardless of the dosage input or plasma concentration. Although this assumption is not

strictly true, the apparent rate of elimination is quite constant at the dosages and corresponding plasma concentrations where toxicity begins to occur, i.e., above 20 mg/100 ml. The following simple model correlates quite well with the published data:

$$A = D/\gamma - M$$

where A is the rate of accumulation of drug in the body per unit time (hour or day); D/γ is the dosage rate per unit time (hour or day); and M is the maximum elimination rate per unit time.

The more detailed model of Levy (Refs. 7 through 10) was also used by the Panel in computer simulations.

Levy and coworkers have extensively studied the problem of saturable metabolism. They have explained many of the apparent discrepancies in the literature using computer simulations based upon the average values of kinetic parameters describing saturable metabolism obtained experimentally from healthy vol-

unteers. These simulations indicate that simply by increasing the daily dosage by 50 percent from 2 to 4 g daily as four equal doses every 6 hours, the total amount of drug in the body at steady state will increase from 1.3 g to 5.3 g, a 400 percent increase (Ref. 7).

They also show that the time to reach the steady state plateau greatly increases with dosage levels in the OTC range. Their simulations show that a dose of 0.5 g (7½ gr) when given every 8 hours will reach a constant maximum level of salicylate in the body (plateau level) of less than 0.5 g after 2 days of dosing. However, if two tablets were taken every 8 hours, the amount in the body would continue to increase for at least 7 days reaching a total body load six times greater than that reached in the one tablet dosage.

After careful consideration of the various risk factors discussed above, the Panel developed the following table for standard and nonstandard dosage units:

Relationship between dosage unit, frequency and hourly dosage rate

Dosage unit ¹ (mg gr)	Initial dosage units ² (mg)	Frequency ³ (tablets/hours)	Dosage units/day ⁴ (tablets mg)	Hourly dosage rate ⁵ (mg/hour)
325 (5)	2 to 3 (650 to 975)	2 after 4	12 (3,900)	163
400 (6.15)	1 to 2 (400 to 800)	1 after 3	9 (3,600)	133
421 (6.48)	1 to 2 (421 to 842)	do.	9 (3,789)	140
485 (7.46)	1 to 2 (485 to 970)	1 after 4 or 2 after 6	8 (3,880)	122
			8 (3,500)	162
500 (7.69)	1 to 2 (500 to 1,000)	1 after 3 or 2 after 6	8 (4,000)	167
			8 (4,000)	167
650 (10)	1 (650)	1 after 4	6 (3,900)	163

¹ The amount of aspirin contained in a single dosage unit (tablet).

² The maximum number of dosage units (tablets) that cannot be exceeded when dosing is initiated.

³ The number of dosage units (tablets) per time interval (number of tablets taken after each time interval (hours) repeated dosing).

⁴ The maximum total number of dosage units (tablets (mg)) that cannot be exceeded in 24 hours regardless of the initial number of tablets taken or the frequency of repeated dosing.

⁵ The amount of aspirin (milligram) taken at each time interval divided by the number of hours in a time interval gives the hourly dosage rate.

(ii) *Other factors increasing risk.* It is emphasized that the upper dosage level of 4,000 mg aspirin daily for a limited period of time (7 to 10 days) may frequently be below the optimal adult daily dosage required for anti-inflammatory effects in patients with rheumatoid arthritis but above that needed by the vast majority of "normal" adults for occasional use as an analgesic and antipyretic agent. This upper dosage was selected by the Panel as the upper limit above which a significant risk of toxicity increases dramatically in the majority of the target population. Furthermore, in some individuals other factors may increase the risk of exceeding salicylate plasma concentrations that are considered safe.

Any factors, such as diet, diuretics or other drugs which may affect the acidity of urine will be greatly magnified at the 4,000 mg daily dosage level. Levy and Leonards (Ref. 11) found the average salicylate plasma concentration of 13 normal adults receiving 1 g aspirin four times daily (4,000 mg daily) for 7 days was 15.0 mg/100 ml plasma (standard

deviation is 4.6) if urine pH was kept above 6.2 by administration of sodium bicarbonate. When urine pH was allowed to fall to the usual range below 6 (5.6 to 6.1), the average plasma salicylate levels increased to 27.0 mg/100 ml (standard deviation is 7.9) which is above the desired level to avoid ototoxicity.

It should be noted that the plasma salicylate level of 27 mg/100 ml but not the level of 15 mg/100 ml would usually be suitable for treatment of rheumatoid arthritis. Thus, subtherapeutic levels might occur in patients who were adjusted to a dosage satisfactory at normal pH levels but greatly reduced if the patient also was taking antacids which increase the urine pH. For this reason, Levy and Leonards (Ref. 11) recommend that in the treatment of rheumatoid arthritis the urine pH should be routinely monitored particularly if antacids are being taken.

The data of Brewer (Ref. 12) illustrates several points which form the basis of the Panel's recommended dosage schedule. In this study, 32 children ranging in age from 2 to 15 years with rheu-

matoid arthritis (mean age 9.4 years) were given a dosage of aspirin based upon the body surface area. A dose of 800 mg/m² aspirin was given every 4 hours for four doses and no drug was administered during the night. During the first 12 hours this hourly dosage rate (200 mg/hour/m²) resulted in a mean increase in the steady state plasma concentration from 35 mg/100 ml at 8 a.m. to 48 mg/100 ml at 8 p.m. Thus, the net plasma concentration accumulation rate (A) was +10 mg/L/hour during a dosage input of 200 mg/hour/m², and -10 mg/L/hour during zero input. Therefore, during dosing the values of the equation, (dC/dt)Vd = D/γ/m² - Vm, are (10 mg/L/hour) Vd = 200 mg/hour/m² - Vm, and during the second 12 hour period of zero input (-10 mg/L/hour) Vd = -Vm. The apparent volume of distribution (Vd) can be calculated from the equation 2 (10 mg/L/hour) Vd = 200 mg/hour/m². Therefore, Vm = 100 mg/hour/m². If the mean dosing rate exceeds 100 mg/hour/m², the plasma concentration will not reach a plateau but will continue to increase during dosing for the entire 10-day dosing period.

It is important to note that the maximum safe rate determined in this study for an average adult of 1.73 m² surface area is 173 mg/hour which is only slightly higher than the upper hourly rate recommended by the Panel.

The Brewer study also illustrates the effect of using a dosage regimen in which the hourly rate exceeds the maximum elimination rate for part of the day even though the total dosage is below the critical daily dosage. The hourly rate was 200 mg/hour/m² for 12 hours during the day and during the second 12 hours, the rate was zero. Although the mean hourly rate was 100 mg/hour/m², the daily dosage is also just below the maximum rate. The increased hourly rate in the first 12 hours results in a plasma accumulation from 36 mg/100 ml, the upper desired therapeutic level for rheumatoid arthritis, to 48 mg/100 ml which is in the potentially toxic range because the dosage used by Brewer was on the average just equal to the mean maximum elimination rate for this group.

It would be expected therefore that the maximum individual elimination rates will be just above and below this standard dosage input rate and therefore the range multiple dose plasma concentration will be very large. This is in fact the case. The plasma levels range from 14 mg/100 ml to 62 mg/100 ml at 8 a.m. and 27 mg/100 ml to 77 mg/100 ml at 8 p.m. for this dosage regimen.

For these children, the mean dosage calculation from body weight was 33.8 mg/kg (standard deviation is 5.3), and therefore, the ratio of body weight to surface area was 23.7 kg/m² (standard deviation is 5.3). Therefore, the mean maximum dosage per kg of body weight for this group would be:

$$\frac{100 \text{ mg/hour/m}^2}{23.7 \text{ kg/m}^2} = 4.2 \text{ mg/hour/kg or } \frac{33.8 \text{ mg/kg}}{(2)(4 \text{ hours})}$$

$$= \frac{8.45}{(2)} = 4.2 \text{ mg/hour/kg or } 101.4 \text{ mg/kg/day.}$$

From the study of Makela et al. (Ref. 13), it is clear that use of body weight to determine the dosage in children can be misleading and lead to toxicity because the ratio of body weight to surface area changes with different age groups. The average kg/m² ratio for this group of children was 23.7 kg/m² but would be about 40 kg/m² for an adult. When surface area is used to calculate the equivalent dosage for adults a maximum hourly input rate for a 70 kg adult (1.73 m²) would be 173 mg/hour which is in good agreement with the maximum hourly rate (167 mg/hour) recommended by the Panel. If body weight is used to calculate the adult dosage, the corresponding dosage would be 7,000 mg/day or 280 mg/hour.

Dosage forms which contain more than 10 gr must be taken at intervals which will generally not sustain blood levels unless the plasma levels are above 20 mg/100 ml (Ref. 14). They are therefore justified only for treatment of rheumatoid conditions under the direction of a phy-

sician. Most of the sustained release type microspherules do not significantly prolong the release of the drug. The plasma sustained levels are more a result of the prolonged duration in the body rather than delayed release during absorption (Ref. 15).

(iii) *Change of dosage interval with constant daily and hourly dosage rates.* Because of limited published data, the Panel used analog and digital computer simulations to study the effect of increasing the dosage interval when the daily and hourly dosage rates were maintained constant at the recommended level of 4,000 mg daily and 167 mg hourly. The total amount of salicylate in the body at steady state was similar at clinically realistic dosage intervals of 3 to 8 hours. The maximum amounts of drug in the body and plasma concentrations just after dosing and the minimum concentrations just before dosing at steady state that were obtained using the model and average values given by Levy and Tsuchiya (Ref. 7) are shown below:

Relationship between dosage and dosage interval (with constant daily and hourly dosage rates) to steady state concentration

Dosage interval (hours)	Average dosage rate (milligram/hour)	Total daily dosage (milligram) and number of dosage units per day	Steady state: Total body load after 5 days	
			Maximum amount in body (milligram)	Minimum amount in body (milligram)
Dosage (milligram):				
167	1	167	4,282	4,133
500	3	167	4,472	4,133
650	4	167	4,718	3,882
1,000	6	167	4,866	3,702
1,330	8	167	5,393	2,156
4,000	24	167		

From these simulations, it appears that as long as the total daily dose and the mean hourly dosage regimen are kept constant, reasonable increases in the dosage interval of 3 to 8 hours will not greatly increase the total maximum and minimum body load of salicylates at steady state. As the dosage interval is increased from 3 to 8 hours, the difference between the total maximum and minimum amounts of salicylate in the body is less than 10 percent providing the dosage per dosage interval is also adjusted to maintain the same average dosage rate every hour.

(iv) *Maximum safe single dosage.* The Panel concludes that a large adult dosage of 975 to 1,000 mg may provide increased therapeutic benefit in some cases without significantly increasing the probability of toxicity provided that the dosage is administered only once as a single dosage or as the initial dosage in a multiple dosage regimen. The use of an initial (loading) dosage is a common practice in designing multiple dosage regimens for many drugs. The multiple dosage regimen results in an accumulated amount of drug in the body

at steady state which is greater than the amount produced by a single maintenance dosage.

For most drugs which follow linear kinetics, the use of a higher initial (loading) dosage permits the desired steady state drug level in the body to be reached more quickly without changing the ultimate steady state drug level that is reached for a given maintenance dosage. For drugs such as the salicylates, which follow nonlinear kinetics, the amount of the loading dosage is more critical. If the dosage is too large or given repetitively, it may actually increase the final amount of drug in the body at steady state that is reached with a given multiple dosage level. The maximum initial dosage recommended by the Panel is only for use as a single nonrepeated dosage or as the initial dosage used only to initiate a multiple dosage schedule. The recommended maximum initial dosage is recommended, therefore, on the assumption that it will be used only once as a margin of safety for inadvertent or noncompliant use. Repetitive use of the 975 to 1,000 mg maximum single dosage at the usual dosage intervals would

significantly increase the dosage rate and therefore significantly increase the risk relative to any possible increase in analgesic or antipyretic effect.

The maximum single dosage was selected as the single dosage which produces salicylate plasma levels (6 mg/100 ml to 10 mg/100 ml) comparable to those achieved by the minimum dosage (325 mg) in a standard multiple dosage regimen known to be effective and free of major side effects. Thus, the maximum single dosage will produce rapid increase in plasma levels in multiple dosing which can be maintained by smaller dosages of 325 to 650 mg given every 4 hours.

Leonards (Ref. 15) found that comparable plasma salicylate levels of less than 10 mg/100 ml were produced by administration of 1,300 mg (20 gr) aspirin in three different ways. A total of 1,300 mg was given as a single dosage of one 1,300 "sustained release" capsule, a single dosage of four 325 mg tablets and two dosages of two 325 mg tablets (650 mg) given 4 hours apart.

The maximum plasma concentration time curves following one 1,300 mg dosage were similar for the sustained-release product and the large dosage of regular aspirin. Thus, the microsphere aspirin product did not produce a sustained plasma level due to a prolonged release or decreased absorption rate but simply because of saturated elimination which occurs independent of the product used.

The larger single dosage resulted in a greater total area under the plasma time curve than the divided dosage. The increase in the total area under the plasma time curves even though these regimens have the same total dosage and hourly dosages illustrates the effect of saturable metabolism which augments plasma levels from a large single dosage compared to the usual 650 mg (10 gr). The plasma concentrations were essentially the same, 8 hours after the initial dosing in both cases. Eight hours after the initial dosing, both dosage schedules resulted in essentially identical plasma levels of about 5 mg/100 ml. This may indicate that a dosage schedule of one 1,300 mg (20 gr) capsule every 8 hours could possibly produce blood levels that would be probably equivalent to blood levels produced by a standard dosage regimen of 650 mg (10 gr) dosage every 4 hours since the hourly rate is the same 167 mg/hr. Although the final plasma concentrations are similar, the increased area under the curve for the higher dosage may indicate potential differences in the two regimens, however. Additional data on the mean plasma levels and variability about the mean after several days of multiple dosing are required before the 1,300 mg (20 gr) capsule can be considered a safe dosage form for OTC analgesic and antipyretic use. The Panel is concerned that while this dosage form may be appropriate for treatment of conditions requiring high dosages such as arthritis, it offers no advantage in the treatment of pain or fever. It lacks flexibility when adjusting dosages.

(2) *Relationship between plasma concentration (and dosage) and toxicity.* Although it has not been possible to establish the plasma levels of aspirin or salicylic acid required for analgesic effects, estimates are available on the blood levels associated with several types of toxic effects.

The levels of aspirin following usual dosages of 600 mg are relatively low (2 mg/100 ml) and decline rapidly (half-life about 20 to 40 minutes). Aspirin levels have not been correlated with toxicity. Plasma levels of salicylic acid, however, correlate well with probability of toxicities.

Tinnitus is the most frequent and reliable symptom of salicylism which occurs at salicylate levels of about 20 mg/100 ml. Other early symptoms of salicylism include deafness, headache, vertigo, vomiting and hyperventilation. Above 30 mg/100 ml, irritability and psychosis may occur (Ref. 16). A target concentration of 20 mg/100 ml for the treatment of rheumatoid arthritis is usually sought in the treatment of adults while children can often tolerate higher doses (30 mg/100 ml) in the treatment of rheumatoid arthritis, but monitoring for toxicity is essential (Refs. 17 and 18). Children often develop other symptoms (nausea, hyperventilation) before experiencing tinnitus (Refs. 13 and 17).

Done found a very poor correlation between serum salicylate concentrations at the time of admission and the severity of salicylate intoxication (Ref. 19). The serum salicylate concentrations were extrapolated back to the time of ingestion, assuming a half-life value of 20 hours ($k=0.03465$ hour), and a much better correlation was observed. Of additional significance was the fact that the correlations were similar for both children and adults indicating that serum salicylate concentrations may provide a reasonable basis for comparing the potential of different dosage regimens to produce toxicities in adults and children.

The reversible effects of salicylates on hearing function appear to be the earliest and most useful indicators of toxic salicylate serum levels. Although permanent hearing loss has occurred with the use of salicylates (Ref. 20), this is relatively uncommon. Since the great majority of effects are rapidly reversible and correlate quite well with individual plasma levels except for patients who are already deaf, the incidence of tinnitus and common reversible hearing loss are the most reliable and earliest indicators of potentially toxic doses.

Salicylates can produce two effects on hearing function, tinnitus which is a ringing sensation, and deafness which involves a reversible loss of pure tone sensitivity affecting all frequencies. Both effects correlate with individual serum salicylate concentrations.

Progressive loss of the sensitivity to hear pure tones was demonstrated in volunteers receiving doses of three tablets (975 mg) every 4 hours (244 mg/hour) 4 days (Ref. 21).

Similar effects of increasing aspirin

dosage on actual hearing loss were studied by Myers et al. (Ref. 22). Audiometric measurements were made before and after administration of aspirin to 25 patients.

Myers et al. found that a dosage of 5,000 to 8,000 mg of drug was usually necessary to produce tinnitus and subject hearing loss (Ref. 22). In patients with normal hearing, high salicylate concentrations produced a bilateral hearing loss of 20 to 40 decibels for all frequencies which were reversible in all patients within 3 to 10 days.

Hearing loss did not occur below salicylate plasma concentrations of 20 mg/100 ml. Seventeen of 21 patients experienced hearing loss of more than 10 decibels (30 to 40 decibels in most) when salicylate concentrations were above 20 mg/100 ml. The hearing loss increased as plasma levels increased. Usually, hearing loss reached a maximum at 40 mg/100 ml.

The median dose at which tinnitus occurs was 4.5 g daily with a range of 2.4 to 6.0 g in a study by Ropes (Ref. 23) and at 5.3 g in the study by Mongan et al. (Ref. 24). Neither tinnitus nor deafness occurs at salicylate levels below 20 mg/100 ml which is greater than required for analgesia and antipyresis for 95 percent of patients.

(3) *Relationship between analgesic effects, dosage and salicylate plasma concentrations.* Although it has not been possible to relate analgesic effect with plasma salicylate concentrations, a relationship between oral dose and analgesic effect has been well-established for several different types of clinical pain.

In almost all well-controlled studies, analgesic effect cannot be distinguished from placebo at dosages below 325 mg. However, higher dosages of 650, 975 and 1,300 mg have been shown to be significantly different from placebo. (See Part III, paragraph B.1.a.(1) below—Effectiveness.) Dosages above 650 mg do not result in a significantly greater incidence or degree of pain relief in most studies. In some studies, however, dosages of 975 mg (three 325 mg tablets) to 1,300 mg (four 325 mg tablets) appeared to have a greater analgesic effect based on dose-response curves which appear to be increasing above 650 mg. The difference between the larger dosages compared with 650 mg generally could not be shown to be statistically significant but the apparent increase in the dose-response curve above 650 mg dosages suggests that greater pain relief may be obtained in some individuals with some types of pain with single dosages of 975 to 1,300 mg.

Although the dose-response curves in a few studies suggest that larger dosages may produce a slightly greater incidence of analgesia than a 650 mg dosage, there are important limitations in this assumption.

First, the relationship of increased analgesia to increased dosage is not linear but, like many drugs, the effect is proportional to the logarithm of the dosage. Second, the increase in response is generally relatively small because the dose-response curve is relatively flat requiring

large increases in the dosage to obtain a relatively small increase in analgesic response.

A third consideration is that most studies of analgesic effects have involved only single dosages. There is relatively little information on the dose-response curves after multiple dosages.

Although limited, current data appeared to justify that an initial dosage of 975 mg may prove more beneficial than 650 mg for alleviating pain in a few individuals. For reasons discussed below, an increase in dosage above 650 mg would probably not greatly increase the potential of systemic toxicity if taken only once or twice. If the larger dosage is taken according to the usual multiple dosage schedule, significantly increased potential for toxicity will occur. Furthermore, there are no data available to show that multiple dosages greater than 650 mg will provide any greater clinical benefit for analgesic and antipyretic effects.

Although it is not possible at this time to correlate analgesic effect with the plasma salicylate concentrations, it is possible to determine the plasma salicylate concentrations that are attained with the dosages known to produce analgesia. Since toxicity correlates with plasma salicylate concentrations much better than with the dosage of salicylates, it is appropriate to determine and compare the toxicity potential of dosages and dosage regimens required for a certain therapeutic effect, e.g., analgesic or antirheumatic effects, by comparing the corresponding plasma salicylate concentrations.

The maximum salicylate plasma levels which are achieved with recommended multiple dosages with all different types of salicylates are less than 15 mg/100 ml (Refs. 15, 25, 26, and 27). Even the highest possible effective single dosage, 1,300 mg (20 gr), doesn't usually result in plasma levels which exceed 15 mg/100 ml (Ref. 15). Thus, 20 mg/100 ml is both the lower toxic limit and also the concentration which should not be exceeded with multiple dosing of 650 mg every 4 hours or the equivalent. However, repeated administration of dosages above 650 mg at the usual dosage interval will accumulate in the body to produce higher concentrations that can be expected to produce toxic symptoms in a significant number of the population, i.e., greater than 5 percent of the population.

(4) *Relationship between plasma concentrations and anti-inflammatory effect in rheumatoid arthritis.* In contrast to analgesic and antipyretic efforts, the suppression of inflammation increases with the dosage of salicylates even beyond the point of toxicity (Ref. 28). Mills states that the therapeutic objective is to employ as large a dosage as possible short of toxicity and the most common reason for therapeutic failure is use of inadequate doses.

The usual target concentration tolerated by most patients is the range of 20.0 to 25.0 mg/100 ml. This is the region where small increases in dosing can result in very large increases in plasma levels. Special directions must be given

to the patient and, depending on the dosage and condition, special monitoring for adverse effects may be required and therapeutic doses must be determined for each patient.

Fremont-Smith and Bayles (Ref. 29) gave increasing dosages of salicylates to 11 hospitalized patients with rheumatoid arthritis over a period of 5 days until the largest tolerated dose was reached. In most cases, the dosage increase was stopped because of auditory effects, either tinnitus or deafness, which occurred at an average daily dosage of 5.2 g. Fremont-Smith and Bayles established that salicylates produced an important anti-inflammatory effect in rheumatoid arthritis which was in addition to the analgesic effect. This effect, which could be quantitated by decreased joint size, measured by standard jewelers rings, or grip strength, was rapidly reversed when subtherapeutic doses were administered. These authors concluded that all patients with active rheumatoid arthritis, whether mild or severe, should receive salicylates regularly in the largest tolerated dosages. The average maximum tolerated dosage was 5.2 g.

Boardman and Hart (Ref. 30) compared placebo with prednisone, paracetamol, high dosages of salicylate (5.3 g daily), and low dosages of salicylate (2.6 g daily) administered in multiples of 10 gr (660 mg) tablets given in four equal doses daily for 7 days followed by 7 days rest. Therapeutic response was objectively measured by the occurrence of predefined significant changes in joint size, grip strength and also subjectively by patient preference. A significant change in joint size (4 mm or more over 7 days) was produced by high doses of salicylates but not by low doses of salicylate, paracetamol or placebo. Changes in joint size, compared sequentially with placebo, proved the most objective means of assessing the anti-inflammatory effect of salicylates and also prednisone, a drug known to have anti-inflammatory effects but no significant direct analgesic effects. It is significant that the drug therapies with analgesic, but not anti-inflammatory effects, such as paracetamol and low aspirin doses, produced slight improvements in grip strength and patient preference compared to placebo, presumably due to the analgesic effects, but had no effect on joint swelling.

With the high dosage of aspirin (5.3 g/day) improvement of joint size occurred in 5 of 7 patients (71 percent) in the first trial and 7 of 11 in the second trial in which the drug was given in the first or second week of a crossover study with a placebo. The mean decrease in joint size was 5 mm and 4 mm for the two studies. In a study in which a low dosage of salicylate (2.6 g) was compared with a high dosage of salicylate, improvement was noted in 1 of 11 patients in one trial when the low dosage was given first and 2 of 7 patients when the high dosage was given first indicating a possible residual effect of the high dosage of salicylate. Tinnitus occurred in 4 of 18 patients at the higher dosage and in

none of 33 patients receiving the low dosage.

The authors conclude that their study confirms earlier reports that according to their criteria of objective clinical response, anti-inflammatory effects are essentially nonexistent with the lower dosage of salicylates used.

Boardman and Hart (Ref. 30) concluded that "These findings confirm the importance of administering high doses of salicylates in rheumatoid arthritis irrespective of symptoms and their severity if the aim of the treatment is the promotion of nonspecific anti-inflammatory actions."

Graham and coworkers (Ref. 31) state that inadequate suppression of inflammation of rheumatoid arthritis commonly occurs where salicylate plasma levels fall below 15 mg/100 ml. In a study of 12 hospitalized patients with rheumatoid arthritis in which a 4.8 g daily dosage was given and patient compliance and drug bioavailability carefully supervised, assured therapeutic plasma levels (greater than 15 mg/100 ml) were not reached in eight patients (67 percent). The maximum average midday plasma concentration after several days dosing was 12.6 mg/ml with a range of 5.5 to 27.6 mg/100 ml. Low levels of salicylate in these patients were stated to be due to rapid elimination, large volume of distribution or both. Concomitant administration of corticosteroids was also identified as a factor which might be involved in inadequate therapeutic plasma levels on long term therapy even though high dosages were given (3.6 to 4.8 g daily).

In summary, on the basis of pharmacokinetic considerations, the Panel concludes there is an abundance of published literature which clearly establishes that self-medication of even minor symptoms of rheumatoid arthritis constitutes irrational therapy. There is a greatly increased risk relative to benefit that would result from any attempts of untrained laity to determine and monitor an individual dosage regimen required to maximize the great potential benefit from dosages adequate to suppress inflammation and minimize the great potential risk from only slightly higher dosages which can cause serious toxicity.

The available literature clearly shows that in the case of rheumatoid arthritis, aspirin should not be used simply to relieve symptoms but rather to actively treat the disease by giving individualized dosages adequate to suppress inflammation. Because of the unusual pharmacokinetic characteristics of the salicylates only recently recognized, the determination of the appropriate dosage for rheumatoid arthritis requires skilled professional assistance. Furthermore, dosages and duration of therapy required for adequate therapeutic treatment are greater than those considered safe for unsupervised OTC dosing. Many factors must be considered beyond the capability of the general population and indeed requiring skilled clinical judgment and assessment.

In some cases, careful monitoring is required involving clinical laboratory tests, such as determination of plasma salicylate concentration, liver function tests and urine pH, which are not accessible to or interpretable by the untrained general population.

The Panel, therefore, believes that any labeling which encourages unsupervised treatment of rheumatoid arthritis even for relief of "minor symptoms" constitutes an unacceptable risk. The Panel recognizes that because of the large dosages required over a long period of time, it would create an unnecessary economic hardship to require a prescription status for the use of salicylates in the treatment of rheumatoid arthritis. By analogy, insulin can be purchased by diabetics without a prescription for medically supervised use. It would be irrational, however, to suggest that the labeling directions or promotional material should encourage the target population to determine the dosage to relieve their symptoms or attempt to monitor the effects of their drug treatment or their disease progress without laboratory testing and supervision by a physician.

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2. *Statement on standard and nonstandard nonsalicylate dosage schedules.* The components of a salicylate dosage schedule also apply to a nonsalicylate dosage schedule. (See part II, paragraph E.3. above—Analgesic-antipyretic recom-

mended dosage.) Dosage schedules for the use of aspirin, a salicylate, in standard and nonstandard dosage units, were discussed above by the panel. The Panel also considered dosage schedules for the use of acetaminophen, a nonsalicylate, in standard and nonstandard dosage units.

There was much less information available to the Panel on the pharmacokinetics of acetaminophen in animals and man than of aspirin. However, there is good evidence that the pharmacokinetics of this drug are simpler than those for aspirin, and acetaminophen probably shows linear kinetics. However, the Panel finds it reasonable to recommend the use of acetaminophen in the same dosages as those recommended for the use of standard aspirin dosage units, i.e., 325 and 650 mg. (See part II, paragraph E.3.b. above—Recommended dosage for products containing standard dosage units.)

Of particular concern to the Panel in considering the possibility of increasing the dosages of acetaminophen was the paucity of data regarding the toxic effect of acetaminophen from single dosages that exceed the dosages recommended for chronic use of the drug for longer than the 5-day interval in children or the 10-day interval in adults, or from dosages that exceed the maximum adult daily dosage of 4,000 mg. Elsewhere in this document the Panel has discussed the toxicity of acetaminophen and its relationship to dosage level. (See part III, paragraph B.1.b.(2) below—Safety.)

Until data based on clinical efficacy studies and appropriate toxicological studies are available to justify an increase in the dosage of acetaminophen, the Panel believes it unwarranted to introduce dosages that exceed those recommended for aspirin. Also, the Panel concludes that only nonstandard dosage units of 500 mg may be recognized for acetaminophen in addition to the standard dosage unit of 325 mg since the Panel is unaware of any other nonstandard dosage unit currently available in marketed adult strength products containing acetaminophen as the single active ingredient. Therefore, regarding the dosage schedule for acetaminophen in nonstandard dosage unit of 500 mg, the Panel concluded that the same dosage should apply to acetaminophen as that recommended for the use of nonstandard aspirin dosage unit of 500 mg. (See part II, paragraph E.3.c above—Recommended dosage for products containing nonstandard dosage units.)

3. *Statement on children's dosage. a. Introduction.* The Panel has reviewed OTC drug labeling for currently marketed products containing aspirin. The Panel finds that there is a lack of a single recognized pediatric dosage schedule. Initially, the Panel attempted to compile a pediatric dosage schedule based upon common features of dosage schedules presently found in the labeling of marketed pediatric products. This representative dosage schedule is given below in Pediatric Schedule A.

The Panel also sought comments from the drug industry, through the industry liaison Panel member, regarding a rec-

ommended pediatric dosage regimen for aspirin products. One drug manufacturer (Ref. 1) submitted data containing a review of the medical literature regarding pediatric dosages of aspirin, survey information on the aspirin dosages currently used by practicing pediatricians and data pertaining to the pharmacology and pharmacokinetics of aspirin dosages through consultation with pediatric clinical pharmacologists. In addition, a new regimen was proposed by the drug manufacturer discussed below as Pediatric Schedule B.

To support the submission, data and comments were presented that the currently labeled OTC pediatric dosage schedule (Pediatric Schedule A) is inadequate (Ref. 2). It was stated that the dosage in the labeling is too low particularly in the youngest age group. Because of this, therapeutic failure may cause consumers to either exceed the labeled dosage or repeat dosing before the recommended 3-hour interval. This was proposed to the Panel as a cause for overdosing. This new dosage schedule was proposed to prevent the problem of overdosing by initiating treatment with an adequate dosage and then repeating after 4 hours to maintain the desired effect.

The Panel further modified this proposal (Pediatric Schedule C) which is discussed more fully below. It should further be noted, that based upon a review of the use of aspirin in children, the Panel also considered the pediatric dosage schedules for acetaminophen, aspirin salts, and all other salicylates. While not included in the example for aspirin in Pediatric Schedule C, the Panel has included appropriate pediatric dosage recommendations for Category I ingredients, where applicable, in the appropriate sections of this document.

b. *Discussion.* The following dosage schedule based upon current recommendations given on many aspirin-containing products currently marketed for OTC use, was initially considered by the Panel:

Pediatric schedule A—representative current pediatric dosage schedule on marketed products for 81 mg (1.25 gr) aspirin tablets

Age (years)	Number tablets taken every 3 h (single dosage)	Total dosage (milligrams)
Under 3.....	(1)	81
3.....	1	81
4 through 5.....	2	162
6 through 9.....	3	243
10 through 14.....	4	324

† As directed by physician

As was pointed out by one drug manufacturer, this dosage schedule was selected primarily on the basis of safety considerations to assure minimal potential for toxicity, particularly in the youngest group (Ref. 1).

In a survey of 2,241 pediatricians regarding the current pediatric dosage schedule on marketed products of as-

using different pharmaceutical forms of acetaminophen (Ref. 4).

The plasma half-life has been reported to be from 1 to 3 hours (Ref. 1). In an unpublished study (Ref. 5), the mean plasma half-life using several pharmaceutical forms was 148 ± 43 minutes.

Acetaminophen is relatively uniformly distributed throughout most body fluids (Ref. 1). Binding of the drug to plasma proteins is variable and depends on the dose. During acute intoxication, as much as 20 to 50 percent may be bound to plasma proteins (Ref. 1). Dearden and Tomlinson (Ref. 6) studied the protein binding affinities of some p-substituted acetanilid derivatives including acetaminophen and found that at therapeutic doses the association constant was low, which would permit high free drug concentration in blood and plasma for a relatively long period of time.

Acetaminophen is conjugated in the liver to form glucuronide and sulfate conjugates. Cummings et al. (Ref. 7) showed that acetaminophen is eliminated mainly by these two pathways. By chromatography and infrared spectrophotometry they characterized the sulfate and glucuronide of acetaminophen. They found that 26 percent of acetaminophen administered was excreted as the sulfate and 49 percent as the glucuronide.

It seems that the formation of acetaminophen sulfate in man may be capacity-limited in the 1 to 2 g dose range (Ref. 8). This has been shown by Levy and Yamada by the fact that acetaminophen sulfate excretion reaches a plateau following the administration of 2 g acetaminophen. Acetaminophen is also conjugated to a lesser degree with cysteine and the corresponding mercapturate.

The metabolites of acetaminophen have been separated and determined quantitatively in urine by gel filtration using Sephadex G 10 (Ref. 9). These authors also found the most important metabolites to be the glucuronide and sulfate. Other metabolites found were S-(1-acetamino-4-hydroxyphenyl)-cysteine and 1-acetamino-4-hydroxyphenyl mercapturic acid. Using this technique minor quantities of free acetaminophen were also found in the urine. Using this technique the total recovery was 95 to 100 percent and the administered dose was accounted for as follows:

- 30.5 to 58.5 percent as glucuronide.
- 17.5 to 33.9 percent as sulfate.
- 4.5 to 6.1 percent as mercapturate.
- 0.4 to 5.9 percent as cysteine conjugate.
- 3.5 to 4.5 percent as free acetaminophen (Ref. 9).

It has been suggested that the hydroxylated metabolites are responsible for methemoglobin formation and hepatotoxicity (Ref. 1). The administration of acetaminophen to patients with impaired renal function results in increased accumulation of acetaminophen conjugates in the plasma because of poor excretory capacity but only in minor changes in the plasma concentrations of free acetaminophen (Ref. 1).

The metabolism of acetaminophen has been shown to be markedly changed by

the concurrent administration of salicylamide (Ref. 8). The authors found evidence of competitive inhibition by salicylamide in the formation of acetaminophen glucuronide and sulfate. This effect was counteracted or prevented by the administration of L-cysteine (a source of sulfate). This interaction may have therapeutic and/or toxicological implications since the inclusion of salicylamide in an analgesic mixture will inhibit the two major processes for the elimination of acetaminophen. This interaction with salicylamide becomes more important if one considers the capacity-limited formation of sulfate described above (Ref. 8). On the other hand, concurrent administration of salicylic acid has been found not to exert any significant effect on the formation of acetaminophen glucuronides or sulfate or in the half-life of acetaminophen (Ref. 10).

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The Panel considered all pertinent data and information in arriving at its conclusions and recommendations. The Panel was charged with the review of OTC internal analgesic, antipyretic, and antirheumatic drug products. After carefully reviewing all of the available data, the Panel has classified the data into analgesic, antipyretic and antirheumatic agents. See part II, paragraph I, above—(D.C. 100.10.10.)

III. ANALGESIC AGENTS

A. GENERAL DISCUSSION

The Panel has defined OTC analgesic drugs as agents useful to relieve occa-

sional minor aches, pains and headache. These agents are intended for the relief of the type of pain that is self-limited and requires no special treatment or prior diagnosis by a physician. Such analgesic agents are commonly referred to as the mild analgesics in contradistinction to the strong analgesics such as the potent narcotic or morphine-like analgesics. The mild analgesics can be chemically divided into two main subgroups: Those agents chemically related to the strong analgesics, e.g., codeine, ethoheptazine, and propoxyphene; and those analgesics like aspirin, with antipyretic and anti-inflammatory or antirheumatic activity, e.g., salicylates, salicylamide, aniline derivatives, phenylpyrazoles, etc. It is the latter group of mild analgesics that have generally been associated with OTC use.

The mild analgesics which are acceptable for OTC use include the salicylates, e.g., aspirin and the nonsalicylates, e.g., acetaminophen. All of these agents are administered orally and in special cases rectally. Since these agents are not as potent as the strong analgesics the milder agents are most effective for relief of mild to moderate pain. Mild analgesics probably achieve their effect through several mechanisms. The salicylates which are the most commonly used OTC analgesic agents are believed to alleviate pain by both a peripheral and a central nervous system (CNS) effect. Direct effects of salicylates on the CNS have been described and suggest a hypothalamic site for the analgesic as well as the antipyretic effects. This is supported by the fact that analgesic doses do not cause mental disturbances, hypnosis, or change in modalities of sensation other than pain. Both the peripheral and CNS factors contribute significantly to the pain relief afforded by this class of drugs.

The types of pain amenable to relief by OTC analgesics are generally those of relatively low intensity, particularly headache, myalgia, arthralgia and other pains arising from integumental structures. The salicylates have lower maximal effects than do the narcotic analgesics and hence are used only for pain of mild to moderate intensity. The salicylates are more widely used for pain relief than any other class of drugs.

Although OTC analgesics may effectively ameliorate the pain due to various physical conditions, disease entities, or specific physical sites, the listing of a multitude of conditions and sites in order to be factual and all inclusive would not only result in a lengthy list that would tend to be confusing but could also mislead the consumer by the implied assumption that the product treats the physical condition and/or disease rather than just temporarily relieves the pain associated with the physical condition and/or disease. For this reason, the Panel has recommended that OTC analgesics be simply indicated "For the temporary relief of occasional minor aches, pains and headache".

The Panel concludes that no OTC analgesic product should be taken by adults for more than 10 days or by children for more than 5 days except under

PROPOSED RULES

the advice and supervision of a physician. If the consumer feels the need to continue self-medication beyond 10 days, it may be indicative of an underlying serious condition requiring medical supervision. Self-medication without consulting a physician may in some conditions cause irreparable damage. It is the Panel's opinion that if symptoms require the use of an OTC analgesic for more than 10 days, the individual is sufficiently ill to require consulting a physician. The 10 day limit is based on historical precedent and past marketing experience. The Panel has concluded elsewhere in this document that the duration of use of all analgesics should be limited to 5 days for children under 12 years of age (See part II, paragraph F.3. above—Statement on children's dosage.) Therefore, the Panel recommends that all OTC analgesics contain the warning for adults, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician", and for children under 12 years of age, "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which analgesic agents are generally recognized as safe and effective and are not misbranded.*

CATEGORY I—ACTIVE INGREDIENTS

The Panel has classified the following analgesic active ingredients as generally recognized as safe and effective and not misbranded:

Aspirin	Magnesium salicylate
Acetaminophen	late
Calcium carbaspirin	Sodium salicylate
Colchicine salicylate	

a. *Aspirin.* The Panel concludes that aspirin is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Aspirin is by far the most widely used OTC ingredient in the U.S. In fact, almost 19 billion dosage units are sold annually. During the 75 years that have elapsed since aspirin was introduced to the U.S. market, and because of its immense popularity in this country, it has been extensively discussed in the medical and scientific literature.

Aspirin is useful in mild to moderate pain not only when the pain is localized but also when it is widespread. Studies on cancer pain suggest that aspirin may also relieve mild to moderate pain of visceral origin.

Thousands of articles have been written on aspirin since the first pharmacological data were reported in the literature by Dreser in 1899 (Ref. 1). Virtually all of the experiments discussed in the articles showed aspirin to be superior to placebo in "mild" to "moderate" pain. Kantor states that "modern clinical pharmacologic testing has established that aspirin is an effective analgesic in a variety of pain states" (Ref. 2). Beaver, in an extensive discussion of mild analgesics in 1965, summarized the findings of over 40 controlled human

analgesic studies which demonstrated the superiority of aspirin to placebo (Ref. 3). The Panel has included the following table which summarizes the studies reported by Beaver (Ref. 3):

Controlled human studies demonstrating the superiority of aspirin to placebo prior to 1965

Investigator(s)	Type of patient, etiology of pain, or both	Aspirin dose (milligram)
Beecher et al.	Postoperative	600.
Boyle et al.	Mixed chronic	650.
Brennan	Postoperative dental, outpatients	650.
Bruni and Holt	Postpartum	650.
Carlsson and Magnusson	Headache, outpatients	1,000.
Cass and Frederik	Mixed chronic	300 to 650.
Cass et al.	Mixed chronic	325 to 600.
Currier and Westerberg	Headache, outpatients	650.
DeKornfeld and Lasagna	Postpartum	600.
DeKornfeld et al.	do.	650.
Feinberg et al.	Mixed musculoskeletal, outpatients	325 or 650.
Forrest	Mixed acute and chronic	300 and 900.
Frey	Headache, inpatients and outpatients	650.
Houde et al.	Cancer	600.
Houde & Wallenstein	do.	400, 600 and 900.
Kantor et al.	Postoperative and fracture	600.
Do.	Postpartum	600 and 1,200.
Lasagna et al.	do.	600 (?).
Magee & DeJong	Headache, outpatients	600 and 1,200.
Mairs et al.	Mixed chronic and acute	325.
Murray	Headache outpatients	163, 325 and 650.
Orkin et al.	Postpartum	600.
Settel	Mixed chronic	650.
Sevelius & Colmore	Postpartum	325 (?).
Sunshine et al.	Mixed acute	650.
Uhland	Postpartum and mixed	625 or 650.
Valentine & Martin	Postoperative	325.
Zelvelder	Mixed chronic and acute	500.

Beaver also noted that because of the consistency of aspirin's analgesic activity in well-controlled analgesic studies, most researchers often included it as a standard in their experiments. For example, Lasagna (1962), in a series of 23 separate consecutive studies conducted on patients with postpartum pain (after childbirth) found in 22 of these studies that the analgesic response to 600 mg of

aspirin was superior to that of placebo (Ref. 4). Similarly, Houde demonstrated a significant superiority of aspirin over placebo in 9 of 10 studies in patients with cancer (Ref. 5).

The Panel has included the following table which summarizes some other more recent studies which also demonstrate the superiority of aspirin to placebo.

Controlled human studies demonstrating the superiority of aspirin to placebo since 1965

Investigator(s)	Type of patient, etiology of pain, or both	Aspirin dose (milligram)
Bloomfield, et al. (reference 6)	Episiotomy	600.
Bloomfield and Hurwitz (reference 7)	Tourniquet and episiotomy	1,200.
Bloomfield et al. (reference 8)	Episiotomy	650.
Calimlin et al. (reference 9)	Postoperative	650.
Cooper and Beaver (reference 10)	Oral surgery	650.
Hill and Turner (references 11 and 12)	Postoperative	600.
Lamphier et al. (reference 13)	Postoperative	325.
Moertel et al. (reference 14)	Pancreatic cancer pain	650.
Moertel et al. (reference 15)	Various, mild to moderate	650.
Moertel et al. (reference 16)	Cancer	650.
Murray (reference 17)	Headache	648.
Parkhouse et al. (reference 18)	Postoperative	300 to 1,200.
Parkhouse et al. (reference 19)	Postoperative	600.
Stenport (reference 20)	Orthopedic, postoperative	600.

In 1967, Murray compared placebo, 648 mg aspirin, 325 mg acetaminophen plus 325 mg salicylamide, and 487 mg acetaminophen plus 487 mg salicylamide in medical and pharmacy students with pain due to headaches (Ref. 17). He found that aspirin produced relief in 78 percent of the cases, placebo in 46 percent and the acetaminophen-salicylamide mixtures in 69 percent and 76 percent, respectively. All medications were found to be statistically superior to placebo but no significant differences were found among the drugs tested. The importance of this study is that the pain

evaluated was that from common headache, the most frequent reason for aspirin ingestion.

The blood level below which aspirin is ineffective as an analgesic has not been adequately demonstrated because analgesia has not been shown to correlate directly with levels of salicylates in the blood. However, Beaver noted that the use of graded doses can illustrate the threshold phenomenon (Ref. 3).

In another study by Murray, a group of medical and pharmacy students used graded doses of aspirin to treat headache (Ref. 21). He showed that 163 mg

and 325 mg doses of aspirin did not statistically differ from placebo response. Results were significant, however, in those using 650 mg of aspirin. An intermediate dose of about 500 mg was not used in this study. It would appear that a minimum dose of between 325 and 650 mg is necessary for significant headache analgesia, but additional studies are necessary to confirm this.

In addition, once some measurable level of analgesia is achieved, its duration and intensity also do not necessarily correlate with salicylate levels in the blood (Ref. 3).

However, with regard to intensity of analgesia, Murray demonstrated an increase in analgesia when the dose of aspirin was increased from 325 mg to 650 mg (Ref. 21). A study by the Veterans' Administration Cooperative Analgesic Study Group also showed a difference in analgesic effect between 300 and 900 mg aspirin in patients with post-operative pain (Ref. 22). In this study even the low dose of 300 mg was significantly better than the placebo.

In another study, Modell and Houde showed a dose related increase in pain relief when 400 mg, 600 mg and 900 mg aspirin were administered to patients with cancer (Ref. 23).

Kantor found that within a population of postpartum patients there were two response groups. The patients whose main complaint was pain following episiotomy (a surgical incision made to aid removal of the infant from the vagina) were able to discriminate between 300 mg and 600 mg doses of aspirin while those patients whose main complaint was uterine cramp pain could not (Ref. 2).

Bloomfield et al. in a double-blind study performed in 1967, were unable to show a significant difference between the analgesic effects of 300 mg and 600 mg doses of aspirin. However, both levels of aspirin were significantly more effective than placebo (Ref. 6). Later in 1970, Bloomfield et al. confirmed Kantor's results regarding the differing levels of effectiveness of aspirin in relieving the pain of episiotomy (Ref. 7).

Hill and Turner (1969) approached the analgesic evaluation problem from a different point of view. In a double-blind study, aspirin was compared to the narcotic analgesic meperidine in patients with post-operative pain ranging from "mild" to "severe." They concluded that aspirin was preferred at the milder levels of pain while meperidine was preferred at the severe pain levels (Ref. 11). However, these same researchers in another double-blind study in patients with pain following gynecological surgery could not differentiate meperidine, aspirin and placebo "in the patient population as a whole" but could distinguish them when patients were classified as to the initial severity of their pain (Ref. 12). This latter study could have been insensitive if the pain intensity had not been considered and illustrates one of the inherent difficulties in analgesimetry.

Moertel et al. (1971) have evaluated the analgesic effect of 650 mg aspirin as

compared with 60 mg codeine sulfate in patients with pain due to unresectable carcinoma (cancer) and found that pain relief with aspirin exceeded that of codeine (Ref. 14).

Moertel et al. (1972) compared 650 mg aspirin to 250 mg mefenamic acid, 50 mg pentazocine, 650 mg acetaminophen, 650 mg phenacetin, 65 mg codeine, 65 mg propoxyphene, 25 mg promazine, 75 mg ethoheptazine, and placebo all given orally to patients with pain due to unresectable cancer (Ref. 16). They concluded that aspirin was "superior to all agents tested."

Recently, Moertel et al. (1974) studied aspirin as a single ingredient and in combination. Aspirin 650 mg again proved significantly better than placebo. Neither 32 mg pentobarbital nor 65 mg caffeine appeared to increase efficacy in patients with cancer. However, adding 65 mg codeine, 25 mg pentazocine, or 9 mg oxycodone did significantly increase pain relief (Ref. 15).

While the effectiveness of aspirin is undisputed, there are limitations to its use which must be kept in mind. There are wide individual variations in response to all analgesics, and while aspirin is generally effective in relief of mild to moderate pain, it is only of limited value in relief of severe pain.

The Panel recognizes that pain is only a symptom of an underlying pathologic state and if it is severe or persists, medical attention should be sought. Thus, it finds the following warning necessary, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician".

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(2) **Safety.** As noted earlier in this document, aspirin is the most widely used single drug in the United States. The Panel believes that in light of this extensive use and long marketing history and the relatively low incidence of serious toxic effects associated with short term use of presently recommended doses, the safety of aspirin has been well-established for the majority of the population and the risk/benefit ratio is low. However, the Panel wishes to make clear that this does not mean that aspirin has no adverse effects. In fact, the Panel has identified eight areas of concern where aspirin may have some potential for adverse effects including effects on organ systems, i.e., gastrointestinal tract, central nervous system, kidney, liver and the blood; specialized effects on hypersensitive individuals, persons with certain disease states or during pregnancy; or when used concomitantly with other drugs. The Panel believes that subsets of the population at risk can be identified so that adequate

labeling can be established to provide for safe OTC use of the drug. The safety of aspirin is discussed below. The Panel has reviewed the metabolism of aspirin elsewhere in this document. (See part I, paragraph K, above—Absorption, Distribution, Biotransformation (Metabolism) and Excretion of Aspirin and Salicylates in Man.)

Because of the extensive use and research on this drug, the Panel has been able to identify many of the safety considerations and has summarized them in the following table:

SUMMARY OF SAFETY CONSIDERATIONS WITH USE OF ASPIRIN

ADVERSE EFFECTS ON THE BLOOD

Aspirin interferes with blood clotting. Persons with a history of blood coagulation defects, or receiving anticoagulant drugs or with severe anemia should avoid the drug.

ADVERSE EFFECTS ON THE GASTROINTESTINAL TRACT

The drug may potentiate peptic ulcer, cause stomach distress or heartburn. Aspirin causes an increase in occult bleeding and in some persons massive gastrointestinal bleeding.

ADVERSE EFFECTS ON HYPERSENSITIVE INDIVIDUALS

Aspirin produces allergic and anaphylactic reactions in hypersensitive individuals, especially certain types of asthmatics, ranging from rash, hives and swelling to asthmatic attacks which may be life-threatening.

ADVERSE EFFECTS DURING PREGNANCY

Aspirin interferes with maternal and infant blood clotting and lengthens the duration of pregnancy and parturition time. Aspirin produces teratogenic effects in animals and increases the incidence of stillbirths and neonatal deaths in humans.

ADVERSE EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Aspirin when taken in overdose produces stimulation (often manifested as tinnitus) followed by depression of the central nervous system.

ADVERSE EFFECTS ON THE KIDNEY

Aspirin may rarely cause an increase of existing severe kidney disease.

ADVERSE EFFECTS ON THE LIVER

High doses may produce a reversible hepatic dysfunction.

ADVERSE EFFECTS OF CONCOMITANT USE WITH OTHER DRUGS OR BY PERSONS WITH CERTAIN DISEASE STATES

Aspirin interferes with some anticoagulant and antidiabetic drugs, some drugs used for the treatment of gout and may have an additive ulcer-producing effect with some drugs used in arthritis.

ADVERSE EFFECTS RESULTING IN IRON DEFICIENT ANEMIA

Aspirin used chronically may cause persistent iron deficient anemia.

(i) *Adverse effects on the blood.* In addition to the well-known association between aspirin ingestion and gastrointestinal bleeding discussed below, aspirin and salicylic acid have been implicated but not always proven as factors in bleeding from the skin, throat (posttonsillectomy), nose, rectum, vagina, postsurgical wounds and dental extraction sites (Refs. 1 through 6). The major hemostatic mechanisms involved are the effects of aspirin and salicylates in large doses on prothrombin production and the effects of aspirin in small doses (but not salicylates) on platelet function, which results in an increased bleeding time and possibly other effects such as fibrinolysis (Ref. 7).

(a) *Decrease in prothrombin production.* High doses of aspirin and salicylic acid (6,000 to 10,000 mg daily) taken for several days can cause hypoprothrombinemia, i.e., a decrease in the amount of prothrombin (blood clotting factor II) in the circulating blood (Refs. 1 and 4) which may be reversed by vitamin K (Ref. 5). However, it is important to emphasize that this effect of salicylates does not usually result in clinically significant alteration of the coagulation mechanism except in patients who may be particularly susceptible. Susceptible patients include those receiving anticoagulant therapy; patients consuming high doses of aspirin or salicylates chronically, e.g., patients with rheumatoid arthritis; patients with liver disease which limits the production of prothrombin (blood clotting factor II); and patients with malabsorption syndrome or gastrectomy leading to a deficiency of vitamin K, which is a substance required for prothrombin synthesis (Ref. 8).

As noted above, hypoprothrombinemia is produced by both aspirin and other salicylates when taken in high doses. In one study a daily total dose of 3,200 mg sodium salicylate produced no change in prothrombin time, 6,600 mg produced a slight change and 10,000 mg produced a marked change in prothrombin time (Ref. 6). Aspirin or salicylate-induced hypoprothrombinemia has been implicated in posttonsillectomy bleeding, epistaxis (nose bleed), and postdental extraction bleeding (Refs. 9 and 10), although other mechanisms such as a platelet effect (discussed below) may be involved.

(b) *Increased bleeding time and inhibition of platelet aggregation.* Aspirin increases bleeding time and inhibits the *in vivo* and *in vitro* aggregation of platelets.

Bleeding time is defined as the duration of time that bleeding continues after a superficial puncture of about 1 mm is made in the skin. This occurs with doses of aspirin far below those required for a hypoprothrombinemic effect. The effect of aspirin on bleeding time in a patient with bleeding tendencies was noticed many years ago by Frick who attributed it to an effect of aspirin on capillary fragility (Ref. 11). Later, Quick showed that 2 hours after ingestion of 1,300 mg aspirin, but not sodium salicylate, a small

but significant increase in the bleeding time occurred in normal subjects. A much greater increase was observed in patients with mild coagulation defects such as von Willebrand's disease and hereditary telangiectasia (Ref. 12). Quick postulated that aspirin, due to the presence of the acetyl group, may interfere with or compete with some vascular factor, such as cholinesterase, involved in the vascular tone of small vessels (Ref. 13). However, the results of a recent study submitted to the Panel, demonstrated, by an *in vitro* method, that aspirin did not have any effect on cholinesterase inhibition (Ref. 14). In the study, aspirin, salicylic acid and physostigmine (a known inhibitor) were compared. The dosages of aspirin and salicylic acid were correlated to the average amount of non-protein bound aspirin and salicylic acid found in human plasma up to 2 hours after ingestion of two aspirin (650 mg) tablets. The findings indicated inhibition with physostigmine and none with aspirin or salicylic acid. The investigators concluded that "this information, obtained with dilute enzyme preparations, suggests that *in vivo* cholinesterase concentrations are too substantial for aspirin doses, at least recommended doses, to have any influence." Still, others have proposed that inhibition of prostaglandin synthesis leads to vasodilation and pooling in the microcirculation (Ref. 5). While, as yet undiscovered, direct effects on the blood vessel or vasoactive mediators may prove to be a factor, it is presently well established that the primary effect of aspirin on bleeding time and hemostasis is due to a potent irreversible effect on platelet function which inhibits the *in vivo* and *in vitro* aggregation of platelets.

The effects of aspirin on platelet function were shown almost simultaneously by several independent groups (Refs. 15, through 20). The effect of a single dose of 1,500 mg aspirin on platelets will persist 2 to 3 days and not completely disappear for 4 to 7 days (Ref. 15). Since this is roughly the life span of a platelet, it indicates irreversible damage to platelet function.

Weiss and Aledort reported that bleeding time was increased by a mean value of 3.3 minutes in 10 normal male subjects receiving 350 mg aspirin (Ref. 16). They first reported that aspirin interfered with platelet connective tissue reaction by inhibiting the release of adenosine diphosphate (ADP) which results in prolongation of bleeding time.

Mielke et al. showed the standard Ivy Test to be very reproducible when the wound is standardized ("template bleeding time") (Ref. 21). Aspirin 975 mg (15 gr) increased the mean bleeding time from 5.5 minutes to 9.5 minutes on repeated tests by different investigators (Ref. 19). The population distribution of this trait appeared to be heterogeneous.

Mielke and Britton found that a 300 mg dose of aspirin each day maintained the prolongation of bleeding time and that no greater effect was obtained with higher doses (900 or 2,700 mg) (Ref. 22).

Other analgesic drugs which show marked inhibition of platelet aggregation include indomethacin, ibuprofen, mefenamic acid, and amidopyrine. Less effect was noted with oxyphenbutazone. No effect was noted with sodium salicylate or phenacetin (Ref. 23).

The importance of the platelets as the first line of defense in hemostasis has been established in recent years (Refs. 24 and 25). Platelets adhere to exposed collagen fibers within seconds after damage occurs to small vessels. This interaction results in a release of ADP which facilitates platelet aggregation into a loosely (first phase) and then tightly (second phase) packed plug. The plug formation precedes the formation of a fibrin network which eventually forms a clot. It is now known that aspirin inhibits ADP release in phase one and/or phase two aggregations and also in the initial interaction with collagen fibers. Plug formation may be relatively unimportant when major arteriolar damage occurs because other available mechanisms are more effective; but it is thought to be an extremely important hemostatic mechanism in capillary (oozing) bleeding (Refs. 24 and 26).

This type of bleeding is now believed to be involved in the types of gastrointestinal bleeding that are potentiated by aspirin (Refs. 25, 27, 28, and 29) as well as other sites of bleeding such as the posttonsillectomy tonsillar bed, or surgical wounds, or tooth sockets following dental extractions (Refs. 25 and 30). The demonstrated effect of aspirin on platelet function and the importance of this process in the hemostasis of oozing type of small vessel bleeding provides a consistent mechanism for the wide variety of sites of bleeding that have been associated with aspirin. Some of these types of bleeding are briefly reviewed below.

Nonthrombocytopenic purpura (bleeding in the tissues in a patient with a normal platelet count) associated with aspirin ingestion has been described as a hypersensitivity reaction (Ref. 31). However, idiosyncrasy was ruled out in three cases of purpura in children with normal platelet counts who received usual doses of aspirin (Ref. 32). The authors attributed the bleeding to a demonstrated platelet dysfunction due to inhibition of ADP release following aspirin therapy, rather than vascular or hypersensitivity reactions. It is of interest that in two cases with no family history of bleeding disorders, the patients were sisters (9-year-old and 14-month-old). However, the father on two occasions within a 3-year period had experienced severe gastric bleeding after a single intake of 2,000 and 1,000 mg doses of aspirin, respectively.

Buettinghaus and Tenhaeff (1973) stated that 16 of 24 patients taking aspirin developed hematoma (a swelling filled with extravasated blood) in the wound regions following abdominal surgery or hysterectomies (Ref. 33).

De Vries and Ten Cate have suggested that thrombocyte damage may be responsible for many cases of menorrhagia (excessive menstrual discharge), post-

extraction bleeding in dentistry, and chronic purpura (hemorrhage into the skin resulting in discoloration) (Ref. 34).

Several cases of massive hemorrhage from the tonsillar bed following topical application of aspirin through gargles or aspirin-containing chewing gums have been reported (Ref. 35). Hemorrhage was observed in 8 percent of 100 posttonsillectomy patients medicated with aspirin (Ref. 36). The bleeding occurred on the 6th or 7th postoperative day and could be controlled only with packing and suturing. No hemorrhage occurred in the 100 patients medicated with acetaminophen in an identical manner. Similar results were also reported by Hersh who carried out a controlled study in patients having dental extractions (Ref. 30). Hersh (Ref. 30) conducted a randomized controlled study in patients undergoing dental extraction. Those not taking an aspirin-containing analgesic in the 7 days prior to dental extraction were given either aspirin or acetaminophen for post-tooth extraction pain. Significantly more bleeding was noted among those who received aspirin. Of those patients among the 516 studied who had taken aspirin in the 7 days prior to extraction and who were continued on aspirin, the incidence of postextraction bleeding was the largest of the three groups studied.

A high incidence of posttonsillectomy hemorrhage was also reported by Fox and West (Ref. 37) in children given an aspirin-containing chewing gum. The incidence of bleeding was said to be decreased by 99 percent when use of the gum was discontinued. In view of these reports, the Panel has recommended that all aspirin oral product formulations to be chewed (chewable tablets or gums) should contain the following warning: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician". The Panel has discussed chewable tablets and gums earlier in this document. (See part II, paragraph J.2.a. above—Solid dosage forms.)

The effects of aspirin on hemostasis in the newborn may be particularly hazardous since infants metabolize drugs slowly and are particularly susceptible to central nervous system hemorrhage (Ref. 25). Bleeding episodes in newborns may be higher in those whose mothers have taken aspirin during the 2 weeks prior to delivery. Alteration of platelet function in infants of mothers who ingested aspirin within 2 weeks of delivery has been reported by Bleyer and Breckenridge (Ref. 38), and Corby and Schulman (Ref. 39).

Bleyer and Breckenridge have studied the effects of prenatal administration of aspirin on the blood clotting of newborns. Two potentially serious drug effects were detected in infants born of mothers who had taken ordinary doses of aspirin during the last 2 weeks of pregnancy. They indicated that an aspirin-induced decrease in clotting ability may have clinical relevance particularly during difficult traumatic deliveries or in the presence of other clotting defects (Ref. 38). The effects of aspirin on ma-

ternal and newborn hemostatic mechanisms are discussed in more detail later in this document. (See part III, paragraph B.1.a. (2)(iv)(c) below—Effects on maternal and newborn hemostatic mechanisms.)

(c) *Relationship between systemic platelet effects and gastrointestinal bleeding.* Massive gastrointestinal bleeding which is discussed below, is the most frequent serious bleeding problem associated with aspirin. Several authors have recently pointed to the probable role of aspirin-induced platelet dysfunction in gastrointestinal bleeding (Refs. 5, 15, 24, 26, 29, and 40). There is growing evidence that the systemic effect of aspirin on platelets is a significant factor in a causal relationship between aspirin ingestion and subsequent gastrointestinal hemorrhage. Several lines of reasoning and recent experimental evidence support this conclusion.

Aspirin-induced platelet dysfunction will significantly promote bleeding when the platelet plug is the primary factor in hemostasis. This is usually true for the oozing type of bleeding which occurs from capillary beds. An argument against the role of platelet dysfunction in gastrointestinal bleeding has been that bleeding occurs from ulcers which involve extensive tissue and arteriolar damage (Ref. 26). This type of bleeding requires hemostatic mechanisms other than platelet plugs, such as vasoconstriction and fibrin clots, to stop bleeding. Even a significant reduction in the platelet function would not be sufficient to alter the degree of bleeding from these types of sites (Ref. 25). However, recent studies involving direct endoscopic observation of the bleeding lesions have shown that bleeding occurs most often not from ulcers but from inflamed mucosal tissue which is partially denuded of surface epithelium exposing engorged, hyperemic and dilated capillaries in the underlying lamina propria. This histological picture is characteristic of acute gastritis and duodenitis which gastroenterologists state are most often involved in massive gastrointestinal hemorrhage associated with recent aspirin ingestion (Refs. 28 and 41). It is also precisely the vascular condition which many hematologists state is most dependent upon platelet plugs to stop bleeding (Refs. 25, 26, and 29).

Gast (Ref. 42) has pointed out that alteration of platelet function alone is usually not sufficient to initiate bleeding. This is evident in the bleeding episodes due to aspirin described above which usually involve tissues subjected to prior injury, e.g., tonsillectomies. Thus, gastrointestinal bleeding involving platelet dysfunction would generally require other factors to be present to initiate epithelial and capillary damage and perhaps to promote local blood flow (Ref. 43). This is consistent with the relatively infrequent and sporadic incidence of massive gastrointestinal hemorrhage relative to the high incidence of aspirin use and current theories on the multiple factor etiologies of massive gastrointestinal bleeding (Ref. 44). It is also consistent with the difficulty of de-

veloping a suitable animal experimental model or designing adequate epidemiologic studies to define causal relationships. Some experimental evidence to support the role of platelet function in gastrointestinal hemostasis was presented by Schmid et al. (Ref. 31). These authors showed that decreased platelet function produced by aspirin, but not sodium salicylate, correlated with the extent of blood loss following aspirin ingestion. It is perhaps significant that virtually every compound tested thus far (including indomethacin and phenylbutazone), showing a significant deleterious effect on platelet function, has also been demonstrated to cause massive gastrointestinal bleeding. Recently, amidopyrine which has strong deleterious platelet effects was reported to be the cause of massive gastrointestinal bleeding (Ref. 45).

More information is needed on the relationship between gastrointestinal bleeding and platelet function. However, the Panel believes there is convincing evidence that the systemic effects of aspirin on platelet function are quite likely to be a factor in the aspirin-induced gastrointestinal hemorrhage. This systemic effect is independent of the dosage form used.

For the various reasons discussed above, the Panel has concluded that because aspirin can promote or increase bleeding after it has been absorbed into the bloodstream all preparations containing aspirin regardless of formulation should bear the following warning: "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician". The Panel concludes that this recommended warning should also apply to all salicylates. (See part III, paragraph B.1. below—Category I Labeling.)

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(ii) Adverse effects on the gastrointestinal tract. Aspirin has several adverse effects on the gastrointestinal tract. These range from relatively mild effects such as gastric distress (minor stomach pain, heartburn or nausea), superficial mucosal irritation and minor occult (unseen) bleeding, to less frequent but more serious effects such as mucosal erosion, ulceration or life-threatening massive bleeding from a variety of gastrointestinal sites. The Panel concludes that all products containing aspirin should include the labeling warning, "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

The direct and indirect roles of aspirin in producing or potentiating these different types of mucosal damage or bleeding in the gastrointestinal tract are complex and have been controversial. Disagreement, in part, has been due to the many interacting variables related to drug use and to the disease processes involved.

Disease variables of interest relative to safety and labeling include the increased incidence, and severity of adverse effects associated with aspirin use, the site and mechanisms involved and whether aspirin causes, potentiates or exacerbates particular types of gastrointestinal conditions. Important drug variables considered by the Panel include the usual dose required to produce these effects, and whether the effects involve acute (1 to 5 days) or chronic (several months) use of aspirin. Particular attention was given to claims that adverse effects may be reduced by a particular type of dosage form such as buffered tablets or highly buffered effervescent solutions. Buffered aspirin can reduce the incidence of minor effects but not serious disorders, such as massive bleeding.

The Panel concludes that aspirin should not be used by individuals with a recent history of peptic ulcers or gastrointestinal bleeding because of the increased incidence of gastrointestinal bleeding in such individuals following acute and chronic aspirin ingestion. Furthermore, because recurrent gastric distress is such a common symptom in upper gastrointestinal tract disease which predisposes individuals who experience massive, life-threatening, gastrointestinal hemorrhage regardless of the presence or absence of ulcers, the Panel recommends that individuals with gastric distress should not take aspirin without the advice of their physician.

There is now sufficient evidence to indicate that some individuals taking aspirin chronically may develop gastric ulcers. Therefore, use of aspirin in chronic conditions such as arthritis is not advised without proper medical supervision and surveillance to avoid development of these untoward effects.

Muir and Cossar (Ref. 1) in 1961 stated that a plethora of information supports the following conclusions: "People with peptic ulcer should not take aspirin; people who have aspirin dyspepsia are in danger of serious gastric hemorrhage under circumstances as yet undefined."

(a) *Gastric distress.* Gastric distress or gastric intolerance including dyspepsia (heartburn), nausea and epigastric pain is a subjective response that can occur after usual doses of aspirin and salicylates in about 2 to 10 percent of the normal population (Refs. 1 through 7). The incidence or severity of gastric distress caused by aspirin is not necessarily related to acute gastric erosion (Refs. 7 and 8) and massive bleeding can occur with no pain (Ref. 9). However, dyspepsia prior to and after aspirin ingestion occurs more frequently in patients with peptic ulcers, gastritis and duodenitis (Refs. 10 and 11).

Buffered aspirin tablets are claimed to reduce the incidence of gastric distress to aspirin which may be true in a small number of normal individuals (Refs. 12 and 13). (See part II paragraph J.2.a. above—Solid dosage forms.) The Panel has discussed a suitable labeling claim for buffered aspirin products which is classified as Category III and discussed elsewhere in this document.

(See part VI, paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Gastric distress appears to provide one of the best means of identifying a high percentage of individuals who may be at risk of gastrointestinal hemorrhage after aspirin ingestion. Gastric distress can be categorized according to its cause as follows: Gastric distress caused by an underlying gastrointestinal disease which predisposes a person to bleeding; gastric distress related to recent aspirin ingestion; and gastric distress related to temporary problems unrelated to drug use or serious underlying gastrointestinal disease.

Several studies involving massive bleeding show that most patients experienced gastric distress, usually recurrent epigastric pain prior to their bleeding episode. Gastric distress occurs in 60 to 70 percent of patients with hemorrhagic gastritis (Refs. 14 and 15). In ulcer patients, the incidence of recurrent gastric distress may be 90 percent (Refs. 16 and 17). Patients who develop gastric ulcers because of chronic aspirin use frequently have gastric distress (Refs. 18 and 19).

The incidence of gastric distress after taking aspirin is much higher in patients with severe gastrointestinal disease. Muir and Cossar (Ref. 3) in 1955 stated that dyspepsia after aspirin ingestion is six times greater in patients with peptic ulcer as compared to normal subjects. Roth states that dyspepsia occurs in about 7 percent of normal subjects, 10 percent of rheumatoid arthritis patients and 33 percent of peptic ulcer patients (Ref. 11). Although individuals with an active peptic ulcer are not unusually susceptible to aspirin-induced occult bleeding, they do have an increased susceptibility to dyspeptic symptoms (Refs. 8 and 11).

Vining (Ref. 20) in 1957 reported a higher incidence of gastric distress in rheumatoid arthritis taking aspirin chronically, occurring in about one out of four of this group. However, in a carefully performed study, Stubbe (Ref. 21) in 1958 found no difference in occult bleeding between rheumatoid arthritis and normal subjects indicating as in other studies that there is no correlation between occult bleeding and incidence of gastric distress. (See Part III, paragraph B.1.a.(2)(ii)(e) below—Occult bleeding.)

Alvarez and Summerskill (Ref. 22) in 1958 stated that 80 percent of all patients who experienced major gastrointestinal bleeding after aspirin ingestion had proven histories of either duodenal or gastric ulcer, or dyspepsia.

The Panel concludes that by merely identifying those patients with a history of gastrointestinal ulcer or recurrent gastric distress, e.g., dyspepsia, it may be possible to warn as many as 80 percent of the high risk population.

(b) *Direct mucosal damage.* The Panel concludes that aspirin (and salicylic acid) have a direct local irritant effect on all the surface mucosal cells lining

the gastrointestinal tract (Refs. 1, 6, 10, 23, and 24). The effect is acute and occurs in most normal individuals (Ref. 10) and has also been demonstrated in several animal species (Refs. 6, 25, and 26). Prolonged contact with aspirin produces direct damage (focal necrosis) and sloughing (desquamation and exfoliation) of surface cells (Refs. 6, 8, and 10). Erosion can occur in the mouth (Refs. 6 and 27), rectum (Refs. 28 and 29) and stomach mucosa (Ref. 6) with concentrated solutions of aspirin (Ref. 26), and with particles of plain, buffered and combination aspirin tablets (Ref. 6).

(1) *Mucosal erosion of the mouth.* Aspirin-containing gum has produced a severe lesion of the inner wall of the cheek which promptly healed upon discontinuation (Refs. 27 and 30). Kawashima et al. (Ref. 30) in 1975 reported that aspirin tablets applied directly to the mucous membranes of the mouth for a local anesthetic effect have resulted in oral lesions on the roof of the mouth. Roth et al. (Ref. 6) found that aspirin preparations (tablet) allowed to remain in contact with mucous membranes of the mouth for 30 minutes produce a white opaque buccal mucosa capable of being peeled off with the slightest manipulation. They placed a quarter of several commercial plain, buffered and combination aspirin tablets between the lower lip or cheek and gums of 26 normal subjects for 30 to 60 minutes. In every case the aspirin produced an irregular opaque lesion with sloughing of cells characteristic of acute superficial necrosis.

(2) *Rectal irritation.* The Panel concludes that aspirin taken rectally in a suppository dosage form may have a direct local irritant effect on surface mucosal cells. The irritating effect of rectally administered aspirin can be alleviated by changes in the composition of the matrix of the suppository vehicle. The adverse effects of aspirin appear to be related to the chemical composition of the suppository base (Refs. 31 and 32) and to the rate of absorption of aspirin from the suppository base (Ref. 33).

Aspirin suppositories (1,300 mg aspirin per suppository) made of a cocoa-butter or a carbowax base were administered to dogs every 4 hours for a total dose of 3,900 mg daily for 3 days (Ref. 31). The experimental dogs in the study all showed signs of mucosal irritation. The irritation ranged from a distinct hyperemia to hemorrhagic ulcerative lesions. Perforations and death also occurred. The four dogs receiving the control suppository bases showed no rectal mucosal changes. The authors concluded that "prolonged rectal administration of aspirin suppositories may be potentially hazardous" and recommended that "additional studies to evaluate the extent of irritation and ulcerative hemorrhagic lesions in the human rectum following repeated administrations of aspirin suppositories seem to be indicated." Serum salicylate determinations in 40 human subjects administered 650 mg aspirin orally (tablets) and rectally (cocoa-butter base suppositories) indicated that the oral route pro-

vided significantly higher blood salicylate levels (p is less than 0.001) than the rectal route (Ref. 31).

In a study reported by Cacchillo and Hassler (Ref. 32), 11 male volunteers were administered 650 mg aspirin in one of three different types of suppository bases on 1 day for 3 successive weeks. On the fourth week, 650 mg aspirin (tablets) was given orally to compare the oral route with the rectal route. The three suppository bases were cocoa butter, Carbowax and glycerinated gelatin. There was virtually no rectal irritation from aspirin suppositories formulated with cocoa butter and Carbowax as the bases. Glycerinated gelatin based suppositories showed a high incidence of prolonged burning and pain, and the subjects evidenced a very strong desire to expel the suppository. There was no statistically significant difference between the absorption of aspirin orally and the absorption of aspirin from the Carbowax base only. The authors state that "individual studies must be undertaken to determine for each drug the base best suited for its absorption." In this study, Carbowax unlike the other two bases, not only showed that "the rectal dosage given is equivalent to the oral, as a high degree of absorption through this vehicle is assured when employed rectally", but also that "little or no irritation" occurred.

The rate of absorption of aspirin rectally was related to the incidence of irritation in a study by Borg, Ekenved, Eilofsson and Sjogren (Ref. 33). They formulated suppositories with two neutral triglyceride mixtures as the bases, i.e., Witepsol H15 with a melting range of 33.5° to 35.5° C and Witepsol E75 with a melting range of 37° to 39° C. Male volunteers were administered 750 mg and 1,000 mg aspirin in these formulations in two studies to investigate the absorption of aspirin from the suppositories. In another study, the investigators administered the two aspirin suppository formulations on the first 2 days of the week for 3 consecutive weeks. A dose of two suppositories daily, 8 hours apart, was administered. There was a difference in the rate of absorption of aspirin from the two bases. It was found that a rapid absorption was associated with a high incidence of side effects. Reducing the rate of absorption by changing the suppository base, reduced the intensity and frequency of the side effects. The side effects consisted of burning pain, blood in the feces, diarrhea and tenesmus. The authors point out that with the use of bases giving reduced absorption and reduced side effects, however, the amount of drug absorbed from suppositories "will be highly dependent on the length of time the patient retains the suppository."

(3) *Stomach mucosal damage.* Aspirin has a direct damaging effect on mucosal tissue which is not dependent on the presence of hydrogen ion, bile or other cellular irritants associated with peptic ulcer (Ref. 6). Prolonged contact with aspirin particles or concentrated solution produces lesions in the mucosa of the mouth, stomach, rectum and probably most other mucosal tissue (Refs. 6

and 28). Aspirin tablets placed directly on the gastric mucosa of anesthetized cats initially produced coagulation of mucus and opacification of the adjacent mucosa, similar to the appearance of the buccal (mouth) tissue exposed to aspirin (Ref. 6). These changes were attributed to coagulation of the mucous layer and desquamation (Ref. 8). Multiple small acute lesions showed focal necrosis with underlying secondary capillary damage. The direct mucosal desquamation and focal necrosis produced by aspirin has been observed in man by gastroscopic observations (Refs. 23, 24 and 34), during surgery (Refs. 1, 2, and 6).

The mucous opacity noted after aspirin irritation is related to epithelial exfoliation. Cellular exfoliation can be measured by increased DNA content in the gastric fluids since DNA is found only in cells and therefore reflects sloughed or damaged mucosal cells (Ref. 8). Accumulation of DNA in gastric fluid occurred in about 10 minutes in 9 of 12 subjects receiving aspirin (Ref. 8) which is similar to the percent of subjects showing direct irritation to aspirin in the gastroscopic studies of Douthwaite and Lintott (Ref. 23).

The direct observations by gastroscopist of the effects of aspirin on the gastric mucosa by Douthwaite and Lintott in 1938 have provided basic principles which have been substantiated by many investigators during the past 30 years. Specifically, gastroscopic observations of 16 hospital patients demonstrated the following: In 89 percent of the patients, a local inflammatory reaction of the gastric mucosa was observed ranging from slight hyperemia to submucous hemorrhage; and the occurrence and severity of the reaction was not a function of the brand of aspirin, the acidity of the stomach or the prior appearance or condition of the gastric mucosa. Patients with hyperchlorhydria (excessive acid secretion) had both positive and negative direct irritation responses. Responses were seen in patients with atrophic gastritis, hypochlorhydria (hydrochloric acid deficiency) and achlorhydria (absence of hydrochloric acid). Therefore, gastric acidity is not essential for initial direct irritation. Marked hyperemia with submucous hemorrhage (hemorrhagic erosive gastritis) occurred in 1 of the 16 patients. Salicylic acid also caused direct gastric irritation but was less severe. Contact with 20 percent alcohol for 10 minutes did not have a direct effect on the gastric mucosa.

The initial effects of aspirin, such as mucous destruction, epithelial desquamation, and focal mucosal necrosis takes the appearance of small well-demarcated erosions. This phase is not related to vascular damage or bleeding. It is apparently not dependent on the presence of gastric acid. Progression to visible hemorrhage may be dependent on local effects of gastric acid according to Davenport (Refs. 35 and 36) and/or possibly systemic effects (Ref. 6).

Roth found that phenacetin and acetaminophen have no direct irritating effect on the gastric mucosa (Ref. 6). However, phenacetin is claimed (but not

proven) to slightly increase occult bleeding (Ref. 37), perhaps indicating that the two events are not necessarily related.

(c) *Acid-mediated erosive gastritis.* In the stomach, the direct effect of aspirin or salicylic acid after being absorbed into the mucosal cell renders the cell more permeable to the hydrogen ions of the gastric acid (Refs. 35, 36, and 38 through 43). Absorption of aspirin or salicylic acid into the mucosal cell causes increased permeability via breakdown of the cell barrier, which normally protects the stomach lining from its own acid secretions. Excessive backflux of hydrogen ion into the cell further damages the cell, causing erosion (acute erosive gastritis). Excess hydrogen ions can also pass into the space just below the surface cell (lamina propria), which contains an extensive network of capillary blood vessels. Hydrogen ions can initiate capillary damage and subsequently, minor bleeding occurs into the lumen of the stomach (Refs. 35 through 41, 44, and 45). This mechanism, referred to as the hydrogen ion mediated effect or the Davenport mechanism has been extensively studied in animals (Refs. 35 through 41, 44, and 45). Many investigators believe that it is a major factor involved in the focal erosion and minor bleeding into the stomach (occult bleeding). This mechanism may contribute in some cases to gastritis and major gastrointestinal bleeding (Refs. 44 and 46).

There are some authors who believe that all gastrointestinal effects of aspirin from occult bleeding to hemorrhagic erosive gastritis to major gastrointestinal hemorrhage are all related to this single mechanism involving the back diffusion of acid (Ref. 46). As a corollary, it has been proposed that any preparation which neutralizes gastric acid during absorption will obviate the danger of severe gastrointestinal damage and massive bleeding (Ref. 47).

The Panel concludes that the acid-mediated gastric erosion induced by aspirin is undoubtedly an important factor in some adverse effects of aspirin on the gastrointestinal tract. It is probably associated with increased occult bleeding following single and multiple doses of aspirin. It may contribute at least in the beginning stages of aspirin-induced gastric ulcer caused by chronic doses of aspirin (Ref. 48). It is also probably a factor in hemorrhagic erosive gastritis directly initiated by multiple doses of aspirin. In this case it may initiate major bleeding. However, as will be noted in subsequent sections, there are other factors which can initiate hemorrhagic erosive gastritis and aspirin has other effects independent of gastric acid which may be of equal or greater significance in contributing to massive gastrointestinal bleeding.

(d) *Other mechanisms of aspirin damage.* The Panel agrees that there is very good evidence in both animals and man that the Davenport mechanism is one important effect of aspirin. However, to conclude that this mechanism is the only effect of aspirin on the gastrointestinal tract and thus the only basis

for aspirin's role in initiating, exacerbating, potentiating or facilitating gastrointestinal pathologies is not consistent with current experimental data and clinical studies.

(1) *Additional factors in the Davenport mechanism.* According to the Davenport theory, the absorption of unionized aspirin or salicylic acid into the cell carries hydrogen ion across the barrier into the cell or interstitial spaces where the pH is higher, where aspirin or salicylic acid are ionized and the hydrogen ion is dissociated. Hydrogen ion is thought to cause the release of vasoactive substances such as histamine, from mast cells, in the lamina propria, which initiates capillary bleeding. If the hydrogen ion flux associated with transport of the acids were the only factor, one would expect salicylic acid to cause greater occult bleeding than aspirin since it is more rapidly absorbed. Leonards and Levy (Ref. 49) have shown that salicylic acid (sodium salt) is more rapidly absorbed than aspirin in man, but it produces significantly less occult bleeding. Mean occult blood loss in 13 subjects was 6.3 ml, 1.9 ml, 1.2 ml and 0.7 ml for aspirin, salicylic acid, salicylic acid with buffer, and control respectively.

An explanation for the differences between aspirin and salicylic acid is that the direct cellular effects of aspirin and salicylic acid interfere at different concentrations with biochemical cellular process (Ref. 50) which affect the hydrogen ion barrier. Lower concentrations of aspirin are needed to initiate cellular dysfunction. Indeed the cellular effects of these agents are consistent with the direct mucosal effects seen in nonacid mucosal cells (mouth).

However, this would not explain why several anti-inflammatory agents cause gastric erosions and massive gastric bleeding but do not affect the hydrogen ion barrier and vice versa.

(2) *Relationship between aspirin damage and bleeding.* Studies using the gastric potential difference which is the most sensitive way to measure changes in the hydrogen ion barrier in man show that phenylbutazone and indomethacin in usual doses do not damage the hydrogen ion barrier (Ref. 51). However, they both produce major gastrointestinal bleeding and gastric ulcer (Refs. 51 and 52). These agents do not generally increase occult bleeding (Refs. 53 and 54) indicating the occult bleeding may involve the Davenport mechanism but not massive bleeding.

Conversely, some agents may affect gastric potential but do not cause bleeding. Indeed this was recognized by Davenport (Ref. 40) who raised the question "why does bleeding occur during back diffusion following salicylate injury and not during comparable diffusion after many other forms of injury." Bile can cause changes in the barrier at neutral pH which is said to be augmented by the effect of aspirin (Refs. 40 and 55). Some discrepancies can be resolved by considering additional direct and indirect effects of aspirin and other agents on mucosal blood flow.

(3) *Vascular effects.* In contrast to the Davenport mechanism which assumes the initial effect of aspirin is on the mucosal cell mediated through hydrogen ion possibly by causing release of histamine with secondary vascular involvement, there is evidence that in some types of hemorrhagic erosive gastritis the reverse occurs where the initial effect is on the mucosal vasculature.

Weiss et al. (Ref. 10) state that the primary local effect is direct vascular injury of the capillaries in the lamina propria followed by capillary hemorrhage and hypoxia (deprivation of oxygen) which produces necrobiosis of the neck cells and exfoliation of the gland.

It is now believed that some types of hemorrhagic erosive gastritis are caused by factors which directly initiate histamine release from the mast cells in the lamina propria as opposed to the hydrogen ion mediated release in the Davenport theory (Ref. 39). These factors may be involved in "stress ulcers", and atrophic gastritis. Thus regardless of the initial mechanism, whether hydrogen ion or stress, the common denominator is initiation of histamine release from the mast cells in the mucosal capillary region and initial vascular damage or reshunting of blood flow leading to hypoxia and a secondary cellular effect (Ref. 40).

Local capillary blood flow can apparently be affected by many diverse factors. The mechanism by which vagotomy decreases gastric bleeding may not be a result of decreased gastric acid as commonly stated but reshunting of mucosal blood from the capillaries. Nylander and Olerud (Ref. 56) reported that blood was reshunted from the mucosal capillaries through the direct arteriovenous shunts in the submucosa after vagotomy.

(e) *Occult bleeding.* Occult (unseen) bleeding is a common predictable occurrence related to normal aspirin ingestion. The average person (70 percent of the population) taking one or two tablets of aspirin 3 or 4 times daily will lose from 2 to 5 ml of blood per day into the stools due to the direct effect of aspirin on the gastric mucosa (mucous membrane of the stomach). Some individuals, about 10 percent of the population, may lose as much as 10 ml daily (Ref. 57). Occult blood loss is not decreased by food although aspirin dyspepsia is (Ref. 58).

This minor occult bleeding is not, usually, clinically significant except in those individuals taking aspirin for long periods of time who are anemia-prone or have bleeding tendencies (Refs. 49, 59, and 60).

The Panel has discussed the association of aspirin with iron deficient anemia elsewhere in this document. (See part III, paragraph B.1.a. (2) (ix) below—Adverse effects resulting in iron deficient anemia.)

The mechanisms involved in occult bleeding have been extensively studied in animals (Ref. 26) and to a lesser extent in man (Ref. 61). There is general agreement among most authorities that the primary mechanisms involve first, absorption of aspirin into the cell, followed

by the direct effects of aspirin on cellular metabolism and the integrity of the mucous membrane which initiates the subsequent indirect effects of gastric acid through the Davenport mechanism. By interfering with the integrity of the mucous membrane, aspirin increases the permeability of the membrane to the hydrogen ion which either further damages the cell or passes into the underlying space (lamina propria) containing the extensive capillary beds. Hydrogen ion either directly or indirectly through histamine causes capillary damage and small amounts of blood are lost into the lumen of the stomach.

The exact mechanisms involved in occult bleeding are not completely understood, however. Although gastric acid is known to be an important variable, it apparently is not essential since increased occult blood loss following aspirin is small but still greater than control values even in patients with a complete absence of gastric acid (achlorhydria) (Ref. 22).

In some studies there was no correlation between the number of erosions observed and the amount of occult bleeding (Refs. 42 and 62). In fact, carefully done studies (Ref. 62) show that visible erosions are not necessary in order to have increased occult bleeding. This may mean that the effect of aspirin to increase membrane permeability to hydrogen ion may require a lower concentration or require less exposure to aspirin than is needed to produce direct cellular damage and exfoliation. It may also indicate that multiple effects are involved.

Occult bleeding can be readily measured by well-known techniques used for the detection of blood in the feces, such as the use of radioactively-tagged red blood cells (Ref. 57). Therefore, there are many studies and reliable data available on the relationships between occult stomach bleeding and different types and formulations of analgesics (Ref. 58).

There is good evidence that the addition of sufficient buffering to decrease gastric acidity and increase the pH of the gastric contents will significantly reduce, but not necessarily eliminate, occult bleeding. However, highly buffered aspirin preparations will increase occult bleeding in normal subjects if given as multiple doses for 2 to 3 days (Ref. 63). In a few susceptible individuals who are otherwise apparently normal any aspirin preparation including highly buffered aspirin solutions, will greatly increase occult bleeding (Ref. 63).

While these individuals with unusual susceptibilities may provide some insight into the factors related to clinically important massive upper gastrointestinal bleeding, the average occult bleeding following aspirin ingestion in normal individuals or in individuals with peptic ulcer apparently has no relationship to massive bleeding (Refs. 6 and 9).

There appears to be no difference between the average increase in occult bleeding in normal individuals and major bleeders. Correlations between occult bleeding and massive bleeding have

never been shown. Occult bleeding and massive gastrointestinal hemorrhage could be considered as two distinct clinical entities (Refs. 7 and 8). The failure to recognize this difference has been stated to be responsible for much of the confusion in the literature (Ref. 8). Occult bleeding is a predictable occurrence in most normal people. Massive bleeding is relatively rare and unpredictable.

Persons with active peptic ulcer (Refs. 7 and 8) or persons who have recently experienced a massive gastrointestinal hemorrhage (Refs. 7 and 10) do not show greater occult bleeding after small doses of aspirin than normal subjects. These subjects, however, do have a greater propensity for recurrence of massive bleeding (Refs. 7 and 10).

Watson and Pierson (Ref. 64) in 1961 showed that occult bleeding was not greater in persons taking anticoagulants even though prothrombin activity was greatly reduced. Massive bleeding, however, has been associated with hypoprothrombinemia resulting from high doses of aspirin. (See part III, paragraph B 1 a. (2) (i) (a) above—Decrease in prothrombin production.) The amount of occult blood loss is less in individuals who have atrophic gastritis (Refs. 8, 61, and 65), and it occurs less frequently than in normals, presumably because these patients have decreased gastric acid. But, patients with atrophic gastritis are often involved in aspirin-induced massive bleeding and are at much greater risk of bleeding following aspirin than the normal population (Refs. 61 and 65).

The Panel concludes that occult bleeding resulting from aspirin ingestion appears to have very little correlative or predictive value in the diagnosis or study of the major clinically important gastrointestinal effects produced by aspirin such as ulceration and massive bleeding.

(i) *Gastric ulcers.* The Panel concludes that chronic use of aspirin may directly cause gastric ulcers (Refs. 16 through 19 and 66 through 86). Several types of studies show that chronic aspirin use significantly increases the incidence of gastric ulcers but not duodenal ulcers (Refs. 80, 81, and 82). Chronic use of aspirin is associated with an increased incidence of uncomplicated nonbleeding ulcers, bleeding from ulcers and perforated gastric ulcers (Refs. 18, 86, and 87). Epigastric pain is common in all of these cases. Continued use of aspirin can delay ulcer healing even though ulcer therapy is started (Ref. 18). Discontinuation of aspirin leads to rapid recovery (Refs. 3 and 18). Readministration of aspirin can re-activate gastric ulcer (Ref. 17).

Acute use of aspirin may activate symptoms of both gastric and duodenal ulcers. The symptoms and signs include both epigastric pain and massive gastrointestinal hemorrhage.

The role of acute aspirin use in the exacerbation of existing peptic ulcers has been noted by several authors over the past twenty years (Refs. 16 through 19 and 66 through 86). Evidence that chronic use of aspirin will increase the incidence of gastric ulcers has not been widely appreciated. In the opinion of the

Panel a causal role of chronic aspirin use and increased incidence of peptic ulcer is supported by several types of evidence. These include the demonstration that aspirin causes ulcers in animal models; direct observation of isolated cases in man; several recent well-controlled studies (in which disease-induced analgesic ingestion biases were eliminated); demonstration of increased gastric ulcer incidence in a population in which increased chronic use occurred due to abuse; evidence that characteristics of the lesion are different in aspirin users than nonaspirin users; and evidence that the site of the ulcer lesion can be affected by the dosage form used.

The Boston series (Ref. 84) conservatively estimated that 10 out of every 100,000 aspirin users would develop a non-bleeding gastric ulcer requiring hospital admission. This study estimated that one-eighth of all gastric ulcers were related to aspirin and Cameron found one-third of all new non-bleeding gastric ulcers are caused by chronic aspirin ingestion (Ref. 19).

Jorgensen and Gyntelberg (Ref. 88) determined the life incidence of peptic ulcer to be 9.2 percent in a sample of 5,249 men aged 40 to 59 in Copenhagen which is similar to the incidence reported in the U.S. In a one year followup study on 4,753 males the year incidence of peptic ulcer was 1.2 percent. Only 15 percent of these were new (previously diagnosed) ulcer cases and only 24 percent were hospitalized. Thus hospitalized new ulcer cases during the year accounted for only about 3.6 percent (15 percent \times 0.24) of total cases for the year.

Thirty percent of subjects ingested aspirin regularly compared to 16 percent of controls (p is less than 0.02). In only one of these subjects was aspirin taken for ulcer symptoms.

It can be estimated that 16 percent of the ulcer cases were associated with aspirin which is equivalent to a 19 percent annual incidence rate (19 per 1,000) for men between 50 and 59. However, only 3.6 percent of these (15 percent \times 0.24) would represent hospitalized new cases. Thus if only hospitalized new cases were used to calculate possible annual cases of aspirin-induced ulcer in 50 to 59-year-old men, one would conclude that the annual incidence associated 0.68 cases per 1,000 or 68 per 100,000 total population in the age group 50 to 59. This is similar to the estimate given by Levy of 10 per 100,000 of all adults taking aspirin since the incidence in women and younger adults would be lower. Thus the total incidence of aspirin related gastric ulcer may be higher than generally assumed.

There appears to be almost universal agreement that aspirin should not be used in persons with peptic ulcer, particularly those with gastric ulcers. Cameron (Ref. 89) states, "... the evidence presented suggests that patients with gastric ulcer should be urged to avoid aspirin." Similar warnings have been urged by Roth (Ref. 6), Brown and Mitchell (Ref. 86), Schneider (Ref. 24), Muir and Cossar (Refs. 2 and 3) and Weiss (Ref. 10).

Acute use of aspirin can precipitate massive hemorrhage in gastric and duodenal ulcer patients. The mortality of massive bleeding in peptic ulcer patients is about 8 to 10 percent (Refs. 67 through 70).

The Panel believes that initiation or exacerbation of stomach ulcers, stomach irritation and intestinal inflammation occurs in a significant number of individuals who take aspirin. Particularly at risk are those with a history or symptoms of gastrointestinal problems. Accordingly, a warning should state that individuals who have a history of ulcer, intestinal bleeding and stomach distress should not take aspirin without first consulting a physician.

Peptic ulcer has been estimated to occur in 5 to 10 percent of the general population at one time or another (Ref. 67). In 1967 it was estimated that 3.5 million individuals suffered from gastric ulcer (Ref. 70). Less than 0.5 percent of ulcer patients are hospitalized annually, involving hemorrhage in about 25 to 30 percent of these admissions (Refs. 67 and 68). Duodenal ulcer is about eight to ten times more frequent than gastric ulcer but the annual incidence of new cases per 1,000 adult male population at risk is 3.7 for duodenal ulcers and 1.4 for gastric ulcers. Gastric ulcers occur twice as frequently in men as in women (Ref. 69).

The direct ulcerogenic effect of long term aspirin use and massive bleeding following short term use are not necessarily related to the same factors. Gastric ulcers related to prolonged use of aspirin do not necessarily result in massive bleeding even though aspirin is frequently ingested by these patients (Ref. 15). Furthermore, aspirin is associated with massive bleeding in patients with duodenal ulcers but there is no evidence that aspirin produces duodenal ulcers (Ref. 84).

Kiser (Ref. 18) commented that the role of aspirin in the production of gastric ulcers has been underestimated because most studies have not dealt with the effects of prolonged aspirin ingestion with the exception of the studies by Douglas and Johnson (Ref. 74) and Muir and Cossar (Refs. 2 and 3).

Cameron (Ref. 19) points out that the protocol for a large Veterans Administration cooperative study on gastric ulcer published in 1971 excluded patients taking ulcerogenic compounds such as corticosteroids and phenylbutazone but did not mention aspirin. Patients and physicians in Cameron's study seldom associated aspirin with their ulcers.

(1) *Evidence for a causal role in gastric ulcer.* (i) *Direct observation in animals and man.* The properties of aspirin that produce direct erosive effects have been discussed earlier relative to acute erosions. Large acute erosions have been observed directly after drug intake in several instances (Ref. 3). Chronic administration of aspirin to animals consistently produces gastric ulcers (Refs. 18 and 66).

(ii) *Increased incidence of ulcer in analgesic abuse.* The unusually high incidence of analgesic use in Australia,

particularly in women, provides evidence for a causal relationship between aspirin, usually in combination, and chronic peptic ulcer. This population is significant from an epidemiologic point of view, not only because of the very high prevalence of chronic, daily aspirin use but also the significantly greater incidence of daily use by women compared to men, first noted by Billington in 1960 (Refs. 71 and 72). The increased use of analgesics by women who take analgesic compounds is clearly for other than gastro-intestinal symptoms. If increased chronic use of aspirin does result in a higher incidence of gastric ulcer, then this effect should be clearly evident in the Australian population. A correlation between increased analgesic use and increased incidence of ulcer was shown by Douglas and Johnson (Ref. 74) and confirmed by several others (Refs. 16, 17, 19, 76, 77, and 78). It is possible that phenacetin, an ingredient in almost all abused analgesic combinations, contributes to ulcer production. However, phenacetin alone does not have a direct damaging effect on the gastric mucosa (Ref. 6). Furthermore, ulcers are rare in patients taking phenacetin compounds not containing aspirin even though kidney disease continues to develop (Ref. 73).

It is possible, however, that the combined effect of phenacetin and aspirin may be greater than aspirin alone for the same reasons discussed later in the section on the effects of aspirin on the kidney. (See part III, paragraph B.1.a. (2) (vi)—Adverse effects on the kidney.)

Douglas and Johnson of Australia (Ref. 74) reported that 90 percent of 78 chronic gastric ulcer patients took a proprietary compound containing aspirin, phenacetin and caffeine. Most patients were chronic headache sufferers with pain predating the ulcer and were daily users of analgesic compounds containing aspirin. Compounds with phenacetin (or salicylamide) and caffeine were preferred by over 50 percent of this group. The usual reasons for use given by chronic users were chronic headache (41 percent), nerves and tension (31 percent), arthritis (21 percent), and indigestion (7 percent).

Gillies and Skyring (Ref. 77) in an interview study found a statistically significant association between chronic use of high doses of aspirin and the incidence of gastric ulcer. Fifty-seven percent of patients with active gastric ulcer had taken aspirin daily compared to 22 percent of controls. In earlier case-control studies, Gillies and Skyring (Ref. 77) found a significant correlation between high intake of aspirin and gastric ulcer but not intestinal ulcer.

Duggan and Chapman (Refs. 81 and 82) found a correlation between the incidence of gastric ulcer in women and the consumption of large amounts of aspirin, mainly as APC powders taken for headache. No such correlation for duodenal ulcer in either sex or gastric ulcer in males was found. Duggan (Ref. 82) followed all patients with acute perforated peptic ulcer in an Australian hospital over a 4-year period. The proportion of women in this series was very high (24

percent) compared to the usually very low incidence of gastric ulcer in women in British literature. The association between the use of high doses of aspirin over prolonged periods and the incidence of gastric ulcer was highly significant statistically particularly for the women. In men, 28 percent had a heavy intake of aspirin and 45 percent of ulcer patients took no aspirin. In the women, 62.5 percent had a heavy intake and only 25 percent took no aspirin. The authors state that aspirin abuse is the environmental factor responsible for the excess of gastric ulcer in middle-aged Australian women.

In a further study, Duggan (Ref. 90) analyzed the prognostic factors of 1,634 patients with acute gastrointestinal hemorrhage and found 66 percent of the cases had chronic ulcer and 25 percent involved an acute lesion. The total mortality was 11 percent. There was a statistically significant association between gastric ulcer and the incidence of chronic aspirin use. These patients had the worst prognosis. However, the reason for the poor prognosis probably reflects habituation of the individuals to the APC powder which was the usual compound taken by women in Australia. In other series, aspirin-induced gastric ulcers healed rapidly with a good prognosis when aspirin was withdrawn (Ref. 15). In the Duggan study the overall mortality for all forms of major gastrointestinal hemorrhage was 11 percent. The mortality of peptic ulcer patients who had gastrointestinal hemorrhage was 8.5 percent and was not related to whether or not the patients took aspirin.

(iii) *Case-control studies with controlled drug intake.* There have been three case-control studies in gastric ulcer patients that have been designed to avoid bias due to analgesic drug intake related to gastrointestinal pain.

Cameron (Ref. 19) in a prospective study with matched controls found that chronic aspirin use (15 tablets per week for 1 month or more) was associated with gastric ulcer in 53 percent of 61 patients compared to 10 percent of controls. When patients who took aspirin for their symptoms of ulcer were excluded, 45 percent of 40 ulcer patients took aspirin. The difference between ulcer cases and control subjects was highly significant statistically. When the same correction was applied to duodenal ulcer patients only 16 percent of the remaining 25 duodenal ulcer patients were regular aspirin users which was not statistically different (p is greater than 0.1) from controls.

(iv) *Characteristics of aspirin-related gastric ulcer lesions.* Aspirin-related gastric ulcer patients have lesions which are generally of the same shape, size and appearance as in nonaspirin ulcer patients. However, the location and distribution of aspirin-induced lesions in the stomach and the condition of the surrounding mucosa appear to be different. Interestingly, the distribution of aspirin lesions is apparently a function of the dosage form as well as the drug.

McDonald (Ref. 91) found that aspirin-related ulcers occurred most frequent-

ly on the greater curvature of the antrum. He claimed that only the aspirin-related ulcers were found in this region and were surrounded by normal pyloric gland mucosa. In the Minnesota series of Cameron (Ref. 19), the ulcer was within 1 inch of the pyloric sphincter in 65 percent of patients with gastric ulcer associated with heavy aspirin use, as compared to 21 percent of gastric ulcer patients taking no aspirin (p is less than 0.05). Cameron (Ref. 89) in 1975 noted that 90 percent of the ulcers related to regular aspirin use (15 tablets weekly or more) were in the antral region compared to 50 percent of the ulcers in patients who took less than 15 aspirin tablets per week (occasional and non-users).

In some parts of Australia, however, where powders rather than tablets are almost exclusively used, aspirin-related ulcers are not located in the antral region and, indeed, Gilles and Skyring (Ref. 78) excluded all antral ulcers from their study. The differences in the peristaltic movement of tablets and powders are considered the reason for the differences in the location of lesions in studies in these two countries (Ref. 19). Other differences have been noted in the patients. The aspirin-related ulcer patient was younger (57.9 years compared to 66.4 years) and included fewer females (53 percent compared to 71 percent) than the nonaspirin ulcer patient. Smoking did not appear to be more frequent than in controls in these aspirin-related ulcer patients in contrast to the nonaspirin related ulcer patients who appeared to have a greater incidence of smoking compared to matched controls.

(v) *Acute exacerbation of ulcers.* Kiser (Ref. 18) described the effects of continued aspirin administration on five chronic gastric ulcer patients. Two had mild anemia with no overt bleeding. Delayed healing occurred with continued aspirin use. All healed well when aspirin was discontinued. Reoccurrence was observed when aspirin use was reinstated.

Alp et al. (Ref. 17) stated that the ulcer patients who continue to smoke, drink and take aspirin have a much higher incidence, 87 percent compared to 49 percent, (about a two-fold increase) of reactivation of ulcers. Exacerbation or recurrence of ulcer symptoms following aspirin ingestion was demonstrated by Muir and Cossar (Ref. 3) for 14 of 34 gastric ulcer patients who recalled taking aspirin within 24 hours of their symptoms.

Several other authors have shown that activation of ulcers occurs shortly after acute aspirin ingestion (Refs. 12 and 13).

(g) *Massive gastrointestinal bleeding.* By far the most serious adverse effect of the action of aspirin on the gastrointestinal tract is massive upper gastrointestinal bleeding, which can be life-threatening (Ref. 87), often requiring surgical intervention and which also has a high mortality risk (Ref. 87). The mechanisms and factors involved in massive gastrointestinal bleeding are not completely understood. It is a relatively rare event which in most cases does not ap-

near to be predictable relative to the dose frequency of use of aspirin.

Although the incidence of massive bleeding is low, relative to the frequency of aspirin use, the total occurrence is not insignificant. Three different recent reports from the Boston Collaborative Surveillance program and incidence figures supplied by other groups indicate that the number and severity of adverse effects on the gastrointestinal tract produced by aspirin are quite significant (Refs. 28, 92, and 93).

In a recent survey, aspirin was the second most frequent drug involved in adverse effects that were serious enough to require hospitalization. Two out of every 1,000 hospital admissions were attributed to aspirin. Massive bleeding was second only to digitalis intoxication as the most frequent cause of drug-induced hospital admission, and aspirin products were involved in over 60 percent of the cases (Ref. 92). Of greater significance is the fact that the mortality rate associated with this condition is high (Ref. 92). Death occurs in 4 to 10 percent of all patients with gastrointestinal bleeding including those associated with aspirin ingestion (Refs. 15 and 16). Even greater mortality rates are involved in those patients requiring surgery to stop bleeding (Ref. 87).

Miller (Ref. 93) also compared the incidence of adverse reactions in 1,615 hospitalized patients receiving usual doses (300 to 600 mg aspirin in 70 percent of patients). The incidence of gastric distress such as heartburn, indigestion, nausea, vomiting was only 1.9 percent. The incidence of gastrointestinal bleeding, including hematemesis and epistaxis, was 0.7 percent (12 per 1,615) of all patients receiving aspirin (7 per 1,000).

A third report by Levy (Ref. 84) estimated the frequency of major gastrointestinal hemorrhage that was unrelated to any known predisposing factors such as ulcers, gastritis. The incidence of massive bleeding in regular "heavy" aspirin users was estimated at 25 per 100,000 (0.25 per 1,000).

The very low figure in the third study is undoubtedly an underestimate due to the design of the study, which is discussed below.

Numerous clinical studies have indicated that from 30 to 80 percent of all persons (Refs. 4, 22, 85 through 87, and 94 through 101) entering the hospital for massive gastrointestinal bleeding have taken aspirin within the past 24 to 72 hours. Recent epidemiological studies conclusively show that acute use of aspirin is causally related to massive bleeding (Refs. 84 and 95). The Panel believes that aspirin can potentiate bleeding in patients having a variety of gastrointestinal lesions including acute erosive gastritis (Refs. 15 and 102), chronic atrophic gastritis, stress ulcer, gastric ulcer (Refs. 19, 79, 82, and 84), duodenal ulcer (Ref. 84) and duodenitis (Ref. 69).

There are now convincing studies which indicate that aspirin is a definite factor associated with increased incidence of severe gastrointestinal hemor-

rhage in susceptible individuals. Therefore, the Panel concludes that the labeling should include the warning, "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

(1) *Evidence for aspirin-causation in major bleeding.* Important criteria in establishing a causal relationship between a drug and disease are satisfied when a particular type of lesion associated with the drug can be identified; when a mechanism involving the drug can be established, consistent with all data, or by identification of a particular high risk group.

The possibility of comparing the incidence of aspirin use and the incidence of bleeding from different types of lesions is dependent upon the diagnostic procedures used such as x-ray, laparotomy, gastroscopy and histological examination of biopsies. Radiological (x-ray) methods detect chronic ulcers but not erosions or acute (superficial) ulcer. Detection of erosive gastritis requires gastroscopic examination or, occasionally, observation during surgery. More recently it has been established that acute hemorrhagic gastritis associated with aspirin may be one of several types (incomplete gastritis, atrophic, hyperfunctional etc.) which can only be established if biopsies of mucosa are examined microscopically. Even histological studies involving single biopsies may miss some types of lesions.

(i) *Direct observation of bleeding in subjects.* Hemorrhagic erosive gastritis has been directly observed during aspirin studies designed to test other responses. In a few cases, bleeding was severe enough to require surgery. Bleeding erosions containing fragments of aspirin tablets have been reported (Ref. 6). A representative case was described by Roth (Ref. 6) who described an example illustrative of massive hemorrhage secondary to the gastric erosion after acute use of aspirin. Surgical intervention was necessary and revealed two 1-cm round lesions (the size of the tablets). The appearance of the lesions resembled acute focal hemorrhagic gastritis including desquamation of surface epithelium and capillary breakdown in the focal area.

The authors state that there could be no doubt about the causative relation of aspirin to the punched out bleeding erosions but questioned the persistent bleeding from two small erosions involving only capillary breakdown. They concluded that occasional massive bleeding probably requires the local effect to initiate the bleeding but also some undefined effect such as hypersensitivity or a capillary or coagulation defect.

Several other authors have observed mucosal erosions and hemorrhage associated with aspirin particles by gastroscopic examination (Ref. 23) and during surgery (Ref. 3).

(ii) *Correlation of individual bleeding response with variable drug intake.* Individual cases showing reversible susceptibility to bleeding when aspirin is increased or withdrawn are given by Weiss

(Ref. 10), Hurst (1 case) (Ref. 34), Kelly (3 cases) (Ref. 85), Waterson (Ref. 103) and Brown and Mitchell (Ref. 86).

(iii) *Case-control clinical studies.* In the opinion of the Panel, there is sufficient evidence from experimental and clinical studies involving different experimental designs to warrant the conclusion that aspirin ingestion is a contributory factor in increased incidence of major gastrointestinal hemorrhage.

Most clinical evidence involves retrospective case-control studies comparing the incidence of aspirin use in cases compared to a variety of control populations (Refs. 4, 19, 22, 84 through 87, 90, 92, and 94 through 101).

Because aspirin is frequently taken by patients for symptoms of their gastrointestinal disease, it is particularly critical to evaluate this potential bias in all studies showing an increased incidence of aspirin use associated with a particular disease condition. There are several studies, however, in which the available information clearly shows that the drug was not taken for symptoms related to the disease condition and the control group was matched for all important variables except bleeding (Refs. 2, 22, 84, and 95).

Because gastric distress is such a common component of gastrointestinal disease, in some studies all cases of acute upper gastrointestinal hemorrhage in individuals with a known history of gastrointestinal disease, were excluded as possible cases involving aspirin as a causal gastric pain associated with peptic ulcer or contributory factor (Refs. 2 and 84). These studies do not consider the important possibility that aspirin taken either for unrelated reasons or for the chronic gastric pain associated with peptic ulcer or gastritis will initiate bleeding from existing lesions.

(iv) *Case-control studies eliminating bias due to drug use for gastrointestinal symptoms.* Langman (Ref. 104) has reviewed several of the case-control studies concluding that a clear association between aspirin and major gastrointestinal hemorrhage was evident but could not be shown to be a causal relationship. A causal relationship could not be shown because it could not be ruled out that aspirin may have been taken for symptoms of massive bleeding. The Panel believes that some of the criticisms of the control groups, made by Langman, were possibly appropriate but also some were arbitrary and not based on any substantive evidence known to the Panel. Furthermore, the fact that the percent of persons taking aspirin in the case group was greater than control in all of the different types of studies is important since it is highly unlikely that a systematic bias would be involved for all groups in all the studies (Refs. 4, 19, 22, 84 through 87, 90, 92, and 94 through 101).

The choice of Alvarez and Summerskill (Ref. 22) in using dyspeptic patients as controls was criticized by Langman (Ref. 104) because these patients may have been warned by their physicians not to take aspirin. In the Panel's opinion this criticism is not valid because the patients

were carefully matched and the "case" group is just as likely to have dyspepsia and be warned by their physician; and dyspeptic patients are probably the best possible control group to assure that the control group would have the same likelihood of taking the drug for symptoms as the case group.

A well-controlled study by Needham et al. (Ref. 95) was designed to meet the criteria described by Langman. They found a definite association between short-term use of aspirin (within 72 hours of hospital admission) and massive upper gastrointestinal bleeding.

A second study also carefully ruled out bias from aspirin being taken for symptoms, a retrospective case-control study of 16,468 patients carried out by the Boston Collaborative Drug Surveillance Program found an association of "heavy" aspirin use (used for 4 or more times a week for 12 weeks) with nonbleeding stomach ulcer and major upper gastrointestinal bleeding in the absence of known predisposing conditions (Ref. 86).

In the Boston study it was estimated that the incidence rate of hospital admissions for major upper gastrointestinal bleeding in individuals without known predisposing conditions, or evidence of intestinal ulcer, and not taking aspirin, to be 11 to 13 per 100,000 per year. The incidence rate in heavy aspirin users was twice as high, being about 28 per 100,000 per year. The yearly incidence rate of new cases of nonbleeding stomach ulcers in individuals not taking aspirin is 3 per 100,000 per year. In heavy aspirin users the rate is about four times higher, 13 per 100,000 per year. Both of these differences were statistically significant. Thus, the increase in admissions for new massive gastrointestinal bleeding, excluding intestinal ulcer, and stomach ulcers that might be attributed to heavy use of aspirin would be about 25 per 100,000 per year. The author concludes that these data are consistent with a causal relationship between regular "heavy" use of aspirin and major upper gastrointestinal bleeding and nonbleeding stomach ulcers. It should be noted that 15 percent of the total patients admitted to the hospitals used aspirin at least once a week for 3 months and 6.3 percent of the total took aspirin four or more times a week for 3 months.

The estimated involvement of aspirin is probably conservative in the Boston study since it involved only new cases. It unfortunately does not provide information on a critical point of concern to this Panel, i.e., the possible increased risk of aspirin use in patients with a history of bleeding or peptic ulcer. It also does not provide information regarding the possible role of aspirin effects on the blood clotting mechanism which might potentiate bleeding from existing intestinal ulcers since this group was excluded from the study. The authors state:

It is worth emphasizing that this study provides no information on the relation of aspirin intake to upper gastrointestinal bleeding in patients who have predisposing conditions such as established chronic peptic ulcer disease. Evaluation of such cases, in a

case-control study would be virtually impossible since there would be no satisfactory way to determine the influence of the disease itself on aspirin use.

The Levy study clearly underestimated the true incidence (Ref. 1). It did not study primed subjects. It only studied subjects with chronic use of aspirin. It therefore ignored the largest group. While this may be true in the cited study, other studies have provided controls to eliminate individuals who may have taken aspirin for the gastrointestinal symptom. Even this does not include those individuals who take aspirin for gastric distress which then precipitates bleeding from primed sites.

Of the total number of cases of peptic (stomach) ulcer (517) and upper gastrointestinal bleeding (467) only 242 cases were used in the study. 356 cases were excluded from the study because of a history of stomach ulcer or stomach surgery and an additional 78 cases were excluded because bleeding occurred after admission. Furthermore, this study did not examine the possible effect of one time or short term ingestion of aspirin on massive bleeding since only chronic use of aspirin (3 months) was studied. It is important to realize that while the study does prove that there is a causal relationship between chronic or heavy use that this study does not prove that only chronic use of aspirin will produce ulcer or gastric bleeding. The study was designed such that only chronic aspirin use was studied. Any individual who had taken aspirin less than 3 months was excluded. All other studies of gastric hemorrhage have examined only acute use of aspirin, usually only 24 to 72 hours prior to bleeding. The association between bleeding and "heavy regular" use (more than 3 times per week) may simply reflect the higher probability of aspirin being ingested during the period of gastric susceptibility even though only a few doses were actually necessary to potentiate the bleeding episode.

It is also of possible significance that the Boston Collaborative Drug Surveillance Study found no evidence of an association between aspirin ingestion and newly diagnosed cases of uncomplicated non-bleeding intestinal ulcer. In the study, 7.9 percent of 63 patients were heavy users of aspirin compared to 6.9 percent of controls. In the 43 patients with newly diagnosed duodenal ulcer who had major bleeding 11.6 percent were heavy aspirin users compared to 6.9 percent of controls which was not statistically significant.

However, this trend of an increased incidence of bleeding in duodenal ulcer patients taking aspirin was found to be statistically significant in the study of Needham et al. (Ref. 95). Chapman and Duggan (Ref. 79) in 1969 also found a relationship between chronic aspirin use and the ingestion of a combination product that contained aspirin, phenacetin and caffeine (APC), and the incidence of peptic ulcer but found no association between duodenal ulcer (intestinal ulcer) and analgesic consumption. Prepyloric ulcers (ulcers near the exit valve of the stomach) were found

in an abnormally high incidence in aspirin users. The association of aspirin with ulcers was highly significant, supporting the concept that aspirin abuse is a cause of chronic peptic ulcer and is the environmental factor responsible for the excess of peptic ulcers in middle-aged women in eastern Australia (Ref. 89).

(2) *Difference between case and control in the frequency distribution of the time between aspirin ingestion and response.* Unfortunately the details of aspirin consumption in patients with major gastrointestinal bleeding has not been given in most studies. The carefully done prospective study of Alvarez and Summerskill (Ref. 22) does provide some useful information in this regard. These workers carefully noted the exact time and reason for aspirin ingestion in 103 consecutive patients in order to determine if the drug was taken as a result of the bleeding rather than being the precipitating factor. The control group of dyspeptic patients with no bleeding were matched for sex but not age. The differences in age, however, are small and insignificant relative to the study.

Two important conclusions can be drawn from their data. First, the difference in the time distribution provides additional support for aspirin as a causative factor in hemorrhage.

Second, the effect of aspirin in producing hemorrhage is acute. If one plots these data as the cumulative frequency of aspirin use, relative to total use, for bleeders and nonbleeders, it is clear that the probability of aspirin ingestion being associated with gastric bleeding declines exponentially with time. The majority of patients who bled took aspirin within 1 day prior to bleeding.

(3) *Characteristics of lesions.* (i) *Bleeding in peptic ulcer patients.* Peptic ulcer patients do not show increased occult bleeding after aspirin (Refs. 8 and 9) but aspirin does increase the incidence of massive bleeding in both gastric and duodenal ulcer patients. Weiss (Ref. 10) states that patients with peptic ulcer are two times more likely to show gastrointestinal bleeding.

When bleeding occurs it often occurs from other sites rather than from the healed or active ulcer (Ref. 15) or bleeding may occur from the ulcer directly (Ref. 102).

Gastro-duodenal hemorrhage following the taking of aspirin is more often due to superimposed acute erosive gastritis than to bleeding from the actual ulcer (Ref. 2).

Several recent studies indicate that acute use of aspirin will increase bleeding in both the gastric and duodenal ulcer patient (Refs. 95, 104, and 105). Furthermore, recent studies establish that the gastrointestinal bleeding associated with aspirin is increased by alcohol consumption (Refs. 104 and 105). In these studies the increased effect of alcohol was often statistically demonstrated only in duodenal ulcer patients and not in the gastric ulcer subgroups of massive bleeding patients (Refs. 95 and 104). The fact that aspirin causes only gastric ulcer

but can potentiate bleeding from both gastric and duodenal ulcers suggests that different mechanisms are involved.

It should be noted that the chronic aspirin-related gastric ulcer is not necessarily a bleeding ulcer. Only 3 of the 61 gastric ulcer patients studied by Cameron had hematemesis or melena in the previous 6 months (Ref. 19). The occurrence of acute lesions associated with patients with chronic peptic ulcers is not necessarily dependent upon aspirin ingestion since they are also seen in patients who were not taking aspirin. Furthermore, the nature of the acute lesions depends upon the probable inciting factors such as stress or alcohol. However, the majority of bleeding associated with lesions in acute gastritis involves patients taking aspirin. It appears that aspirin can potentiate bleeding from acute lesions regardless of whether it initiates the lesion. These lesions are usually the type designated as erosive gastritis.

(ii) *Hemorrhagic erosive gastritis.* Hemorrhagic erosive gastritis is characterized by gastric mucosal hemorrhage from small superficial discrete lesions. Unlike ulcers they do not penetrate beyond the muscular layer (muscularis mucosa) just below the lamina propria (Ref. 15). These lesions are too small to be seen by radiographic examination and are generally detected only by direct observation with a gastroscope during surgery. In studies in which gastroscopic examinations were not performed this lesion is probably included in the "cause unknown" category. Furthermore, these lesions may not be observed if gastroscopy is performed several days after bleeding as they frequently disappear rapidly (24 to 48 hours).

The incidence of gastric mucosal erosions and hemorrhage have been associated with a variety of diseases, including infections, following gastric and nongastric surgery and trauma (brain injury) (Ref. 15). Although the occurrence of hemorrhagic erosive gastritis has been associated with a variety of disease states, alcohol and aspirin alone or together are most frequently identified as the precipitating agents (Ref. 61).

Sugawa, Lucas and Walt (Ref. 105) followed 132 patients with acute erosive gastritis (84 after sepsis or trauma, 40 after alcohol intake and 8 after aspirin ingestion). They were studied by serial gastroscopy and photography using fiberoptic endoscopes. The color, size, shape and distribution of mucosal changes were recorded during early healing phases, and these changes were correlated with microscopic studies.

Mucosal changes in the trauma-sepsis group (stress "ulcer") with mainly black based erosions, were usually restricted to the parietal cell mucosa and were mainly on the greater curvature near the fundus.

Mucosal changes in the alcohol group were more evenly distributed throughout the stomach. It was found that 17 out of 40 patients had striking antral involvement. Red based erosions were the main

lesion in this group. Aspirin erosions were more frequent in the body, but were seen throughout the stomach. An unusual number of patients developed superficial white based ulcerations after aspirin.

Dagradi et al. (Ref. 15) state that the appearance and distribution of lesions in hemorrhagic erosive gastritis are similar regardless of the nature of the inciting agent. They undergo the same course of healing and the clinical spectrum is identical.

There are some differences related to the inciting agent. These differences are exemplified by the series of 106 patients bleeding from hemorrhagic erosive gastritis. The bleeding in 90 percent of the cases was associated with the ingestion of aspirin and/or alcohol just before the bleeding. In 10 percent of the cases, no determinant could be established. In most cases, aspirin was taken acutely, 2 to 3 days prior to bleeding for pain unrelated to gastric condition. Gastric distress was frequently seen in the aspirin-related group and varied from 1 day to several weeks prior to bleeding. Gastric ulcers occurred in 33 percent of the aspirin group but only in 5 percent of the alcohol-related group. Active peptic ulcer was present in 50 percent of the aspirin-related group and only 4 percent of the alcohol group. However, the frequent gastric distress in the aspirin group was unrelated to the presence or absence of ulcers.

Katz and Siegel (Ref. 14) reported that bleeding from acute erosions outnumber acute ulcers as a source of bleeding by 7 to 1, respectively. They described the typical acute gastric lesion as having denudation of superficial epithelium sheared at the neck of the glands with variable hemorrhage in the capillary rich area of the neck. These authors propose that a variety of agents may cause hemorrhagic erosive gastritis through the same mechanism. A variety of inciting agents may cause release of histamine from the mast cells in the lamina propria. They state, "It seems probable that many pathways lead to degranulation of the histamine-laden mast cells in the area about the neck of glands and that capillary injury results whatever the initiating stimulus. Capillary permeability increases, leading to hemorrhage at the neck with tissue anoxia, amputation of superficial epithelium and gross hemorrhage following."

The importance of stress as a precipitating factor for erosive gastritis has been suggested by several authors (Refs. 14, 94, and 96).

The more recent studies of Gelzayd and Gelfand and Gelzayd, Gelfand, and Rinaldo (Refs. 106 and 107) show that aspirin and alcohol may often be involved in duodenitis (inflammation of the intestine) rather than duodenal (intestinal) ulcer. Thirty-two patients had a variable history of epigastric pain (mainly dyspeptic), nausea, vomiting, and hematemesis (passage of blood by vomiting) or melena (passage of blood through the stools). Only three of these people had had a duodenal ulcer. Hem-

orrhagic duodenitis (bleeding resulting from intestinal inflammation) was present in eight patients with anemia and severe enough in four patients to require transfusion.

These bleeding episodes involve sites of bleeding which would not be decreased by highly buffered aspirin in solution since the primed site is already existing. Thus, there is no rationale for using buffered or highly buffered aspirin for concurrent symptoms of headache and alcoholic gastritis. Indeed, the Panel believes it is contraindicated. The Panel has discussed the labeling of such products elsewhere in this document. (See part VI, paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Those who contend that the systemic effect of aspirin is negligible relative to the association of aspirin to massive bleeding have usually made the assumption that the systemic effect must cause the bleeding rather than potentiate existing bleeding. However, based on current information regarding the effect of aspirin on platelet function, it is clear that aspirin will not initiate bleeding on the basis of the platelet effects and most likely will not potentiate bleeding from all types of bleeding sites. Most authorities agree that reduced platelet function will be important only when there is existing bleeding potential at the capillary level. It is of significance that the unique vasculature of the gastrointestinal tract and the importance of capillary blood flow to the lamina propria is the primary factor in acute hemorrhagic erosive gastritis or duodenitis. It is in these situations that aspirin is most frequently involved, accounting for 50 to 90 percent of all cases of massive bleeding from these sites. There are few situations in the body other than gastrointestinal erosions where extensive existing damage to mucosal tissue would involve extensive capillary networks. The capillary bed in the tonsillar region is one such case, however, and as might be expected, bleeding associated with aspirin does not occur in this region unless trauma and existing tissue damage is present e.g. posttonsillectomy. When existing damage occurs and capillary bleeding does occur, massive bleeding from this site can and does take place following aspirin ingestion. It should be clear that aspirin is not acting through the Davenport (hydrogen ion mediated bleeding) mechanism.

In summary, the Panel finds that massive gastrointestinal bleeding frequently is associated with acute aspirin ingestion by patients who have existing lesions which involve capillary type "oozing" bleeding (Ref. 14), such as weeping types of lesions associated with erosive gastritis regardless of the original cause and the more recently recognized duodenitis (Refs. 106 and 107). The tonsillar bed following surgery or inflammation also presents this picture. These lesions are often multiple superficial areas which would be dependent on platelet function for hemostasis since

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they are not under arteriolar control (Ref. 14); massive bleeding is more frequently observed in individuals who have inborn clotting deficiencies. While hemophilia has long been recognized to be a condition which is a contraindication to aspirin use, other clotting deficiencies which are less severe have been detected because of their reaction to aspirin (See part III paragraph B.1.a.(2)(i) above—Adverse effects on the blood.); and large increases of gastrointestinal occult blood loss are frequently associated with individuals who are more likely to have existing mild bleeding sites. The effects of aspirin on platelet function require only small doses. The effect may persist for several days. This dose-time response is consistent with some reports of massive bleeding following one or two aspirin tablets 1 or 2 days before massive bleeding occurs (Ref. 86).

(h) *Interaction with alcohol.* Another aspect of the gastrointestinal bleeding problem is the evidence in recent studies of a synergism between alcohol and aspirin's ability to cause such gastrointestinal bleeding.

In a study which was also designed to overcome the problems outlined, Needham et al. (Ref. 95) found a definite association between the acute use of aspirin (within 72 hours of hospital admission) and massive upper gastrointestinal bleeding, and evidence of a synergism between alcohol and aspirin in the association with gastric bleeding. It is of significance that of the separate diagnostic groups, i.e., duodenal and gastric ulcer, gastritis etc., only the duodenal group showed a high significance in the synergistic effect of aspirin and alcohol in terms of an increased incidence of bleeding. While this may be because of the low numbers of patients in the other categories, e.g., gastritis, it is important to note that acute ingestion of aspirin had a significant effect on duodenal bleeding and a synergistic effect with alcohol in bleeding from duodenal ulcers even though there is presently no evidence that even chronic aspirin usage is implicated in the incidence of non-bleeding duodenal ulcers (Ref. 86). This gives support to the hypothesis that aspirin may support or potentiate bleeding from gastrointestinal lesions even though aspirin alone may not initiate the lesion.

It is also significant that in this study alcohol alone did not increase the risk of bleeding, but did potentiate the effect of aspirin. It is also of interest to note that 13 percent of the total number of patients took aspirin for stomach pains, and 4 percent for hangover. The authors conclude that there seems to be a good case for warning the public of the dangers of aspirin since the combination of headache and upset stomach are often related to alcohol ingestion and might be a frequent reason for use of aspirin.

(i) *Formulation effects.* Some authorities claim that the mechanism involved with major gastrointestinal bleeding is the same as occult bleeding, i.e., involving direct cellular damage mediated through, and therefore requiring, avail-

able hydrogen ion (Ref. 22). As a corollary to this hypothesis, it has been claimed that highly buffered aspirin solutions which decrease occult bleeding would also obviate major bleeding (Refs. 37 and 47). While the direct acid-mediated gastric erosion may undoubtedly contribute or even in some cases initiate massive bleeding it is clear that this is not the only, and in fact probably not the most important mechanism involved in aspirin-induced massive bleeding.

There are several lines of reasoning to support this conclusion. Mucous membrane damage to the stomach produced by direct contact with aspirin and occult bleeding are responses that are predictable under given experimental conditions. Increased occult bleeding is observed in about 70 percent of the normal population taking normal therapeutic doses (Ref. 108). Massive bleeding has not been simulated in the laboratory and occurs sporadically and unpredictably in the aspirin taking population.

Even though highly buffered aspirin solution decreases the average occult bleeding loss in most studies (Ref. 75), frequently in these studies using highly buffered aspirin, one or two subjects who have taken highly buffered aspirin solution have sporadic, large increases in gastric bleeding. These "atypical responders" or "outliers" have occult bleeding losses which are often significantly greater statistically than the average for all subjects in the study (Ref. 77). Studying occult bleeding without regard to the unusual excessive bleeder or eliminating these "outliers" from the study begs the issue that buffering decreases blood loss and probably ignores the very type of exaggerated responder which is so characteristic of massive gastrointestinal bleeding.

Locally applied aspirin produces massive bleeding from capillary beds of tissues which do not secrete hydrochloric acid such as the tonsillar areas of the throat (See Part III paragraph B.1.a.(2)(ii)(b)(1) above—Mucosal erosion of the mouth), particularly following tonsillectomy when abraded oozing tissue is involved.

Enteric-coated aspirin products designed to release aspirin in the intestine where the acidity is low, produce significant increases in occult gastrointestinal bleeding, particularly in individuals who are more prone to such bleeding, e.g., the elderly (Ref. 1).

The Panel recognizes that a direct correlation between a reduction in occult bleeding and a reduction in occasional massive gastrointestinal bleeding has never been demonstrated.

Chronic aspirin ingestion appears to increase the incidence of stomach ulcers to a greater extent than duodenal (intestinal) ulcers presumably due to the hydrochloric acid effect in the gastric mucosa (mucous membrane of the stomach). However, aspirin appears to be implicated in massive bleeding associated with duodenal ulcer patients to the same or greater extent as in patients with stomach ulcers or erosive gastritis (stomach inflammation) (Ref. 79). This

supports the hypothesis that the effect of aspirin on massive bleeding may not be dependent on the same factors as those factors related to direct mucosal damage in the stomach.

While the Davenport mechanism may contribute to or even in some cases initiate massive bleeding, it would appear not to be the only mechanism involved.

For the various reasons discussed above, the Panel concludes that because aspirin after it has been absorbed into the blood stream can promote or increase bleeding, all preparations containing aspirin regardless of formulation should bear a warning: "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

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(iii) *Adverse effects on hypersensitive individuals.* Aspirin has long been recognized to produce allergic type reactions in hypersensitive individuals (Refs. 1 through 9). Hypersensitivity reactions are varied, including the following types: Effects on the respiratory tract ranging from shortness of breath to severe asthma attacks; effects on the skin including urticaria (hives), angioedema (neurotic edema) (giant hives), edema and rash; and anaphylactic shock involving laryngeal swelling, which blocks air pathways, and a precipitous drop in blood pressure (shock) which can result in death if not rapidly treated.

(a) *Incidence of adverse effects.* The incidence of hypersensitivity reactions (dermal and pulmonary) has been estimated to be about 0.2 percent of the general population (Refs. 8 and 9). However, a much higher incidence of hypersensitivity is found in some subgroups. Six to 20 percent of asthmatics are sensitive to aspirin (Refs. 10 through 13). About 20 percent of patients with chronic urticaria will experience exacerbation when given aspirin (Refs. 14 through 16). The Panel concludes that these adverse effects occur in a significant proportion of the population. They can be serious and even life-threatening in some instances (Refs. 4 through 6). Although very rare, death has occurred within minutes following ingestion of only one or two aspirin tablets in individuals who were known to be hypersensitive to aspirin (Refs. 5 and 6).

(b) *Adequate labeling information.* Because of the known risk of a severe aspirin hypersensitivity reaction, the Panel concludes that groups at high risk, such as persons with asthma and persons with a known allergic reaction to aspirin (e.g., shortness of breath, skin rash, hives) should be warned not to ingest the drug without consulting a physician.

The Panel recommends that all products containing aspirin should be labeled with the warning: "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

The Panel also considered the suggestion (Ref. 17) that the warning to asthmatics should be directed only to the asthma subgroup known to be most often involved and that salicylic acid or acetaminophen can be recommended to this and other aspirin sensitive groups as a safe alternative. Evaluation of these and other considerations relating to recommended labeling statements involved assessment of the current information regarding the following: Identification of

the mechanism(s) involved and the role(s) that aspirin plays in the pathogenesis of different types of hypersensitivity reactions; characterization of subgroups that can be used to identify individuals that have a significantly higher risk of reaction with aspirin; and identification of other drugs, particularly analgesics, that do or do not have cross-sensitivities with aspirin.

The Panel finds there is still considerable disagreement and there are unresolved questions regarding these important considerations, but some generalizations can be drawn on the probable mechanisms involved and susceptible subgroups. These are complex and exceptions are numerous.

The Panel concludes that aspirin can precipitate hypersensitivity reactions by different mechanisms in different groups of patients who may have entirely different characteristics. The acceptable types of substitute analgesics would also appear to be entirely different for the different groups.

(c) *Major types of hypersensitivity reactions.* Information reviewed by the Panel suggests at least two major types of hypersensitivity reactions to aspirin which differ in mechanism, usual type of response and cross-sensitivities with other agents (Refs. 18 and 19). There may be overlap of individuals in these categories.

It appears that the group usually exhibiting an asthmatic response to aspirin does not usually have atopic characteristics. Rather, they show the usual triad of aspirin hypersensitivity, nasal polyps, and late, abrupt onset of asthma (Refs. 10 through 12). Current evidence suggests this group involves a nonimmunologic hypersensitivity mechanism possibly related to the effects of aspirin on inhibition of prostaglandin synthesis (Refs. 20 and 21). Cross-sensitivity is commonly seen with other prostaglandin synthesis inhibitors including indomethacin, flufenamic acid, mefenamic acid, ibuprofen and phenylbutazone (Refs. 20 and 21). Analgesic agents which do not affect prostaglandin synthesis such as salicylamide, salicylic acid and acetaminophen do not usually show cross-sensitivities in this group (Ref. 20). Exceptions have been noted however (Ref. 13).

The second group are those who usually exhibit dermal reactions, such as urticaria or angioedema (Refs. 14, 15, 16, and 19), but may also have asthma following aspirin ingestion (Ref. 19). They often exhibit typical atopic constitutions (Ref. 19). This group also appears to be susceptible to anaphylaxis (Ref. 19). The mechanism involved in this group is possibly mediated by immunologic response as indicated by a positive rat mast cell reaction (Ref. 19). This group appears to be more susceptible to cross-sensitivities with salicylic acid and acetaminophen (Ref. 19).

Thus, although some generalizations can now be made regarding the type of reactions most likely to occur in a group with particular characteristics, the interrelationships are complex, not precisely defined, and not likely to be under-

stood by the majority of patients. It is sufficient to state that these relationships are not discernible and cannot be self-diagnosed by a lay person. Consequently, at this time, no statement would be any more meaningful to the user of aspirin than the general warning against its use by those known or likely to be hypersensitive to aspirin.

(d) *Asthma.* Asthma may range from mild brief attacks to severe and prolonged attacks and, rarely, deaths. Severe angioedema, bronchial asthma, cyanosis, asphyxia, coma and death within minutes have been reported in hypersensitive individuals (Refs. 1 through 4).

Conflicting figures are given in the literature regarding the incidence of aspirin hypersensitivity in the general population and the asthmatic population, depending on the population studied and the method of assessment (Refs. 8 through 13, 17, 22, and 23). Objective measurement of pulmonary function after oral challenge appears to be an effective means of establishing sensitivity. There is some risk involved in challenge tests because deaths have been reported (Ref. 22). Skin tests have not been found to be an effective means of detection (Ref. 15).

McDonald et al. (Ref. 22) studied 42 asthmatic patients who had no history of asthma after taking aspirin. Patients with an unequivocal history of asthma after taking aspirin (aspirin intolerant) were excluded from the study. Patients who had no history of asthma associated with aspirin were selected for aspirin challenge during a time when the patient's asthma was stable. A dose of 600 mg aspirin was given as two tablets which also contained 150 mg magnesium hydroxide and 150 mg aluminum hydroxide per two tablets. Other tablets, containing 200 mg magnesium hydroxide and 200 mg aluminum hydroxide per tablet and no aspirin, which were similar in size and appearance, were given as a control, in crossover fashion, to the same patients. Respiratory signs were measured by spirometry and a Jones Pulmonor. Eight of 42 (19 percent) challenges were positive. These results, combined with 14 patients with a history of intolerance to aspirin, yield a prevalence of aspirin intolerance of 8 percent in the asthmatic population studied by these investigators. The number of patients who were intolerant to aspirin showed a statistically significant increase in the presence of nasal polyps, sinusitis and steroid dependence when compared to all new asthmatic patients examined during the 2-year period.

Many other authors have noted a particularly high incidence of aspirin sensitivity in asthmatic patients with nasal polyps, chronic sinusitis and eosinophilia. In general, aspirin-induced asthmatics have not fitted the usual characteristics of the typical "allergic" patient. The allergic patient most familiar is one who when exposed to some allergen (reagin), such as pollen or a food, develops "hay fever" watery and itchy eyes,

runny nose (allergic rhinitis) and bronchospasm. Secondary symptoms may involve urticaria, allergic asthma and, rarely, anaphylactic shock. Allergy of this type belongs to a subgroup of the so-called "immune" class of disease termed atopy (Type I, reagin-mediated allergic hypersensitivity). In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunoglobulins which has the peculiarity of attaching itself to a certain type of cell, mast cells in the tissues and basophils in the blood. With the arrival of the allergen (reagin), union between the allergen and the antibody attached to these cells occurs and leads to the release of active substances such as histamine which in turn cause the symptoms we call "allergic."

In contrast to the atopic group, most aspirin-sensitive asthmatics do not have any of the usual indications of an immunological reaction. They have been termed Type II, intrinsic, nonallergic type (Refs. 17 and 24).

Falliers states that aspirin-sensitive asthmatics are usually the Type II, intrinsic, nonallergic type and are quite different from asthmatics not sensitive to the drug (usually Type I atopic asthmatics). Based on his study of 1,298 chronic asthmatics, between the ages of 6 to 16 years, the 25 children sensitive to aspirin were mainly the typical "abrupt-late-onset" intrinsic types with nasal polyps. He states that the majority of the atopic (reagin-mediated or Type I allergic hypersensitivity) are said to carry no greater risk of aspirin sensitivity than the general population. The distinguishing characteristics of the low risk patient are: An early onset of atopic (reagin-mediated) asthma; a family history of allergy; and specifically asthma, atopic eczema, and rhinitis. In contrast to the large number of asthmatic adults who are sensitive to aspirin (approximately 10 to 20 percent), the number of asthmatic children who are allergic to aspirin is only about 2 percent, according to Falliers (Ref. 24). Falliers has recommended to this Panel that the label warning for aspirin should state, "some asthmatics (intrinsic nonallergic type) may react adversely and therefore should not use aspirin without medical advice." One difficulty of this suggestion is that many asthmatics may not know which category they are in and could not self-diagnose their condition. A second more important reason is that some aspirin-sensitive children do in fact have atopic characteristics. For example, in five children with asthma induced by aspirin, Yunginger et al. (Ref. 23) found that four were in the group considered by Falliers to be low risk. These four had no history of nasal polyps and were characterized by atopic constitutions including sensitivities to seasonal pollens, a family history of allergies and positive skin tests.

The mechanism involved in the intrinsic nonallergic aspirin-sensitive asthmatic probably includes the effect of aspirin on prostaglandin synthesis (Refs. 20 and 21).

Polish workers recently demonstrated bronchoconstriction in patients with aspirin hypersensitivity after administration of five drugs which inhibited prostaglandin synthesis (Refs. 20 and 21). Indomethacin produced decreased peak expiratory flow in all 11 patients tested after a dose of 5 mg. Therapeutic doses of mefenamic acid and flufenamic acid, and 200 to 400 mg phenylbutazone produced a bronchoconstrictor effect in most patients. These five drugs all inhibited microsomal prostaglandin synthetase. Salicylamide, acetaminophen, benzydamine and chloroquine did not inhibit prostaglandin synthetase and did not produce bronchoconstriction.

(e) *Urticarial (dermal) hypersensitivity reactions.* Speer states that the most common manifestations of aspirin sensitivity are urticaria (hives) and angioedema (giant hives) rather than asthma (Ref. 15). Urticarial reactions (hives) are generally considered as part of the general aspirin sensitivity syndrome. However, dermal and respiratory reactions frequently occur independently. Different mechanisms may be involved. These patients frequently have other allergies (food, drugs) and do not necessarily exhibit the usual signs of late onset and nasal polyps found in aspirin-induced asthmatics. In 112 patients found sensitive to aspirin (1.5 percent of all patients seen in a 10-year period), there were 74 cases of urticaria and/or angioedema and 38 cases of asthma. Of interest is the fact that four of these patients also reacted to acetaminophen. Of these, three developed urticaria and one asthma.

In contrast to aspirin-induced asthma which is usually precipitated only by aspirin and not salicylic acid, both aspirin and sodium salicylate will exacerbate chronic urticaria in 20 to 25 percent of cases (Refs. 14 through 16).

Phills et al., using the rat mast cell technique, which is thought to detect IgE immunoglobulin reactions, were able to distinguish between two groups of patients hypersensitive to aspirin (Ref. 19).

Dermal reactions are not usually life-threatening. There are indications that life-threatening anaphylactic shock is often associated with patients with dermal rather than asthmatic reactions to aspirin. Thus while typical (intrinsic, nonallergic) aspirin hypersensitive patients (Type II) can frequently use salicylic acid or acetaminophen or other analgesics which do not inhibit prostaglandin synthesis without cross-sensitivity, this does not appear to be true with urticarial and possibly anaphylactoid type reactions in the atopic type (Type I) aspirin responders.

The American Academy of Allergy in 1973 (Ref. 25) approved the following resolution:

While recognizing that acetylsalicylic acid (aspirin) is a valuable drug, the American Academy of Allergy recommends that a formulation containing aspirin and advertisements promoting the formulation should clearly indicate that the preparation contains aspirin and that aspirin can be harmful to some persons.

The Panel is in agreement with this resolution.

In summary, since aspirin has long been recognized to produce allergic type reactions in hypersensitive individuals, the Panel recommends that all products containing aspirin should be labeled with the warning: "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

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(iv) *Adverse effects during pregnancy.* The Panel has reviewed the effects of aspirin on various aspects of pregnancy as studied and extensively reported in the literature. The investigations on the effects of aspirin ingestion during pregnancy have focused on the following aspects: Teratogenic effects (malformation of offspring); the incidence of stillbirths and neonatal deaths (deaths at or shortly after birth); the effect of aspirin ingestion on the length and duration of pregnancy and parturition time (length of labor and delivery); and the impairment of hemostatic mechanisms by aspirin (but not other salicylates) on the mother as well as on the newborn infant.

In the discussion below, the Panel has elected to separate and review the available data according to the above effects. Teratogenic potential and fetal lethality will be discussed in terms of both animal studies and human retrospective and prospective studies. Secondly, prolongation of the duration of pregnancy and parturition time in animals and in human retrospective studies will then be summarized. Lastly, the effects on maternal and newborn hemostatic mechanisms will be described followed by the Panel's conclusions and recommendations.

(a) *Teratogenic potential and fetal lethality.* (1) *Animal studies.* Warkany and Takacs (Ref. 1) reported for the first time in 1959 that both methyl and sodium salicylate were teratogenic in rats. The drugs were administered to pregnant rats subcutaneously from days 9 to 11 of pregnancy. However, the doses used were, on a weight basis, much greater than the therapeutic doses used in man. Females received either single subcutaneous injections of methyl salicylate in doses of from 0.1 to 0.5 ml (the mg/kg dose was not specified) or sodium salicylate in doses of 60 to 180 mg (maximum 900 mg/kg based on the assumption of a 0.2 kg rat). In addition, the teratogenic doses (doses which caused malformations) were found to be quite close to doses lethal to the embryo (developing offspring) and toxic to the mother (Ref. 1).

Larsson, Bostrom and Eriksson (Ref. 2) in 1963 showed that large doses of salicylates, 10 mg (maximum 500 mg/kg based on the assumption of a 0.02 kg mouse) sodium salicylate, administered

intramuscularly to pregnant mice induced malformation in the embryos. A feature of particular interest was that these malformations occurred either in vascular (blood vessel) or skeletal tissues both know to contain acid mucopolysaccharides. The authors hypothesized that the teratogenic effects of salicylates in mice were related to the inhibition of mucopolysaccharide synthesis and suggested that the embryos seemed to be most sensitive when the injections were given on the 12th and 13th day of gestation.

Larsson and Eriksson (Ref. 3) in 1966 investigated the effects of time of administration of salicylates to pregnant mice on the incidence of fetal death and fetal resorption. They compared two mouse strains identified as A/Jax and CBA strains and found that they had different teratogenic susceptibility. Sodium salicylate, 500 mg/kg of body weight, was given intramuscularly in a single dose on one specific gestation day (either day 9, 11, 13, 15 or 17) to pregnant primiparous mice of A/Jax and CBA strains and to their reciprocal crossings. It was found that the fetal resorption rate increased steadily the later in pregnancy sodium salicylate was given to the A/Jax strains and to hybrids from A/Jax females crossed with CBA males. In contrast, in the CBA strain, and to the progeny from CBA females crossed with A/Jax males, the resorption rate was low even after injection of sodium salicylate in late pregnancy. Vascular anomalies were studied and it was noted that the highest incidence of vascular anomalies occurred after injection of sodium salicylate on the 15th day of gestation, whereas anomalies of the ribs and vertebrae showed the highest incidence after injection on the 9th day. Again, the A/Jax strain, and the progeny from A/Jax females crossed with CBA males were shown to be the most susceptible. The authors suggested that in drug tests for teratogenic potential the drug should also be given after the period of organogenesis and that special attention should be focused on fetal lethality.

Eriksson (Ref. 4) in 1970 studied the role of dosage and frequency of administration of sodium salicylate on fetal mouse damage as well as a possible protection against such damage when pentobarbital was given as a pretreatment. There was little or no effect on the fetus when a dose of 150 mg/kg of body weight was administered to the mother on day 17 of pregnancy. At a dose of 500 mg/kg of body weight given to the mother on day 16, death occurred in 70 percent of the fetuses. Subcutaneous and subcapsular liver hemorrhages were found in 39 and 13 percent of the living fetuses, respectively. Macroscopically visible submucosal hemorrhage in the stomach was seen in 22 percent of the surviving fetuses. When a dose of 750 mg/kg was administered, four out of ten pregnant females died within 24 hours. Five of the remaining six pregnant females gave birth before being sacrificed and the fetal lethality in one litter was 100 percent. When 75 mg/kg pentobarbital was

administered on days 15 and 16 of gestation followed by 500 mg/kg salicylate on day 17, fetal death was significantly decreased. Although these observations are interesting, it must be noted that here again extremely high doses were used since the LD₅₀ for females of the strain used (A/Jax) was determined to be 760 mg/kg of body weight.

Studies in rhesus monkeys by Wilson (Ref. 5) have shown that doses of aspirin five to six times higher than the teratogenic doses used in rodents produced embryotoxicity and fetal malformations in this species. It should be emphasized that the daily dose of 500 mg/kg was considerably in excess of that likely to be used therapeutically in pregnant women.

According to Wilson (Ref. 6), this "margin of safety" has been made less secure by the observation of Kimmel, Wilson and Schumacher (Ref. 7) that the teratogenic potential of a given dose of aspirin in rats can be appreciably increased by the concurrent administration of benzoic acid, a widely used food preservative. Levy, Amsel and Elliott (Ref. 8) have shown that benzoic acid elevates salicylate blood levels in man by inhibiting salicylic acid formation, but whether such interaction could raise the salicylate concentration in maternal blood sufficiently to cause embryotoxicity still remains an open question. The Panel has further discussed the role of benzoic acid-containing ingredients later in this document. (See part VI, paragraph B.2. below—Benzoic acid-containing ingredients.)

Since these and other reports have appeared, questions are sometimes raised about the possible embryotoxicity of salicylates, particularly aspirin, in view of its widespread use as an analgesic and the high doses used in arthritis. For purposes of comparison, it should be noted that the use in the average adult female of the recommended maximum daily dosage of 3,900 mg aspirin would be equivalent to 70 mg/kg for an average 55 kg (120 lb) woman.

Recently, Beall and Klein (Ref. 9) have reported a study in rats using a dose of 250 mg/kg (administered on days 7 through 10 of pregnancy) with and without food restrictions. They found that the controls (group I) (food ad libitum, no drug administration) had 2.6 percent of abnormal progeny. Group II (250 mg/kg aspirin and food ad libitum) had 23.8 percent of abnormal fetuses. Group III animals on a restricted diet (6 g daily) had an incidence of abnormal fetuses of 5.3 percent. However, Group IV receiving 250 mg/kg aspirin plus food restriction had an incidence of 95.8 percent malformed fetuses.

The types of anomalies observed included rib anomalies, craniorachischisis, umbilical hernia, scoliosis, anophthalmia, cleft lip and palate, etc.

The data also show a significantly increased number of resorptions in group IV when compared to groups I, II, and III (p is less than 0.05). The litter size of control group I was 11.6 ± 1.54 , for group II it was 9.4 ± 1.45 , for group III it was

13.1 ± 0.56 and in group IV it was 6.4 ± 1.51 . This seems a marked decrease in litter size in group IV when compared to other groups, although the authors do not mention the significance of this factor. These data indicate that, in rats, the combination of food restriction and aspirin affected fetal development more than did aspirin alone.

In summarizing the animal studies as they might be related to humans, several important points should be noted. As has already been emphasized, on a weight basis the doses used in the animal studies were excessively high and approached or were at lethal levels in comparison to the usual human adult dosage. Not only were these doses at lethal levels for the animals, but considering that the lethal dose for man ranges from 400 to 600 mg/kg, the animal doses were also at levels that would be lethal to humans (equivalent to 84 to 96 aspirin 325 mg (5 gr) tablets). When pregnant mice were given lower doses, such as a dose of 150 mg/kg, there was little or no adverse reaction. As noted above, the total maximum daily dose of aspirin recommended by the Panel for an average woman is approximately 70 mg/kg, about one-half the dose in mice of 150 mg/kg. However, extrapolation from animal data to humans is not always a matter of simple arithmetic and conversion of doses on a mg/kg basis. It is a well-known fact in toxicological assessment that species vary in the susceptibility to toxic agents and often it is required by government agencies that doses 10 or 50-fold of those intended for human use be used in animals for the assessment of toxic potential.

This interspecies variation could be due to susceptibility of the target organ (or growing embryo) or to differences in absorption, metabolism, distribution or excretion. Interspecies differences in metabolism are extremely common.

(2) *Human studies.* Studies related to the use of salicylates by pregnant women were reviewed by the Panel to make an assessment of the risks involved. Obviously, ethical and moral reasons preclude specially designed randomized studies that would examine the effects of salicylates on pregnancy. The Panel has therefore had to rely mainly on retrospective studies, i.e., previous clinical experience or statistical records which are subject to many valid criticisms and from which conclusive evidence cannot be definitively drawn. Several retrospective studies in humans attempting to determine if a correlation exists between aspirin ingestion and fetal malformations have been reported in the literature.

A retrospective survey of malformed infants resulting from 833 pregnancies during the period between 1964 to 1966 was performed in Wales by Richards (Ref. 10). The mothers of the malformed infants were matched with an equal number of controls, women who had given birth to normal infants. The findings were based on interviews in the homes of each mother of a malformed infant and her matched control. In ad-

dition to the retrospective nature of the study, the dosages of salicylates, the duration of treatment, and the medical histories of the mothers were not given. Richards reported that a very highly significant greater (p is less than 0.001) percentage of women (22.3 percent) delivering malformed babies, had taken salicylates during the first trimester of pregnancy than had women who had not taken salicylates and delivered normal babies (14.4 percent). It is interesting that in these populations of women following pregnancy, the incidence of salicylate ingestion was relatively low, i.e., only 36.7 percent of the 833 subjects had taken salicylates.

The author concluded that the results of the investigation "suggest that either salicylates have a teratogenic effect or that the conditions for which they are given have such an action." It should be noted that in addition to salicylates, other drugs had been taken by some of the women during pregnancy such as antibiotics, sulfonamides, steroids, sedatives, iron, oral contraceptives, antiemetics, etc. However, the women taking salicylates did not all take these various drugs.

The retrospective study included a statistical evaluation of each drug administered to the mothers to determine whether there was a statistically significant relationship between the drug and the malformation found in the infants. The author acknowledged that there are several limitations to a retrospective study that cannot be overlooked, and that "a large number of tests of significance were performed and many of these apparently significant differences could have arisen merely by chance." The author performed a total of 1,025 tests of significance and indicated that of the 101 tests that showed statistical significance, he considered that 51 of these statistically significant results could have occurred merely by chance.

In reviewing the study, the Panel finds several limitations which prevent a valid interpretation of the findings. Even the author acknowledges limitations to a retrospective study including the fact that the results may be affected by bias on the part of the interviewer or the mother; events, drugs and dosages may have been forgotten; emphasis was placed on the whole of the first trimester, whereas the critical periods of development are short and occur at different times for different organs; and lastly that since a large number of tests of significance had been performed, many of these apparently significant differences could have arisen mainly by chance. The Panel recognizes these deficiencies and especially the fact that the statistical analyses were not planned in advance of the study. It is also important to note that the study was not designed specifically to evaluate the effects of salicylates or other drugs but to evaluate congenital malformations and environmental influences in pregnancy. Many factors besides drugs were evaluated such as illnesses during first trimester, smoking and diet habits, employment, accommodations, water supply, etc.

Nevertheless, the Panel concludes that regardless of the circumstances, the Panel views the summary conclusions of the authors as very important. Namely, the fact that Richards found many statistically significant differences between cases and controls, those of greatest interest (and possible importance) being: (i) Use of salicylates, (ii) certain other drugs (antiemetics) and (iii) the effects of diet in the first trimester considered to be unbalanced or doubtful. Of importance to this Panel, the author found that the taking of salicylates in the first trimester resulted in the following significant differences: Defects on the central nervous system (p is less than 0.05), of the alimentary tract (p is less than 0.01), miscellaneous defects (p is less than 0.05) and talipes (club foot) (p is less than 0.01) (for all organ systems p is less than 0.001).

In another retrospective study by Nelson and Forfar (Ref. 11) reported in 1971, the effects of drugs administered during pregnancy and their possible association with congenital abnormalities of the fetus were compared. Virtually all 1,369 of these women (1,333 out of 1,369) had taken one or more drugs during pregnancy. Only 2.1 percent of mothers in the abnormal group and 2.9 percent of mothers in the control group had not taken any drug. Most mothers who had taken analgesics delivered normal infants. In the study 97 percent of the mothers took prescribed drugs and 65 percent OTC drugs. Aspirin was one of the drugs included. More specifically, the aspirin ingestion during pregnancy of 458 mothers of malformed infants was compared with the ingestion of aspirin by 911 mothers of normal infants. Of mothers delivering normal infants, 54.3 percent took aspirin during the entire period of pregnancy as compared with 62.2 percent of mothers delivering malformed infants. This was reported to be a statistically "highly" significant difference (p is less than 0.01).

Approximately 50 to 60 percent of the mothers of the malformed infants and also the mothers of the normal infants had taken two to five different drugs during pregnancy. Approximately 15 to 20 percent of both groups of mothers had taken 6 to more than 10 drugs during pregnancy. The drugs consisted of analgesics, antacids, antiemetics, antibiotics, appetite suppressants, barbiturates, bronchodilators, cough medicines, diuretics, hormones, hypnotics and tranquilizers, iron, sulfonamides and vitamins. Tests for significance had to be done for each class of drugs for the same groups of mothers. In the case of some drugs, the actual numbers were too small to show significant results which could not alone exonerate a drug from possible teratogenic effects. In other instances, although a greater number of mothers of malformed infants took a particular drug than the control mothers, it might not necessarily mean that the drug had a teratogenic effect.

Twenty-three different analgesic preparations had been used by the women. Statistical comparisons were made between the analgesics used during the

whole of pregnancy, the first trimester and the first 14 and 56 days and all abnormalities observed (which were further divided into major and minor abnormalities). The data showed that analgesics were used by a significantly high proportion of mothers of infants with "all and minor" abnormalities during the whole of pregnancy and "all" abnormalities during the first 56 days of pregnancy. The authors specifically note that "aspirin was taken by a significantly higher proportion of mothers of all abnormal infants and of infants with major abnormalities in the whole of pregnancy and of infants with all abnormalities in the first trimester." It was specifically concluded that the increased occurrence of congenital abnormalities associated with analgesics appeared to be related to the aspirin content.

The data further showed no significant differences for aspirin for the first 14 and 56 days. However, there was a significant difference for the first 28 day period where 8 out of 458 mothers (1.75 percent) in the "all" abnormalities group had taken aspirin compared to 3 out of 911 mothers (0.33 percent) in the control group (p is less than 0.05). The abnormalities included achondroplasia, hydrocephalus, congenital heart disease, mongolism, congenital dislocation of the hip, hydrocele, talipes, and papilloma of the forehead. It should be noted that Richards (Ref. 10) also observed talipes. Since the average dose of aspirin per mother in the study group was reported to be a little over half that in the control group, this indicates a woman does not necessarily have to be an abuser or take large quantities of the drug to have the fetus at risk.

The authors' summary comments emphasize the need for caution in presuming teratogenic effects on the basis of the associations found in the study. They do recommend that any drug which carries a suspicion of teratogenicity should be avoided during pregnancy unless specifically prescribed. More interestingly, they recommend that OTC drugs such as aspirin should be avoided.

A retrospective study in Finland reported by Saxen (Ref. 12) in 1975 investigated the association between oral clefts in infants and drugs taken by their mothers during pregnancy. Five hundred ninety-nine cases of oral clefts (cleft lips and cleft palates) reported to the Finnish Register of Congenital Malformation in the years 1967 to 1971 were used in the study: The mothers of these malformed infants were compared with matched controls, i.e., mothers of normal infants, for salicylate ingestion during pregnancy. In considering the results, it should be kept in mind that this study was partially prospective and partially retrospective. The information concerning intake of drugs was obtained from welfare center records (prospective) whereas questionnaires were completed by the mothers during their first visit after delivery (retrospective). Although it was reported that in the first trimester of pregnancy 14.9 percent of the mothers of the malformed infants took salicylates as compared to 5.6 percent of the

controls (p is less than 0.001), approximately the same percentage of mothers of malformed infants and of the controls (18.4 and 16.9, respectively) did not remember exactly when during pregnancy they took salicylates. Since a correlation with the intake of other drugs during pregnancy was also studied, the author cautions that when a large number of significant tests are performed, the possibility of chance correlations must be taken into account; but the fact that the significant differences were mostly confined to the first trimester, lessens the probability that these differences arose by chance. Saxen also points out that other drugs administered simultaneously may alter the response to a drug.

A survey in England by Crombie et al. (Ref. 13) reported in 1970, compared the number of aspirin prescriptions issued by physicians to women in early pregnancy who had eventually delivered a congenitally malformed baby, with the number of aspirin prescriptions issued to women who had delivered a normal baby. There was no statistically significant difference between the two sets of mothers. The authors concluded that any relationship between "drug consumption and a congenital abnormality is indirect and possibly more directly related to the morbid conditions for which the drugs were given." This survey included the records of approximately 10,000 women.

In another study by Turner and Collins (Ref. 14) reported in 1975, the infants of 144 mothers who took salicylates regularly during pregnancy were studied with respect to birth weight, perinatal mortality and the incidence of congenital malformations. Since salicylates cross the placental barrier freely and go into the fetal circulation, the study was initiated in an attempt to assess the effects of increased levels of blood salicylate on infants whose mothers regularly took salicylates during pregnancy. After delivery, the babies were divided into groups, i.e., Group I (64 infants) where the mothers had taken salicylates daily and Group II (82 infants) where the mothers had taken salicylates at least once a week. Mothers in Group I were matched with controls for age, parity, gravity, ethnic group and social class. Blood salicylate level determinations showed that when the maternal blood level was high so was the cord-blood level. The mean birth weight of the infants of mothers who took salicylates daily was significantly lower than the mean control birth weight (p is less than 0.005). The birth weight was also found to decrease in relation to the length of time (in years) that mothers had been taking salicylates which suggested that it may not be solely an effect of salicylates on fetal growth but rather a cumulative secondary effect from some maternal factor. When the present and past pregnancies of the women were combined, it was found that the stillbirth rate and the perinatal mortality rate were significantly increased in infants born to the Group I mothers (p is less than 0.01 and 0.005, respectively).

PROPOSED RULES

With regard to teratogenicity, there was no significant increase in malformed infants as compared to controls.

The authors concurred with the suggestions of Richards (Ref. 10) and Nelson and Forfar (Ref. 11), stating that it may well be as suggested by those investigators "that teratogenicity is related to the illness for which salicylates were taken rather than a direct effect of the salicylates themselves." Turner and Collins (Ref. 14) did find that babies of mothers taking salicylates had a significantly reduced birth weight compared with controls. In addition, some babies were born with an elevated cord-blood level of salicylates but this was not associated with hypoglycemia, bleeding or any other obvious clinical disturbance. It is interesting to note that there were more anomalies in the group of women who took salicylates intermittently rather than constantly which suggested to the authors that if there is any teratogenic effect it may be more related to fluctuating levels of salicylate than a constantly elevated level. Turner and Collins concluded, "Our findings do not support the suggestion that salicylates are teratogenic, but they do suggest that chronic salicylate ingestion is associated with an increase in perinatal mortality and with decreased intrauterine growth."

In a recent study reported by Slone et al. (Ref. 15), the results of a prospective study suggest that aspirin is not teratogenic. In the study, which was conducted in 12 hospitals throughout the U.S., 50,282 mother-child pairs were selected for evaluation. Prior to delivery, data were collected on drugs taken, maternal illnesses, complications, etc. However, full details of dosages were not recorded but the heaviest use of aspirin, which was recorded, was for 8 or more days in any lunar month. Aspirin had been the most commonly used drug which was taken by 32,164 women during pregnancy. With regard to evaluating congenital malformations, the first 4 lunar months of pregnancy were studied in which aspirin had been taken by 14,864 women. In fact, during this period, 5,128 women (heavy users) had taken aspirin for at least 8 days during at least 1 of the first 4 lunar months. To fully evaluate the data, the authors developed risk factors for each of the outcomes identified. These included comparisons of the children (with and without each of the outcomes) in terms of such factors as antenatal visits, personal characteristics of mother and offspring, age, illnesses, genetic factors (prior malformed siblings), etc.

The findings of the study in terms of malformations according to aspirin exposure during the first 4 months of pregnancy are as follows:

CONGENITAL MALFORMATIONS FOLLOWING
ASPIRIN EXPOSURE IN EARLY PREGNANCY
GROUPS EVALUATED

Group I: Containing 5,128 "heavily" aspirin-exposed mother-child pairs. (See description of heavy users above.)

Group II: Containing 9,736 aspirin-exposed mother-child pairs.

Group III: Containing 35,418 non-aspirin-exposed mother-child pairs.

Findings of study

Parameter measured	Group I	Group II	Group III
Number malformed children.....	343	663	2,242
Percent of group.....	6.7	6.8	6.3
Relative risk.....	1.06	1.08	1.0

When the children were further divided according to outcome, i.e., uniform malformations (CNS, cardiovascular, etc.) and nonuniform malformations (inguinal hernia and clubfoot), the data show that both aspirin exposure groups were similar to the unexposed group. The standardized relative risk approximated unity. The upper approximate limits (p value less than 0.05) for uniform and major malformations in children who were heavily exposed to aspirin (Group I) were 1.08 and 1.11, respectively. The authors stated that "With regard to any exposure to aspirin (whether heavy or not), the standardized relative risks of uniform and major malformations were 1.00 and 1.01, respectively, with approximate upper 95 percent confidence limits of 1.06 and 1.09."

As with other studies, criticisms were raised which could have obscured possible teratogenic effects. The authors commented in their discussion:

First, chance may explain failure to detect relationships with some of the less common outcomes. Second, even though multiple logistic risk function analysis was used to simultaneously control a wide range of potential confounding factors, the possibility of negative confounding by undetected factors could not be ruled out. Third, a systemic bias in the data collection could have obscured an association. Certainly, observer bias was unlikely in this study because the information on drug exposure was collected before delivery. Fourth, some degree of underestimation of aspirin use was undoubtedly present, since the median time of entry into the study was 21.6 weeks: some women may not have recalled taking aspirin during early pregnancy. However, there was less likelihood of underestimation among heavy users. In addition, misclassification of aspirin users as non-users would have had to be very common to completely obscure an actual association, because the non-exposed group was extremely large.

The data presented here are not in accord with two previous studies (Refs. 14 and 16).

The striking differences between the study of Slone et al. and those of Collins and Turner (Ref. 16) and Turner and Collins (Ref. 14) are not as dramatic as it may appear at first sight. The studies in the American and Australian papers were widely different and probably the main difference lies in the definition of "heavy user" given in the U.S. study. The term "heavy user" as described by Slone et al. appears to be a misnomer as these authors were really studying three non-abusing populations and the outcome could have easily been predicted. A per-

son who has taken eight aspirin or therapeutic dosages in any lunar month or in any of the first 4 lunar months can hardly be called a heavy user.

However, it is noteworthy that Slone et al. (Ref. 15) concluded that the study gave no evidence that aspirin ingestion during pregnancy is associated with congenital malformations. They pointed out that from the statistical analysis the relative risk estimates for uniform malformations and for major malformations make it unlikely that substantial teratogenic effects would have escaped detection. Nevertheless, they were of the opinion that the possibility still remains that grossly excessive exposure to aspirin may be teratogenic. However, they referred to the study of Turner and Collins (Ref. 14) which in their view showed no effect. More importantly, Slone et al. concluded: "Based on a larger body of data, more conventional doses of aspirin as used by pregnant American women do not appear to cause malformations in their offspring."

(b) *Prolongation of the duration of pregnancy and parturition (labor and delivery) time.* Tuchmann-Duplessis et al. (Ref. 17) have recently reported that the administration of 200 mg/kg/day to rats during the last 6 days of pregnancy resulted in a prolongation of the duration of pregnancy, a prolongation of parturition time and the appearance of dystocia (abnormal labor) in some animals resulting in possible secondary death of fetuses in utero. Seventy percent of control dams delivered during day 21 of pregnancy while only 18 percent of the treated dams did (p is less than 0.05). Fetal deaths occurred undoubtedly during but not before parturition and were the result of prolonged parturition and not the result of the toxic effect of aspirin on the fetus in utero.

Lewis and Schulman (Ref. 17) reported a 20 year retrospective study of 103 patients, most of whom had non-specific collagen disease or degenerative musculoskeletal disease, taking doses of aspirin greater than 3,250 mg/day during the last 6 months of pregnancy in which comparisons were made with two control populations. The control populations were chosen as follows: The first control group consisted of 52 pregnant patients with rheumatoid arthritis, "nonspecific collagen disease", or degenerative musculoskeletal disease who were not taking aspirin or other compounds known to affect prostaglandin synthesis; and the second control group contained 50 pregnant women without known disease who were not taking therapeutic doses of aspirin or related drugs. The patients taking aspirin had an average gestation period of over 1 week longer than either control group. These differences were significant (p is less than 0.025). The two control groups did not differ from each other. The change in the mean length of gestation which occurred in the group taking aspirin was associated with increases (42 percent vs 3 percent in controls) in gestation periods lasting more than 42 weeks

(15 days postmature). Patients taking aspirin had a longer length of labor than either of the 2 control groups (12 hours vs 7 hours; p is less than 0.005). Further analysis showed that there were no statistical differences in mean age, parity or growth.

The Panel has summarized some of the findings of the authors in the following table:

Results of study groups

Parameter measured	Group I	Group II	Group III
Length of gestation (days).....	286.1±13.3	275.2±10.6	278.6±6.91
Length of labor (hours).....	12.1±10.6	7.3±4.11	6.96±4.96
Birth weight (g).....	3,077.0±597.0	2,972.0±538.0	3,379.0±460.0
Estimated blood loss (ml).....	340.0±155.0	244.0±114.0	235.0±97.0

The purpose of the study was to evaluate the influence of aspirin, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. Prostaglandins are known to be capable of initiating uterine contractions. Lewis and Schulman indicate that their results support the view that prostaglandin metabolism may be an important determinant of the timing of the onset of spontaneous labor and of its duration. Patients taking aspirin had labors averaging 70 percent longer than those in the control populations.

Collins and Turner (Ref. 16) in an Australian study compared two groups of pregnant women who self-medicated with analgesics regularly, with a group of matched controls. One group of self-medicated women took analgesics in a powder daily (constant takers). A combination of aspirin, salicylamide, and caffeine was taken by 58 percent; 36 percent took a combination of aspirin, phenacetin, and caffeine; and 6 percent used either powder. The second group of self-medicated women admitted taking analgesics at least once a week throughout pregnancy (intermittent takers). Many of the constant takers had self-medicated with analgesics for many years and were "habituated" to analgesics. After the delivery of each patient in Group I (constant takers), the next Australian-born clinic patient to deliver a baby, who was matched for age, parity and gravity

Results of study groups

	Group I	Group II	Control
Anemia in pregnancy..... percent	141	122	120
Antepartum hemorrhage..... do	14	7	4
Postpartum hemorrhage..... do	12	7	2
Transfusion at delivery..... do	12	6	6
Mean duration of pregnancy..... weeks	39.7	39.8	38.7
Duration 36 weeks or less..... percent	5.0	3.0	8.0
Duration 42 weeks or more..... do	16.0	16.0	14.0
Mean duration of labor..... hours	5.6	5.5	4.8
Complicated delivery.....	30	27	11
Caesarian section.....	12	6	2
Stillbirths.....	157	181	0

¹ P is less than 0.025.
² P is less than 0.050.

INFLUENCE OF ASPIRIN ON DURATION OF HUMAN GESTATION AND LABOR

COMPARISONS OF STUDY GROUPS

Group I: Patients with rheumatic diseases taking therapeutic dosages of aspirin with daily consumption greater than 3,250 mg for at least the last 6 months of gestation (103 patients).

Group II: Control patients with rheumatic diseases not taking aspirin (52 patients).

Group III: Control healthy women not taking aspirin (50 women).

Because the numbers in the survey were small, the findings in present and past pregnancies of the women in the study were combined when assessing the antepartum hemorrhage, postpartum hemorrhage and transfusion at delivery, and all of these were found to be significantly increased in the constant takers group (p is less than 0.001). The stillbirths and perinatal death rates of the combined pregnancies of this group were also much greater than in the controls (p is less than 0.01 and less than 0.005, respectively).

In another recent study reported by Shapiro et al. (Ref. 19), the results showed no evidence that aspirin taken during pregnancy is a cause of stillbirth, neonatal death, or reduced birth weight. In this study, the collaborative perinatal project previously described by Slone et al. (Ref. 15) was used. The 50,282 mother-child pairs previously described were reduced to 41,337 mother-child pairs by the following modification:

When a mother was enrolled in the study more than once, a random pregnancy was selected. This was done because perinatal deaths in prior siblings may increase the risk of subsequent perinatal death. Pregnancies lasting less than 7 lunar months were excluded, since as explained below, the definition of heavy aspirin exposure used here was partly dependent upon the duration of pregnancy.

As in the previous study, women were divided into those who were not exposed to aspirin (14,956), those with intermediate exposure but poorly defined (24,866) and those who were heavily exposed (1,515). Heavy exposure was defined for pregnancies lasting at least 8 lunar months, as aspirin taken for at least 8 days per lunar month in at least 6 lunar months. For pregnancies of 7 lunar months duration, the drug had to be taken for at least 8 days in each of at least 5 lunar months.

The findings of the study in terms of stillbirths and neonatal deaths according to aspirin exposure during pregnancy are as follows:

STILLBIRTHS, NEONATAL DEATHS, AND MEAN BIRTH WEIGHTS FOLLOWING ASPIRIN EXPOSURE DURING PREGNANCY

GROUPS EVALUATED

Group I: Containing 1,515 heavily aspirin-exposed mother-child pairs.

Group II: Containing 24,866 intermediate aspirin-exposed mother-child pairs.

Group III: Containing 14,956 non-aspirin-exposed mother-child pairs

Findings of study

Parameter measured	Group I	Group II	Group III
Number stillbirths.....	21	296	203
Percent of group.....	1.4	1.2	1.4
Number of neonatal deaths.....	17	252	168
Percent of group.....	1.7	1.0	1.1
Mean birth weight (g) [Standardized (\pm S.E.M.)]:			
White.....	3,223(\pm 20.4)	3,268(\pm 4.6)	3,260(\pm 6.1)
Black.....	3,074(\pm 17.0)	3,047(\pm 4.6)	3,046(\pm 6.2)

The findings demonstrate that in this study there is no evidence that aspirin taken during pregnancy is a cause of stillbirths, neonatal deaths or reduced birth weight. The fact that white children were associated with slightly reduced birth weight and for that matter neonatal deaths could have been in the authors' views due to chance. Opposite trends were evident in black children.

Criticisms of the study by Slone et al. (Ref. 15) discussed above are equally valid here. However, it is the conclusion of Shapiro, et al. that "based on our data, we find no evidence that aspirin as used by pregnant women in the United States is related to perinatal mortality or low birth weight."

(c) *Effects on maternal and newborn hemostatic mechanisms.* (1) *Interference with maternal hemostatic mechanisms.*—In the study of Lewis and Schulman previously mentioned (Ref. 18), the average blood loss at delivery in patients in Group I, patients taking large doses of aspirin for at least 6 months of gestation, was 340 ± 155 ml compared to 244 ± 114 ml and 235 ± 97 ml in the two control groups. This difference was found to be significant (p is less than 0.025) when the results were assessed using Student's t -test.

Collins and Turner (Ref. 16) also found that the incidence of antepartum hemorrhage defined by the authors as "bleeding greater than a show, after 28 weeks gestation," and postpartum hemorrhage defined by the authors as "a blood loss of 600 ml of blood or more in the first 24 hours after delivery," was significantly increased (p is less than 0.001) when group I (constant takers) was compared to controls. In the same study, the authors also found that the incidence of patients requiring transfusions at delivery was markedly increased when groups I and II (constant and intermittent takers) were compared to the control group (12 percent (6 percent versus 0 percent, respectively)).

(2) *Effect of aspirin on newborn hemostasis.* Bleyer and Breckenridge (Ref. 20) studied the effects of prenatal administration of aspirin on newborn hemostasis. Fourteen newborn babies who had been exposed to aspirin during the week prior to birth were compared to 17 children whose mothers had not taken aspirin. The two potentially adverse drug reactions detected were platelet dysfunction and diminished factor XII (Hageman Factor) in neonates born of mothers who had taken ordinary doses of aspirin during the last week of pregnancy. Aspirin-induced platelet dysfunction may have clinical relevance particularly during difficult traumatic deliveries

or in the presence of other hemostatic defects. The authors conclude that "until the clinical significance of these findings is more fully evaluated, it would seem prudent to restrict aspirin during the last month of pregnancy."

Preliminary studies of premature infants whose mothers have ingested aspirin during the week preceding delivery suggest that this drug might be a risk factor to these infants and produce clinical bleeding (Ref. 21). Studies are now in progress to confirm this preliminary finding.

Haslam, Ekert and Gillman (Ref. 22) have reported one case of a "life-threatening gastrointestinal hemorrhage" requiring two transfusions in one infant whose mother had taken calcium aspirin (3 tablets of 300 mg on each of the last 3 days of pregnancy, making a total of 2,700 mg). The baby required a transfer to a children's hospital because of vomiting blood at 4, 9 and 10 hours of age as well as rectal hemorrhage (30 ml of blood). Platelet function studies showed that platelet aggregation was impaired. Three weeks after the transfusions, the platelet function had returned to normal.

On the other hand, Turner and Collins (Ref. 14) examined the infants born to mothers who took salicylates regularly during pregnancy and found that although these infants had raised cord-blood levels of salicylate, they did not show signs of clinical bleeding.

(3) *Salicylate exposure in the perinate.* Studies demonstrating the presence of salicylic acid in neonatal urine specimens have shown intrauterine fetal exposure to aspirin or other salicylates. Umbilical cord sera from 272 consecutively delivered infants were examined for salicylate by Palmisano and Cassady (Ref. 23). Salicylate levels were unexpectedly found to be above 1 mg/100 ml in 26 of the sera (9.5 percent). The degree of fetal exposure to salicylate was indicated by a mean concentration of 3.3 mg/100 ml with a range of 1.2 to 10.9 mg/100 ml in this group. The mean reserve albumin binding capacity in these infants was significantly depressed (p is less than 0.03). The authors reported that unrecognized fetal exposure to salicylate was surprisingly common during late pregnancy. In view of comparable serum protein concentrations, the depression in the mean reserve albumin binding capacity is unlikely to be related to different albumin concentrations between the positive sera and control sera samples. Since salicylates displace bilirubin from its albumin binding sites (Refs. 24 and 25), this could pose problems in neonatal hyperbilirubinemia. The problem seems to

be of such importance that Palmisano and Cassady have proposed that blood salicylic acid measurements should be included in the clinical assessment and management of neonatal hyperbilirubinemia (Ref. 23).

Turner and Collins (Ref. 14) had shown that the babies of 144 mothers who took salicylates regularly during pregnancy had increased cord-blood salicylate concentrations. Although maternal blood was not always collected immediately after delivery it was always taken while the mother was still in the labor ward and, as expected, when the maternal blood salicylates concentrations were high, so were the cord-blood concentrations. Unfortunately, because of the timing it was not possible to compare maternal and cord-blood levels directly but in most cases the cord-blood concentrations were higher than the maternal concentrations.

It has been previously shown that the concentration of salicylate in the blood of the infant is usually higher than that of the mother (Refs. 26 and 27). This has been interpreted as an indication that the fetus near birth has the pharmacokinetics of a "deep" compartment with respect to salicylate (Ref. 28).

Furthermore, another factor to consider is that the apparent volume of distribution for salicylates is higher in the neonate (300 to 350 ml/kg) than that for similar doses, on a body weight basis, in older children and adults, namely 200 ml/kg (Refs. 29 and 30).

In a recent report Garrettson, Procknal and Levy (Ref. 29) have described the placental transfer and kinetics of elimination of salicylates in an infant whose arthritic mother took 6.5 g/day aspirin during her entire pregnancy. The baby was born with a salicylic acid concentration of 25 mg/100 ml plasma. While salicylate elimination was slower than in normal adults, it was more rapid than in the newborn whose mother had taken only one small dose of aspirin shortly before delivery. The slower rate of elimination in this infant when compared to adults was described as due to immaturity of the glucuronidation pathway and immaturity of the renal excretory mechanism.

(d) *Conclusions and recommendations.* Any relationship regarding the possibility of any teratogenic effect of salicylates in pregnant women has come from retrospective studies which are indirect and are possessed with obvious shortcomings. As conducted, they do not unequivocally demonstrate a teratogenic effect. Some limitations of the study, as indicated by the authors themselves, are that they cannot distinguish between the effect of the salicylates and the effect of the condition for which the salicylates were taken. In those specific studies (Refs. 14, 15, 18, and 19), in which the delivery of women who had taken salicylates during pregnancy was directly observed, no relationship between salicylates and teratogenicity was found. Even in a survey in which a comparison could be made between mothers of normal infants who

had taken salicylates by prescription during pregnancy and mothers of malformed infants who had taken salicylates by prescription, no difference was found that would demonstrate any relationship between salicylates and malformation in the offspring. Of particular significance in these retrospective studies, is the fact that the women in the study who had delivered malformed infants had taken several drugs other than salicylates, either alone or in addition to salicylates. This meant that many tests for significance had to be done during the statistical analysis to determine whether an association existed between the ingestion of a drug and the development of a malformation in an infant. The authors of the retrospective studies recognize these factors as limitations in the studies, and they state that because so many tests of significance were necessary some of the results of the tests may be due to chance.

Most of the studies relating to pregnancy did show that in those women taking salicylates, adverse effects to the mother and the fetus were significantly increased. High levels of salicylates in cord-blood were correlated with high levels of salicylates in maternal blood. In cases where such correlations were found, adverse effects were significantly increased in the mother and in the infant at delivery. In the mother the adverse effects consisted of an increase in the length of pregnancy and labor, and bleeding before and after delivery (Ref. 16). The fetus was adversely affected as evidenced by a decreased birth weight, and an increase in the stillbirth rate, perinatal mortality rate and decreased albumin binding capacity (Ref. 14).

The Panel is particularly concerned with the effects of chronic aspirin ingestion on the fetus, i.e., decreased birth weight, increased stillbirth rate, perinatal mortality and prolonged parturition. As for the acute administration of aspirin, the Panel is concerned with its effects on increasing duration of labor, changing hemostatic mechanisms in the newborn and increasing maternal blood loss. The latter may be a hazard particularly in premature labor and thus at any time during the last 3 months of pregnancy.

For the reasons detailed in the above paragraphs, the Panel concludes that there is a potential hazard to the use of aspirin during pregnancy and recommends the following warning on all aspirin-containing products "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician"

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(v) *Adverse effects on the central nervous system.* The lethal dose of aspirin or other salicylates probably is between 20 to 30 g for adults (Ref. 1) but doses of 200 to 300 mg/kg in children usually require hospital treatment (Ref. 2). The major toxic signs and symptoms arise from stimulation followed by depression of the central nervous system. Stimulation reveals itself in many ways including tinnitus (ringing in the ears), rapid breathing, confusion, unusual or bizarre behavior, vomiting, mania and even generalized convulsions. In severe poisoning, the stimulation is followed by depression as shown by respiratory failure, collapse of the cardiovascular system and coma. Tinnitus has been studied recently in man (with rheumatoid arthritis) by Mongan et al. (Ref. 3). In 59 subjects they noted tinnitus to be present in two individuals taking 12 aspirin tablets (3,900 mg) daily. The highest incidence of tinnitus was reported by those patients (14) taking 16 tablets per day. They found the serum salicylate level was invariably greater than 19.6 mg/100 ml when tinnitus was reported. They also observed a lack of correlation between the total daily aspirin ingestion and serum salicylate concentration. The authors emphasize the fact that patients with preexisting hearing loss will not report tinnitus as plasma salicylate concentrations increase.

It has been known for some time that salicylates produce a reversible ototoxicity manifested by deafness (Ref. 4). This was discussed recently by Jick et al. (Ref. 5) who studied drug-induced deafness in 11,526 hospitalized patients. Following aspirin, deafness was noted in 11 per 1,000 patients exposed. It is important for physicians to monitor patients receiving aspirin regularly at higher dosages for hearing loss as well as the presence of tinnitus. Because tinnitus or ringing in the ears is an early and frequent sign of aspirin or salicylate overdosage and the other symptoms mentioned may vary and be misinterpreted, the Panel believes that the labeling of aspirin and other salicylates should contain the following warning: "Stop taking this product if ringing in the ears or other symptoms occur". This built-in

"early warning system" of overdosage is advantageous in that it alerts users to a potential hazard and thereby contributes to the safe use of aspirin.

However, it should be noted that approximately 100 deaths per year result from accidental poisoning by salicylates and congeners (Ref. 6). Until recently, over one-half the deaths have been of children under 5 years of age. This figure has recently declined to approxi-

Deaths from accidental poisonings due to salicylates and congeners

	1968	1969	1970	1971	1972	1973	1974
Total deaths of children under 5 yr.....	61	58	48	44	46	26	25
Total deaths for all ages.....	120	104	107	105	122	95	88

Thus, salicylate poisoning can result in death and these drugs should not be viewed as harmless household remedies. Some authorities (Ref. 7) feel that the toxicity of the salicylates is underestimated by both the general public and physicians resulting in a higher than necessary incidence of toxic reactions most of which, fortunately, are mild and inconsequential.

However, with the consumption of aspirin exceeding 19 billion doses annually in the U.S. the relatively small number of accidental deaths attests to the safety of the salicylates under present conditions of use. The Panel believes that continued education of the public regarding the proper use and the potential dangers of misuse of these valuable OTC remedies and more informative labeling will result in a progressive decrease in the incidence of toxic reactions to aspirin and related drugs.

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mately one-fourth probably as a result of the introduction of safety closures for medicine containers and educational campaigns.

The Panel has included the following table which summarizes the total number of deaths of children under 5 years and the total number of deaths for all ages from accidental poisonings due to salicylates and congeners for the years 1968 to 1974 (Ref. 3):

and a few individual cases in man have been reported which suggest that aspirin may cause kidney disease or may increase existing kidney disease (Refs. 1 and 2). However, studies in other species of animals have shown no adverse effects (Ref. 3).

In rats, aspirin in combination with phenacetin may augment the nephrotoxic effect of phenacetin through synergistic renal effects (Refs. 3 and 4) producing a greater effect than either aspirin or phenacetin alone. The effects of phenacetin in producing nephropathy are discussed elsewhere in this document. (See part III, paragraph B.2.d. (2) (ii) (b) (2) below—Mechanism of action producing nephropathy.) In view of the much higher incidence of the use of aspirin than of phenacetin and the very few reports implicating products containing aspirin alone with renal papillary necrosis, the principal lesions associated with analgesic renal disease, the Panel finds that it is unlikely that aspirin alone is an initiator of analgesic nephropathies. This view is supported by recent epidemiologic studies which show that aspirin alone is not a cause of permanent (irreversible) kidney disease in man even when taken in high doses for prolonged periods of time (Refs. 4 through 8).

There are some indications that long term (chronic) aspirin consumption even in the absence of phenacetin may cause renal dysfunction in a small number of long term aspirin users (Refs. 9 and 10). The majority of these cases involved abuse of analgesic compounds or treatment of rheumatoid arthritis. It is the Panel's opinion that long-term abuse of aspirin, used alone, is infrequent. Almost all nontherapeutic chronic use has been as a component in a mixture containing another ingredient with greater potential to produce dependence (codeine, caffeine, phenacetin). The other major group involved in long-term use are patients with rheumatoid or osteoarthritis. It is the Panel's contention that for this and other reasons elaborated elsewhere in this document that arthritic patients should not be self-medicating without medical supervision. (See part V, paragraph A. below—General Discussion.) In addition, it is the Panel's recommendation that professional labeling to health professionals adequately alert physicians to the need for periodic renal

function tests for their patients taking large amounts of aspirin. An OTC kidney warning labeling is therefore not necessary.

The Panel concludes that although prolonged use of high doses of aspirin may produce kidney disease in rare instances, the risk involved is insignificant in the recommended target populations when aspirin alone is involved. In the opinion of the Panel, a warning regarding aspirin causing kidney disease is not warranted for OTC use. However, physicians should be alerted that substitution of aspirin alone or in combination, for phenacetin, in patients with existing analgesic kidney disease, may be tolerated in low doses in some patients but contribute to continued renal deterioration in others.

Furthermore, recent evidence discussed below showing acute effects of aspirin on renal glomerular filtration, indicates that perhaps short term use of aspirin may contribute to or exacerbate other types of chronic or acute renal disease. Although a warning label regarding the use of aspirin in patients with existing renal disease would be premature now, this is only because the definitive studies have not been performed to the Panel's knowledge.

(a) *Acute effects (short-term use).* Prescott found that aspirin produces a transient increase in urinary excretion of tubular epithelial cells (Ref. 1). The effect of aspirin was greater than that obtained with phenacetin. The effect does not persist during continued dosing. Two very recent studies have demonstrated that aspirin produces an acute decrease in glomerular filtration rate (Refs. 11 and 12). A mean 10.5 percent decrease in glomerular filtration rate was observed in patients receiving oral doses of 20 mg/kg aspirin (Ref. 10). In another independent study, an intravenous dose of aspirin produced a 30 percent fall in glomerular filtration rate (Ref. 12). This effect is significant since the usual decrease in glomerular filtration rate is only about 20 percent from 25 to 65 years of age (Ref. 13).

It is not known whether these acute effects of aspirin on the kidney contribute to long term analgesic nephropathy. Some authors believe this is unlikely (Ref. 14). The significance of these findings relative to the short-term use of aspirin in patients with acute or chronic renal disease is also not yet known.

(b) *Analgesic nephropathy.* A large number of studies in rats have shown that, in this species, aspirin alone can produce renal papillary necrosis, the primary kidney lesion associated with analgesic kidney disease (Refs. 1, 2, 15, and 16). Combinations of aspirin and phenacetin produced renal papillary necrosis more frequently than aspirin alone. In rats, aspirin alone produced renal papillary necrosis in a generally greater number of cases than phenacetin alone (Ref. 15).

Renal papillary necrosis has also been induced in the dog. However, most animal studies have been carried out in the rat.

The rat kidney is different than that of man. Being unilobular and having a long slender papilla, it has been suggested that the rat kidney may be much more susceptible to papillary damage (Ref. 17). The pig was selected as a more suitable test animal because it has a multilobular kidney similar to that of man and is thought to metabolize salicylate similarly to man. McIver and Hobbs fed aspirin to 11 pigs for 10 months at a dose higher than that usually used by abusers without any evidence of renal injury to any of the animals (Ref. 13).

(c) *Clinical studies.* In spite of the extensive use of aspirin and numerous attempts to show correlation between chronic aspirin use and renal papillary necrosis, there are less than 10 cases of renal papillary necrosis reported in the world literature that are associated with the use of aspirin only (Refs. 1, 6, 9, 10, 18, and 19). The possibility of a causative role of aspirin when used alone in large long term doses has been the subject of several epidemiologic studies.

A recent study of the Boston Collaborative Drug Surveillance program reported by Lawson (Ref. 20) examined a possible correlation between analgesic use and renal function in 6,407 patients and found no correlation. As discussed elsewhere in this document, the negative results of this study are inconclusive because the study design (error due to drug, dose, time) is such that real associations are unlikely to be detected. (See part III, paragraph B.2.d.(ii)(b)(1) below—Epidemiological studies.) This study also could not show any association between renal dysfunction and ingestion of phenacetin compounds.

The better controlled long-term prospective study of Dubach clearly showed an association between analgesic abuse of phenacetin combinations and decreased renal function (Ref. 4). No such correlation could be demonstrated in those patients taking preparations containing only aspirin.

In a recent study by Emkey and Mills (Ref. 5), it was shown that prolonged high doses of aspirin given to patients with rheumatoid arthritis do not cause significant kidney damage. They studied all patients with rheumatoid arthritis followed at the Massachusetts General Hospital Arthritis Clinic who had been taking aspirin for 10 or more years. There were 36 patients whose average age was 60.5 years, mean duration of therapy was 23 years, and mean daily ingestion was 5 g aspirin. The average total amount of aspirin ingested was 42 kg. Studies of renal function and urinary abnormalities revealed that although minor histological or functional renal abnormalities could not be ruled out, no permanent kidney damage could be demonstrated in these patients.

Macklon and coworkers (Ref. 6) initially studied renal function in 17 patients with rheumatoid arthritis who had ingested 5 to 20 kg aspirin. Renal function was assessed by measuring serum creatinine, creatinine clearance and proteinuria. Fourteen of these

patients were followed up after 2 years. No evidence of permanent renal damage was found.

The New Zealand Rheumatism Association Survey in 1974 (Ref. 8) of 763 patients with rheumatoid arthritis and 145 patients with osteoarthritis, showed no association between aspirin (alone) intake and a renal score designed to identify analgesic nephropathy. Analgesic nephropathy was detected in three patients taking APC (aspirin, phenacetin and caffeine) compounds, one taking aspirin and phenylbutazone and one taking aspirin and acetaminophen. The New Zealand Rheumatism Association concluded that there is risk from APC compounds but not aspirin alone. However, aspirin may have an additive or potentiating effect with other analgesics.

Bulger (Ref. 7) found a correlation between the total dose of aspirin ingested and the depression of creatinine clearance in rheumatoid arthritis. These findings were not corrected for age of the patients, and none had a creatinine clearance less than 50 even though one patient took a total dose of 40 kg aspirin.

The Panel concludes, that in view of the much higher incidence of the use of aspirin than phenacetin and the very few reports implicating products containing aspirin alone with renal papillary necrosis, it is unlikely that aspirin is an initiator of serious kidney disease. However, it has been suggested that products containing aspirin, alone, can exacerbate and/or perpetuate the progression of papillary necrosis and renal dysfunction (Refs. 1 and 2). Aspirin may contribute to the nephrotoxic effect of phenacetin through the impairment of renal concentrating mechanisms (Ref. 15) or other possible mechanisms. Burry (Ref. 21) speculates that the initial damage occurs in the ascending limb of the loops of Henle. Ischemia may be caused by inhibition of prostaglandin E₁ synthesis by aspirin. Phenacetin and its metabolites have a profound oxidative effect on cells with salicylate-induced suppression of the hexose monophosphate shunt. Burry and others have suggested that aspirin may contribute to renal papillary necrosis through an additive effect even though aspirin alone is rarely associated with renal papillary necrosis (Refs. 8 and 21).

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(vii) *Adverse effects on the liver.* Several recent studies have confirmed that aspirin causes a reversible hepatotoxicity (Refs. 1 through 9). Increased hepatic dysfunction after aspirin ingestion has been identified by increased serum activity of transaminase (Refs. 1 through 4), serum glutamic oxaloacetic transaminase (SGOT) (Ref. 2), serum glutamic pyruvic transaminase (SGPT) (Ref. 2) and decreased activity of aspirin esterase (Ref. 9).

The increased incidence of hepatotoxicity has generally been observed in children (Ref. 2) and adults (Refs. 7 and 8) of both sexes treated for systemic lupus erythematosus or rheumatoid arthritis requiring moderate doses over a period of several weeks. The effect is apparently a function of dose (Refs. 2 and 10), plasma salicylate level (Ref. 10), the disease state and preexisting liver disease (Ref. 9).

In children treated for juvenile rheumatoid arthritis requiring high plasma

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salicylate levels, over 65 percent experience elevated transaminase activity (Ref. 2).

Seaman and Plotz gave aspirin four times daily at a dose sufficient to obtain a serum salicylate level of 25 to 30 mg/100 ml (Ref. 6). They observed increased transaminase activity in 3 of 18 rheumatoid arthritis patients. Patients with systemic lupus erythematosus required lower salicylate plasma concentrations to produce hepatitis. Some patients experienced a fall in elevated transaminase activity even though the multiple aspirin dosing was continued. Others maintained high transaminase activity until aspirin therapy was stopped or the dose reduced.

Rich and Johnson reported dose-related hepatotoxicity of salicylates in six children with severe rheumatoid arthritis (Ref. 2). Elevated SGOT and SGPT activities were observed in all patients and occurred only when serum salicylate levels were above 25 mg/100 ml. The effects occurred with sodium and choline salicylic acid salts as well as aspirin. A reduction of the dose reversed the effect indicating that the effect is primarily a function of salicylic acid level, rather than aspirin per se and is a reversible process. Clinical symptoms were also manifest in four patients. Liver biopsies were done in two patients which showed histological evidence of liver damage with scattered cell necrosis evident in one case.

Aramaki et al. studied 42 patients with various diseases given 2 g aspirin daily for 3 to 4 weeks (Ref. 9). They concluded that aspirin caused liver damage only in adult patients with impaired liver function. They found aspirin esterase enzyme activities decreased after aspirin administration in 8 of 14 patients with liver damage but slightly increased in those patients without liver disease. The decrease in aspirin esterase correlated with elevated transaminase in six of the eight patients with liver disease.

In view of the recent findings which have confirmed that aspirin causes a reversible hepatitis, especially in children and adults with systemic lupus erythematosus or rheumatoid arthritis and for other reasons elaborated elsewhere in this document, the Panel concludes that arthritic patients should not be self-medicating without medical supervision. (See part V, paragraph A, below—General Discussion.) In addition, it is the Panel's recommendation that professional labeling to health professionals adequately alert physicians to the need for periodic liver function tests. An OTC liver warning labeling for this group is therefore not necessary.

The Panel concludes that although prolonged use of high doses of aspirin may produce hepatotoxicity, the effect is dose related, dependent upon the disease state for which aspirin is indicated, and is a function of any preexisting liver disease. In the opinion of the Panel, a warning that aspirin may cause liver disease not warranted.

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(viii) *Adverse effects of concomitant use with other drugs or by persons with certain disease states.* The Panel has earlier briefly discussed the need for caution in the use of salicylates, especially aspirin, in the presence of serious illness and medical conditions for which prescription drugs are indicated. (See part II, paragraph H, above—Drug Interactions with Analgesic, Antipyretic and Antirheumatic Agents.) Reports have indicated possible drug interactions between the salicylates and other drugs (Refs. 1 through 7). Individuals who are taking prescription drugs may also use OTC analgesics, antipyretics or anti-rheumatics containing salicylates to relieve pain, fever or headache without consulting a physician. Therefore, to alert such individuals that a drug interaction may occur between their prescription drugs and salicylates, the Panel recommends that the labeling of these OTC products contains a general warning against the concurrent use of salicylate-containing products and certain prescription drugs. The warning on products containing salicylates should read "Caution: Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

The effects of a drug may be modified by prior or concurrent administration of salicylates. Such modifications or drug interactions may alter the effectiveness or toxicity of a drug by several mechanisms. Pharmacokinetic interactions and

pharmacologic interactions are the two best understood mechanisms by which salicylates may modify the actions of drugs. In pharmacokinetic interactions, salicylates affect the absorption, metabolism, distribution or excretion of other drugs. Salicylates may also alter the pharmacologic effects of other drugs by producing an additive, synergistic or antagonistic pharmacologic effect. In the interaction of prescription drugs with salicylates, both of these mechanisms operate to modify the effectiveness and/or toxicity of prescription drugs.

Salicylates may interfere with or modify the effect of drugs that are taken for therapeutic use in the following disease conditions:

(a) *Anticoagulants used in the treatment of blood diseases.* As the Panel has noted above, high doses of aspirin and salicylic acid taken for several days can increase prothrombin time significantly. (See part III, paragraph B.1.a.(2)(i)(a) above—Decrease in prothrombin production.) Aspirin in doses below those required for a hypoprothrombemic effect may also increase bleeding time by inhibiting aggregation of platelets. (See part III, paragraph B.1.a.(2)(j)(b) above—Increased bleeding time and inhibition of platelet aggregation.) Aspirin, particularly, should be avoided when oral anticoagulants (especially the coumarins) are taken. Anticoagulants are prescribed for thrombophlebitic and thromboembolic states including post-operative thrombophlebitis, pulmonary embolism and coronary thrombosis.

Aspirin has an additive effect on the action of anticoagulant drugs. Coumarin anticoagulants [coumadin (warfarin sodium), dicumarol (bishydroxycoumarin), acenocoumarol, ethyl biscoumate, and phenprocoumon] as well as indandione anticoagulants (anisindione, diphenadione, and phenindione) would all be expected to act in a similar manner (Ref. 6). The inhibition of platelet aggregation by which aspirin can significantly increase bleeding time, may preclude its concurrent use with heparin.

The available clinical data actually provides conflicting reports with regard to the effects of aspirin on the prothrombin time response to warfarin and other oral anticoagulants. Nevertheless, in view of aspirin's effect on gastric erosion, its inhibition of platelet activity, and its possible direct inhibition of the prothrombin complex, the possibility of inducing a clinically significant problem in patients receiving oral anticoagulants needs to be recognized (Ref. 6). The concurrent use of large doses of salicylates and anticoagulants may lead to severe hemorrhage unless the dosage of the anticoagulant is reduced or the individual stops taking the OTC salicylate (Ref. 2).

The Panel recommends that nonsalicylate analgesics be used in patients requiring oral anticoagulants of the coumarin type. Since documented adverse effects with salicylates have been shown to be directly related to oral anticoagu-

lants, and since the use of anticoagulants must be closely monitored by a physician, the Panel concludes that the term "anticoagulant drug" should be included in the general warning statement. It is the Panel's view that patients currently taking such prescription drugs are under the close supervision of a physician. These patients will be aware that they are taking anticoagulant drugs, and it is important that they be immediately alerted through adequate labeling not to take salicylates concurrently.

(b) *Hypoglycemic effect with antidiabetic drugs.* The hypoglycemic (low blood sugar) activity of the oral antidiabetics (sulfonylureas) may be enhanced by the concurrent administration of salicylates. It should be noted that salicylates, themselves, were among the first compounds used for their hypoglycemic effect. The exact mechanism of the hypoglycemic effect of salicylates is not completely understood. Several mechanisms by which aspirin may decrease plasma glucose levels have been postulated, among which are hepatic glycogen depletion and increased glucose utilization.

It has been reported that the hypoglycemic activity of the antidiabetic drug, chlorpropamide, may be enhanced by the concurrent administration of aspirin (Ref. 6). Chlorpropamide is chemically related to other hypoglycemic agents such as tolbutamide, acetohexamide and tolazamide and a similar interaction with aspirin may possibly occur. The interaction between salicylates and oral antidiabetic drugs would result in a prolonged and protracted fall in plasma glucose levels. The mechanism by which this effect is brought about has been attributed to salicylate displacing the antidiabetic agent from its binding sites rather than to any intrinsic hypoglycemic activity of the salicylates. The displacement would increase the amount of free (pharmacologically active) antidiabetic drug in circulation and increased hypoglycemia would result. The interaction would result in poor control of diabetes (Ref. 5). The only alternative, if both drugs were required, would be to decrease the dosage of the antidiabetic drug during salicylate intake and then to increase the dosage when salicylates were discontinued. This would need to be accomplished under the direct supervision of a physician.

There have been no controlled clinical trials demonstrating a direct relationship between chlorpropamide and aspirin. However, as has been pointed out, the literature does indicate that the hypoglycemic activity of chlorpropamide may be enhanced with use of aspirin, but maybe only at uricosuric doses. Nevertheless, because of this possibility and because salicylates do have hypoglycemic properties, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of diabetes.

(c) *Uricosuric inhibition in gout.* Individuals with gout have high serum uric acid levels. Several prescription drugs are prescribed for gout to decrease uric

acid blood levels by increasing the renal excretion of uric acid (uricosuria). These drugs include probenecid, the sulfinpyrazones and phenylbutazone. Aspirin has been reported to specifically interfere with the uricosuric action of sulfinpyrazone. High serum uric acid levels and mutual suppression of uricosuria occur in humans when both drugs are used concurrently (Ref. 6).

The concurrent use of salicylates with uricosuric drugs results in the inhibition of the excretion of uric acid in the urine (uricosuria inhibition) and thereby results, in effect, in the antagonism of the activity of these drugs (Ref. 5). Uric acid is normally reabsorbed into the body and not excreted by the kidney. The uricosuric agents used in gout block the reabsorption of uric acid from the urine to the plasma and thus increase the excretion of uric acid. It is interesting to note that salicylates alone have a pronounced uricosuric effect in high doses and can be used to reduce high uric acid levels in gout, but in OTC doses, aspirin causes retention of uric acid. Hence in the latter instance the uricosuric effect of the uricosuric agents may be counteracted. This interaction in low OTC doses may cause a suppression of uricosuria which results in uric acid retention in the body; uricosuria is prevented and the therapeutic action of the drug is negated.

Salicylates and uricosuric agents compete for common binding sites on plasma proteins and for active tubular transport in the kidneys. Concurrent administration decreases the binding of the uricosuric agents. The salicylate binding remains unaltered, reducing the excretion of the salicylates.

The Panel concludes that individuals with gout should avoid salicylates. Because salicylates have been shown to antagonize the effects of uricosuric agents, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of gout.

(d) *Ulcerogenic enhancement in arthritis.* Almost all anti-inflammatory agents commonly used in rheumatic diseases can cause gastric ulcers. These agents include aspirin, corticosteroids, phenylbutazone and indomethacin. Although the mechanisms by which the ulcerogenic effect is produced by these agents are not definitely established, the possibility of an increased incidence of gastric ulceration when aspirin is used concomitantly with other ulcerogenic anti-inflammatory agents must be considered.

When corticosteroids and salicylates are taken concurrently, the ulcer-producing effect in the stomach is additive. An increased ulceration hazard occurs. In addition, the corticosteroids may increase the excretion of salicylates so that to achieve a therapeutic anti-inflammatory and/or analgesic effect, the dose of the salicylates must be increased. If the steroids are then withdrawn, the continuing high dose salicylate medication may lead to signs of salicylate toxicity (Ref. 5).

The combined use of indomethacin and salicylates also poses an increased potential for gastric ulceration since both indomethacin and salicylates have an ulcer-producing effect on the mucous membrane of the stomach (Refs. 1 and 5). The use of aspirin with indomethacin is particularly hazardous since aspirin appears to have some inhibitory effect on the gastrointestinal absorption of indomethacin. Aspirin decreases and delays the gastrointestinal absorption of indomethacin causing a decrease in the indomethacin serum level and urinary excretion, and a rise in the fecal excretion of indomethacin (Ref. 6). The concurrent use of the two drugs does not produce an additive therapeutic effect but may increase gastric ulceration.

The Panel concludes that individuals taking antirheumatic agents for the treatment of arthritis should not self-medicate with salicylates. Because salicylates increase the potential for gastric ulceration and because aspirin has been shown to decrease and delay the gastrointestinal absorption of a commonly used antirheumatic agent, e.g., indomethacin, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of arthritis.

(e) *Other drug interactions of varying significance.* The Panel has considered several other interactions between salicylates and prescription drugs which the Panel does not consider warrant inclusion of a warning in the labeling of salicylates. The clinical significance of these interactions is not sufficiently urgent, either because individuals taking these prescription drugs are under close medical supervision, are not taking these drugs chronically or because there is little likelihood of toxicity.

An example of an interaction with a prescription drug that is closely supervised by a physician, is methotrexate. This drug is a highly potent and very toxic drug which is prescribed for individuals with cancer or extensive psoriasis or psoriatic arthritis. Salicylates potentiate the therapeutic as well as the toxic effects of this drug (Ref. 5). The Panel is cognizant of the severity of this interaction, particularly of its immunosuppressive effect. However, because of the severe toxicity of methotrexate, physicians always carefully control the patient's use of all other medications, thereby negating the need for a warning.

Sulfonamides are antibacterials employed primarily in the treatment of urinary tract infections. It has been suggested that the increased antibacterial activity resulting from the interaction with salicylates is due to the ability of salicylates to decrease the serum protein binding of sulfonamides, thus increasing the amount of free drug (pharmacologically active) (Ref. 6). Even though this interaction can be potentially serious, sulfonamides are usually used for treatment of active infections, not for chronic conditions, and thereby do not merit inclusion in a warning.

An interaction which the Panel does not consider enough of a hazard to justify inclusion in the warning concerns the concurrent use of salicylates with drugs that result in changing the pH of the urine. Some substances, such as ascorbic acid (vitamin C), increase the acidity of the urine. The acidification of the urine increases the renal tubular reabsorption of salicylates, thus decreasing the excretion of the salicylates and increasing the salicylate level in the blood (Ref. 5). On the other hand, when substances, such as sodium bicarbonate, are taken, the urine becomes alkaline. Under alkaline conditions, the excretion rate of salicylates is increased, decreasing salicylate levels in the blood (Ref. 3). For salicylates to reach toxic levels in the blood when urine acidifiers are taken concurrently, high doses of salicylates would have to be ingested. The Panel does not believe that this interaction is important since in the usual OTC use of salicylates, it is unlikely that an ascorbic acid salicylate type of interaction would result in toxic salicylate levels in the blood.

For patients with disease conditions that require prescription drugs but which do not require the constant or daily supervision of a physician, the Panel recommends that a warning on the labeling of OTC salicylates is necessary, to warn the patient against serious potential interaction with salicylates. The Panel has therefore concluded that the warning against the use of salicylates with drugs prescribed for specific kinds of disease conditions, i.e., anticoagulants and drugs used in the treatment of gout, diabetes and arthritis, is adequate for the labeling of OTC salicylates.

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- (ix) *Adverse effects resulting in iron deficient anemia.* Occult blood loss is usually not clinically significant (Refs. 1 and 2), but prolonged use of aspirin can result in greater occult bleeding in some patients and cause a persistent, otherwise inexplicable, iron deficient anemia (Refs. 3 through 4). This has been observed in adults, particularly in some studies in rheumatoid arthritis (Ref. 5). At the same time it is known that anemia associated with some rheumatoid diseases will improve when the disease is brought under control with therapeutic doses of aspirin. Aspirin has been recently re-emphasized as an important consideration in the diagnosis of anemia in children (Ref. 6).
- Aspirin causes occult blood loss from the gastrointestinal tract. This has been discussed extensively elsewhere in this document. (See part III, paragraph B.1.a.(2)(ii)(e) above—Occult bleeding.)
- Stubbe (Ref. 1), in a study on the presence of occult blood in the feces due to aspirin ingestion, stated that:
- It has been demonstrated that the loss of blood (produced by aspirin) may not always be ignored; this applies especially to the extent to which the patient is already anaemic and in a bad state generally. The taking of aspirin over a long period is most common in the case of persons suffering from rheumatoid arthritis. Many such patients are anaemic, a state of which has always been regarded as a consequence of the rheumatic process. Now that we know that aspirin can cause bleeding, it may be asked whether this has not likewise often played a more or less important part in bringing about anaemia.
- Holt (Ref. 2), in a study in which gastrointestinal blood loss was measured after aspirin ingestion, found that 69 percent of 35 subjects who were ingesting 40 gr of aspirin (8 tablets daily) were losing blood and that 17 percent lost more than 6 ml (an average of 20-fold over control values). Ten of the 35 were "healthy" volunteers tested at the same doses, all 10 bled with an average blood loss of 5.7 ml daily. Fourteen out of the remaining 25 subjects who bled had an average blood loss of 3.3 ml daily. These latter subjects were patients with negative histories of gastrointestinal bleeding. This difference was found not to be statistically significant. Holt concluded that "This suggests that alimentary bleeding represents a very frequent side effect of aspirin therapy, and in some patients chronic ingestion of salicylates may be accompanied by sufficient blood loss to induce iron deficiency over a prolonged period."
- The first report directly linking the consumption of aspirin with anemia appeared in 1958 (Ref. 3). The authors described two cases of patients with severe anemia due to the ingestion of salicylates. The first, a 39-year-old man, complained of fatigue and exertional dyspnea. For 7 years he had suffered from migraine headaches and had taken an average of 8 to 10 tablets of aspirin weekly. His hemoglobin was 8.4 g/100 ml and there were hematological features of iron deficiency. A history failed to reveal the cause of the anemia, and after responding to intravenous iron therapy he was discharged to the outpatient department where he was followed with oral iron treatment. Six months later he was readmitted to the hospital with severe anemia (hemoglobin 4.2 g/100 ml). He again responded favorably to intravenous iron therapy and then continued iron injections as an outpatient.
- The clinical and hematological findings were compatible with iron deficiency anemia due to chronic hemorrhage. Occult blood tests in the stools were negative while the patient was hospitalized. It was difficult to diagnose the reason for the anemia.
- Then, on two occasions aspirin (10 gr) was administered three times daily and the occult blood tests showed strongly positive results. Confirmation of the relationship between salicylate consumption and the anemia was obtained when the patient was advised to discontinue the intake of aspirin. Iron therapy could soon be discontinued and at the time of publication there was no recurrence of the anemia.
- The other case described in this report was that of a 29-year-old woman who was admitted to the hospital for the treatment of anemia. She also complained from fatigue and exertional dyspnea, as well as epigastric pain and "acid-regurgitation". She had had severe headaches for a year for which she took up to "30 salicylate tablets" weekly. Her history also included a complication of hemorrhage during her "fourth confinement" (fourth child delivery) for which she had received a blood transfusion and iron tablets. Examination revealed severe anemia (hemoglobin of 5.6 g/100 ml) apparently due to iron deficiency. She responded well to oral iron therapy. After leaving the hospital she regularly attended the outpatient clinic. The anemia recurred and required continuous iron therapy which had to be supplemented on two occasions with intravenous iron. She had a dilatation and curetage and then a total hysterectomy. She still remained anemic and did not respond to a 6-month course of oral iron. Her anemia worsened to 4.2 g of hemoglobin per 100 ml and she was again hospitalized. Her serial stool occult blood tests were negative. The diagnosis for the cause of the anemia in this case was again very difficult. The patient was experimentally administered 10 gr aspirin four times daily which was followed by strong occult blood reactions in the stools.
- This patient again was advised against salicylate ingestion and an alternative analgesic was suggested. The patient started to take salicylates after having recovered from the anemia and again her hemoglobin decreased from 14.6 to 11.2 g/100 ml. Eventually, after repeated exhortations the patient stopped taking salicylates and recovered. This latter case has been described in what may seem excessive detail; however, the purpose is to illustrate that in this case, because of the failure to obtain an early correct diagnosis, this woman had to undergo not only anemia of long time duration but dilatation and curetage and eventually even hysterectomy at the age of 29 years.
- Stubbe has described 16 cases of severe iron deficiency anemia due to blood loss associated with aspirin ingestion (Ref. 4). Stubbe comments:

In every patient the use of aspirin, even if not the sole cause, played an important role in the development of the condition. There were no indications of peptic ulcer, profuse menses or haemorrhagic diathesis in any of these patients. It appears that the use of aspirin certainly does not need to be extravagant to play a predominant role. The main feature of these 16 patients, all of whom developed strongly positive benzidine reactions after the administration of aspirin, were:

- (i) reason for taking aspirin: rheumatic complaints, 4; headache, 12 (patients);
- (ii) daily dose of aspirin 0.5-3 g in 15 (patients);
- (iii) Age less than 25 years in 9.
- (iv) Sex 15 females;
- (v) Hemoglobin less than 9.0 g/100 ml in 15.

He then commented on the difficulties of diagnosing this type of anemia: "As a rule aspirin is no longer given after admission, and so the role of this drug will often be masked and will therefore not be found unless one is conscious of this process."

All the patients reported by Stubbe had also a low serum iron and a high iron binding capacity.

Menguy in a review of the clinical, pathological and pathogenetic aspects of gastric mucosal injury induced by aspirin described two other cases of aspirin-induced anemia (Ref. 5). The first case was that of a 60-year-old retired pharmacist with severe iron deficiency anemia. His hematocrit had never risen over 30 percent except immediately after each of the many transfusions he had received. When the attending physician, to whom the patient had been referred, inquired about aspirin ingestion, which had never been explored before, the patient confided he had been taking 2 g aspirin daily over the past 2 to 3 years. Initially, he had taken them for headaches, then it became a "habit." Tests for fecal blood were carried out using ⁵¹Cr-tagged red blood cells during and after the administration of 2 g aspirin daily. After the results of the tests were disclosed to the patient he stopped taking salicylates, and without any transfusion his hematocrit rose from 19 percent upon admission to 25 percent 2 weeks later; a month later it was 34 percent and 3 months later it was normal.

The second case described in this report was that of a 40-year-old woman who was admitted with severe anemia after an episode of melena.

The patient later admitted taking an aspirin-containing preparation (an average of 100 tablets weekly) over the previous 6 months. This one is the only case in the literature reviewed where the anemia was due to excessive doses of an aspirin-containing analgesic preparation.

More recently, five cases of aspirin-induced anemia have been reported to occur in children (Ref. 6). The first case was that of a 3-year-old child who had received 150 mg aspirin nightly as a "sedative". His hemoglobin was 5.2 g/100 ml and his blood showed an iron deficiency anemia pattern. After he stopped taking aspirin, the anemia did not recur.

The second case involved another 3-year-old child with a hemoglobin of 4.3 g/100 ml and his blood again showed an iron deficiency anemia pattern. The results of occult blood tests in the stool were positive on the first 3 days after admission. From repeated history-taking, it was found that the boy had been taking two to three 300 mg aspirin tablets daily for many months as a "sedative". The third case was that of a 14-year-old boy with a hemoglobin of 5.8 g/100 ml and the blood film was classical of iron deficiency anemia. The occult blood tests were positive for the first 5 days after admission. After repeated questioning the boy disclosed that he had been taking 600 mg aspirin daily and often 600 mg at night for 6 months "to relieve mild tooth aches, headaches and sleeplessness."

Case 4 involved a 12-year-old girl with a hemoglobin of 7.1 g/100 ml and again the blood film showed iron deficiency anemia. She eventually admitted having taken 600-1,200 mg aspirin daily for 4 months before admission to the hospital.

Case 5 was a 8-month-old infant who had a hemoglobin of 7.4 g/100 ml and the blood film showed iron deficiency anemia. Stool occult blood tests gave positive results. On closer questioning the parents admitted that the baby had received 2 "junior" 150 mg aspirin daily for the previous 6 to 8 weeks for febrile episodes, teething and as a "sedative". Aspirin was stopped, the anemia responded to iron therapy and the baby remained well thereafter.

The similar pattern in all five children and the complete recovery when aspirin ingestion was stopped suggests strongly that the aspirin ingestion caused the anemia.

All of the cases in this review of the literature suggest that caution should be exerted during aspirin therapy and that when pallor, fatigue and easy exertion are the symptoms the possibility of aspirin-induced anemia should be investigated.

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- (3) Dosage. (i) For products containing 325 mg (5 gr) per dosage unit. (a) Standard schedule. Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not

more than 10 days. Children 11 to under 12 years oral dosage is 437.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) Nonstandard schedule. Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) For products containing 80 mg (1.23 gr) per dosage unit. Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) For products containing more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) per dosage unit. Adult oral dosage is more than 325 mg (5 gr) but not more than 842 mg (12.96 gr) initially, followed by more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) every 3 hours while symptoms persist not to exceed 3,789 mg (58.32 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) For products containing more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) per dosage unit. Adult oral dosage is more than 421 mg (6.48

gr) but not more than 970 mg (14.92 gr) initially, followed by more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) every 4 hours or 842 mg (12.86 gr) but not more than 970 mg (14.92 gr) every 6 hours while symptoms persist not to exceed 3,880 mg (59.68 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) For products containing more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) per dosage unit. Adult oral dosage is more than 485 mg (7.46 gr) but not more than 1,000 mg (15.38 gr) initially, followed by more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) every 3 hours or 970 mg (14.92 gr) but not more than 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(vi) For products containing more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) per dosage unit. Adult oral dosage is more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following specific labeling: (i) **Warnings.** (a) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(b) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(c) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) **Standard aspirin dosage unit.** In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of aspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing aspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin per dosage unit. (See part II, paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that all products containing aspirin be clearly labeled as containing aspirin on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of aspirin per dosage unit. As previously stated, the labeling will not only benefit all

consumers but will alert those individuals having sensitivity to aspirin.

(a) **Products containing the standard aspirin dosage unit.** The Panel recommends that products containing only 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(b) **Products containing aspirin in an amount different than the standard aspirin dosage unit.** While the Panel recommends that products contain only 325 mg (5 gr) aspirin per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of aspirin other than 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(b) **Acetaminophen.** The Panel concludes that acetaminophen is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) **Effectiveness.** This drug belongs to a group of drugs which were introduced into therapeutic use before the era of well-controlled clinical trials. Acetaminophen (N-acetyl-p-aminophenol) was first used by von Mering in 1893 (Ref. 1). Yet, as Beaver has observed, there have been a number of suitably controlled studies of its analgesic effect in man in the past few decades as noted below.

While acetanilid and phenacetin have been used extensively since the time of their introduction, acetaminophen was used very little until Brodie and Axelrod demonstrated that in man, both acetanilid and phenacetin are converted into acetaminophen and proposed that acetaminophen may be the "active" metabolite through which both precursors exerted their pain relieving and fever reducing effects (Refs. 2, 3, and 4).

Flinn and Brodie in 1948 evaluated the effect of 325 mg of acetaminophen in 12 normal healthy females subjected to experimental pain by means of heat radiation. They found that within 30 minutes following administration the pain threshold rose significantly. The analgesic activity was maximal at approximately 2.5 hours and was terminated at about 4 hours after administration. They also showed that the analgesic effect obtained with acetaminophen was significantly superior to that of placebo (Ref. 5).

Zelveler administered repeated doses of 500 mg acetaminophen, 500 mg aspirin and placebo in a crossover study in

patients with chronic pain of different causes and found both analgesics superior to placebo (Ref. 6).

Batterman and Grossman evaluated the analgesic activity of acetaminophen in 234 patients with musculoskeletal pain using doses of 300 or 600 mg 4 times daily for up to 25 weeks. They concluded that with the exception of inflammatory pathological situations acetaminophen was superior to aspirin for the treatment of musculoskeletal pain (Ref. 7).

In a double-blind study Wallenstein and Houde compared aspirin, acetaminophen and salicylamide, all at a dose of 600 mg, against placebo in a population of hospitalized cancer patients. The time-effect curves were similar for acetaminophen and aspirin and both were greater in peak effect and in duration than those for salicylamide and placebo (Ref. 8).

Lasagna, Davis and Pearson (Ref. 9) carried out a double-blind study in 373 patients who had just undergone childbirth. Acetaminophen, phenacetin and aspirin, 600 mg of each, were compared against placebo. They concluded that "in agreement with the findings of other workers, our data show that acetaminophen is, in commonly recommended doses, an effective analgesic which can be satisfactorily substituted for acetylsalicylic acid."

Kantor et al. compared aspirin at two dose levels, 600 and 1,200 mg, acetaminophen at 600 mg, and placebo in patients who had just undergone childbirth and found the three drug treatments were all significantly superior to placebo but not significantly different from each other (Refs. 10 and 11).

Parkhouse and Hallinon (Ref. 12) in a double-blind study in post-operative orthopedic patients, in which a nurse-observer and the patient assessed the pain, found that both 600 mg aspirin and 1 g acetaminophen were easily distinguishable from placebo.

In the study of Moertel, Ahmann, Taylor and Schwartz (Ref. 13) acetaminophen rated fourth after aspirin, mefenamic acid and phenacetin in the patients' ratings which were from 1 to 10 and it rated third in a mean percentage relief of pain. They concluded that acetaminophen or phenacetin would be a reasonable alternative in case of aspirin intolerance.

In *AMA Drug Evaluations* (Ref. 14), acetaminophen effectiveness is described as follows: "The analgesic and antipyretic efficacy of phenacetin and acetaminophen is equal to that of aspirin; however, unlike aspirin, these two analgesics do not have anti-inflammatory or uricosuric effects and thus are not as useful in the treatment of rheumatic diseases."

The Panel reviewed unpublished well-controlled double-blind studies where acetaminophen was studied in patients with headache (Refs. 15 and 16). Acetaminophen 650 mg, was shown to be effective in the treatment of headache. Additionally, in another double-blind crossover study of patients with migraine headache (Ref. 17) patients received (a)

a combination of 65 mg isometheptene, 325 mg acetaminophen and 100 mg dichloralphenazone, (b) 325 mg acetaminophen and (c) placebo. Only the combination showed to be superior to placebo in this type of headache.

In another study, not controlled, a combination of acetaminophen and Vitamin C was studied in 45 patients with pain of different etiology (Ref. 18). The doses used were four to six tablets (containing 330 mg acetaminophen) per 24 hours. Nine of these patients had headache, and positive, favorable results were obtained in all of them. Four of these patients had pain described as neuralgia and all four obtained relief using this dose.

In another uncontrolled study by Perin (Ref. 19) acetaminophen in combination with Vitamin C (doses not given) was evaluated in 1,000 patients with pain of different etiology. Of these, 96 patients were admitted into the study for headache. The results are mostly analyzed in global form for all patients included. However, the following statement is made: "patients with headache reacted well and were alleviated rapidly." Unfortunately, the doses and dosage regimen are not specified for these patients. An additional 66 patients in the study are identified as having "neuralgias and neuritis" but the response of this group of patients is not stated.

In another single-blind study (Ref. 20), 500 mg acetaminophen was compared with a combination of 300 mg acetaminophen, 5 mg hydroxyzine, 30 mg propoxyphene hydrochloride and 30 mg caffeine. One to two tablets of each preparation were given to patients suffering from tension headache. The results showed that 45 percent success was obtained with acetaminophen alone and 90 percent with the combination. This superiority was attributed to the "potentiation of the analgesic agents by hydroxyzine."

The Panel concludes that acetaminophen is effective in relieving the pain of headache, and that it is a general analgesic of proven efficacy as shown by clinical testing. Thus, acetaminophen is considered to be equivalent to aspirin in its analgesic effects, although the lack of anti-inflammatory action might make it less useful in conditions having an inflammatory component (Ref. 21).

(2) *Safety.* Numerous clinical studies have shown that acetaminophen, when taken in recommended doses, is relatively free of adverse effects in most age groups, even in the presence of a variety of disease states. There was no increase in fecal blood loss (Ref. 22). There were no stomach mucous membrane reactions in patients with gastrointestinal illnesses (Ref. 23). There was no interference with the action of drugs which promote uric acid excretion in the urine (Ref. 24). No effects on clotting were seen in hemophiliacs (Ref. 25). However, several studies have shown small increases in blood clotting time in patients using acetaminophen, but concurrent anticoagulant therapy was considered manageable with conventional precautions (Ref. 26).

Larger than normal doses were required to produce a mild methemoglobinemia (a reversible blood disorder) (Ref. 27). The safety of acetaminophen is discussed in detail below. The metabolism of acetaminophen was considered and has been reviewed by the Panel elsewhere in this document. (See part II, paragraph L, above—Absorption, Distribution, Bio-transformation (Metabolism) and Excretion of Acetaminophen.)

A few cases of hypersensitivity to acetaminophen have been reported, as manifested by skin rashes (Ref. 28), thrombocytopenic purpura (characterized by "black and blue" patches on skin and mucous membranes) (Ref. 29), rarely hemolytic anemia (anemia due to red blood cell destruction) and the very serious blood disorder agranulocytosis (Ref. 30). Occasional individuals respond to ordinary doses with nausea and vomiting or diarrhea.

The only contraindications to the use of acetaminophen presently well-established are known hypersensitivities to the drug. Definitive studies are not available on whether or not acetaminophen should be used in patients with certain preexisting liver diseases. The Panel concludes that increased risk may be a possibility in these individuals and recommends that high priority be given to well-designed studies to resolve this issue.

(i) *Animal toxicity.* With regard to the acute toxicity of acetaminophen, the large doses of acetaminophen required to evoke toxic reactions in the studies cited below are considered by the Panel to reflect a wide range of safety. This is especially true when those dosages are compared to the Panel's recommended single dose and daily intake.

The single-dose oral LD₅₀ (dose that kills 50 percent of the animals) of acetaminophen in male rats was reported to be 3,710 mg/kg (Ref. 31), as compared to the previously reported LD₅₀ of 1,650 mg/kg for phenacetin in the female rat (Ref. 32). The LD₅₀ of acetaminophen in the rat is about 300 to 400 times the usual single dose in 50 to 70 kg (110 to 150 lb) adult humans.

In an acute toxicity study by Boyd and Bereczky (Ref. 31), acetaminophen produced early pathologic effects in the rats similar to those seen in the same laboratory in an earlier study (Ref. 32) with phenacetin. Rats dying in 24 hours showed extensive capillary-venous congestion, tubular nephritis and centrilobular hepatitis (kidney and liver inflammatory conditions, respectively). When deaths occurred later with acetaminophen the hepatitis had progressed into hepatic necrosis.

A 100-day LD₅₀ of acetaminophen in the rat was found to be 770 mg/kg daily; the 100-day LD₅₀ was estimated to be 400 mg/kg daily (Ref. 33). Extrapolating to humans ranging in weight from 50 to 70 kg (110 to 150 lb) the latter dose represents about 5 to 7 times the usual maximum recommended daily dose of 3,900 mg.

Boyd further found that his 100-day LD₅₀ in the rat produced atrophy of the

testes and inhibition of the production of sperm in rats and guinea pigs as well (Ref. 34). The sex organs of females were affected to a lesser degree. Other effects noted by Boyd and Hogan (Ref. 33), in rats receiving the 100-day LD₅₀ dose, included kidney and liver damage.

(ii) *Acute toxicity in man.* Several recent reports have also described numerous cases of poisoning in man by large single doses of acetaminophen, apparently usually taken for suicidal purposes. Prescott, Roscoe, Wright and Brown (Ref. 35) observed liver damage in 17 of 30 patients who had taken at least 15 g; one went into a coma induced by liver degeneration and died. In this report, no estimate was given of the lowest dose thought to have caused liver damage. Clark et al. (Ref. 36) studied a series of 60 patients who took doses of acetaminophen claimed to range from 13 to 100 g. Forty-nine developed liver damage, 17 progressed to hepatic encephalopathy (brain damage), and 12 died from fulminant liver failure. Death occurred in 4 to 18 days after the ingestion of the drug. Proudfoot and Wright (Ref. 37) studied 41 cases of acute acetaminophen poisoning, 17 of which showed liver damage. One patient died, 3 developed jaundice and the others showed only biochemical evidence of liver dysfunction. These authors stated that "liver damage is a toxic effect which is present in most patients who ingest more than 15 g of paracetamol" (acetaminophen). In all these series it was noted that other drugs were, or may have been, also taken.

In the U.S. in 1972, 61 cases of acetaminophen overdosage were reported to the National Clearinghouse for Poison Control Centers, Food and Drug Administration (Ref. 38). Of these, 15 reported the ingestion of less than 3.5 g, 23 between 3.5 and 15 g, and 7 ingested more than 15 g. Two of the latter developed toxic hepatitis. No effects of this nature were reported from doses lower than 15 g. In 1971 there were only 3 cases reported in which more than 15 g were ingested. One of these had no symptoms, another experienced some lethargy, and the other experienced nausea, vomiting and abdominal pain. The Panel concludes that single doses less than 15 g are not usually associated with serious liver damage. The much lower incidence of reported acetaminophen hepatotoxicity in the U.S.A. compared to England has been attributed to the well known axiom, if the diagnosis is not suspected, it is not seen, since one investigator reported 156 cases with 4 fatalities in one city alone (Ref. 39).

A dose of 15 g is 23 times the usual recommended single dosage of acetaminophen (650 mg) and about 4 times the maximum recommended daily intake. In estimating the range of safety, the single dosage comparison is probably more appropriate than the comparison of the single toxic dose with the daily divided therapeutic dose. The toxic effect of acetaminophen on the liver is related to glutathione depletion (Ref. 40).

Since acetaminophen is metabolized by the liver the question of the safety of its use in the presence of liver disease should be considered.

In a study of 72 patients with various forms of liver disease given 10 mg/kg of acetaminophen, Fevery and de Groote (Ref. 41) found an increase in both the serum levels and urinary excretion of unconjugated acetaminophen in the presence of certain liver diseases (parenchymal disease with hyperbilirubinemia or obstructive jaundice). Patients with cirrhosis exhibited plasma levels 2 to 3 times higher than those observed in subjects with no liver damage indicating decreased rates of metabolism. No decrease in the blood levels of conjugated acetaminophen or total urinary excretion of the drug could be demonstrated indicating that these two types of observations would not be expected to show differences in metabolism of free drug as would be expected from the pharmacokinetic characteristics of this drug. Vest and Fritz (Ref. 42) observed a lowered ability of the liver to conjugate acetaminophen in six children with infectious hepatitis given 10 or 20 mg/kg of the drug intravenously. In the acute phase of the hepatitis the excretion of conjugated acetaminophen was decreased. However, urinary excretion of free drug or excretion of total conjugated acetaminophen is an insensitive method to observe changes in metabolism of acetaminophen. Direct comparison of blood levels of unchanged drug indicates that the relative rate of conjugation can

decreased significantly without significant differences in urinary excretion of total conjugates. Free acetaminophen disappeared more slowly from the blood. The effects on excretion and blood levels of the conjugates and free acetaminophen reflected a partial inhibition of the conjugation of the drug to its glucuronide and the sulfate resulting in a moderate delay in the total elimination of the drug from the body. In 33 patients with liver cirrhosis, Jirsa and Hykes (Ref. 43) found no effect on the excretion of conjugated acetaminophen but did find a significant decrease in diabetics. Schmid and Hammaker (Ref. 44) observed no significant reduction in the formation of conjugated acetaminophen in five patients with Gilbert's disease (congenital liver disorder) after the administration of 30 mg/kg of acetaminophen but did not study blood levels of unchanged drug. In studies on infants prior to the development of their ability to metabolize this drug, no significant hematologic or other toxic effect were produced by single oral doses of acetaminophen up to 16.6 mg/kg (Ref. 45), or by 100 mg 3 times daily rectally for 3 days (Ref. 46).

There have been no clinical studies of the effect of liver disorders on metabolic pathways other than the glucuronide and sulfate conjugation pathways through which acetaminophen may be metabolized. In this connection Mitchell et al. (Ref. 40) have postulated that a minor

as yet unidentified highly reactive metabolite formed by nonconjugating enzymes (mixed oxidase) is responsible for the liver toxicity of acetaminophen. In normal subjects the concentration of this metabolite is low, and it is further conjugated with glutathione to a nontoxic metabolite. At high doses glutathione stores may be overwhelmed and the reactive metabolite reacts chemically with other compounds in the cell which results in necrosis. It is pertinent to know whether liver disease might affect the liver toxicity of acetaminophen by interfering with the production of this toxic metabolite by nonconjugating pathways and further conjugation with cysteine to a nontoxic substance.

There is evidence in the results of the above studies that in some forms of liver disease there is a decrease in the conjugation of acetaminophen. This effect significantly increases the half-life of acetaminophen to 3 to 4 hours in some cases. It is perhaps significant that in toxic reactions to overdoses of acetaminophen the half-life is usually increased to 4 hours (Ref. 35).

Decreased metabolism of acetaminophen by normal conjugation mechanisms (glucuronide and sulfate) observed in some patients with chronic liver disease, could potentially increase toxicity of acetaminophen by increasing the relative fraction metabolized through nonconjugating pathways to the toxic metabolite. Decreased conjugation could also indicate decreased capacity of the liver to further conjugate the toxic metabolites with glutathione to a less toxic conjugate.

An alternative explanation for the increased susceptibility of chronic alcoholics to the hepatotoxicity of acetaminophen (Ref. 47) is the induction of the microsomal enzyme systems (nonconjugating) by chronic use of alcohol (Ref. 48). However, recent evidence suggests that the overall elimination by conjugation is decreased in alcoholics similar to that observed in other cases of decreased liver function.

Shamszad et al. found that preexisting liver disease significantly decreases the rate of elimination of drug (as evidenced by the increased half-life of unchanged drug in the plasma in patients with cirrhosis (half-life 3.5 ± 1.3 hours) and active alcoholic hepatitis (4.5 ± 1.5 hours) compared to chronic alcoholics with normal liver function (2.2 ± 0.39 hours) and chronic alcoholics off alcohol for 7 days (2.8 ± 0.7 hours)) (Ref. 49).

Thus several types of liver disease result in prolonged half-lives of unchanged drug which are about the same increase (about 4 hours) observed in patients who suffer liver damage after acetaminophen overdose.

One cannot conclude that because an increased acetaminophen half-life occurs in association with acute liver damage caused by acetaminophen, that increased acetaminophen half-life caused by preexisting liver disease will increase the potential or severity of acetaminophen hepatotoxicity. Well designed studies to answer this question are needed. Although the Panel does not have evidence to warrant a warning to persons

with liver disorders at this time, it is noted that there is no evidence to exclude this possibility and the considerations discussed above require that this possibility not be dismissed.

Although the Panel concludes that additional studies are needed to determine if a warning is required for normal doses in adults or infants with liver disease, overdose may result in such severe liver damage that a label warning regarding this effect is obligatory. The basis for such a warning is well documented in several recent reviews of the hazards of acetaminophen overdose, especially with respect to the harmful effects on the liver (Refs. 39, 48, and 50 through 52).

The warning should state: "Do not exceed recommended dosage because severe liver damage may occur".

Kidney damage has been described in numerous cases in which the liver injury has been of primary concern in acute poisoning by acetaminophen, as previously discussed. The nature of the injury to the kidney observed in such acute cases is apparently not related to the type of injury (papillary necrosis) which typically results from long-term abuse of analgesic drugs.

One case of the papillary necrosis type of kidney injury has been reported (Ref. 53) following prolonged use of acetaminophen at a dose of 11 to 18 g daily for 6 months in combination with proportionately large doses of chlorzoxanone. Two other cases, though questionably attributed to acetaminophen (Ref. 54), involved in one case this type of kidney injury which continued after switching to acetaminophen after the consumption of phenacetin-containing analgesics for 14 years. In the other case, the kidney damage developed after 5 years of intake of 1.5 g acetaminophen daily along with other drugs including some drugs containing phenacetin. Master (Ref. 55) reported a case of analgesic-induced kidney injury in a woman who took an average of 1.5 g acetaminophen daily for 10 years, though other analgesics were consumed previously or concurrently. Nanra (Ref. 56) mentioned two other cases of analgesic-induced kidney injury occurring in Australia. He attributed these to acetaminophen alone but he described no details. In none of the above six cases, in which the consumption of acetaminophen was involved, is it clear that this drug was the sole cause of the analgesic-induced kidney damage or that it was the primary drug of abuse.

Abel (Ref. 57) and the Royal Australasian College of Physicians (Ref. 58) have stated that patients fail to recover from kidney injury when their intake of phenacetin combinations is replaced by acetaminophen either alone or in combinations.

In studies on healthy adult human subjects, Prescott (Ref. 59) and Prescott, Sansur, Leven and Conney (Ref. 60) observed a slight increase in the excretion of kidney tubule cells in the urine following the intake of 3.6 g acetaminophen daily for 5 days. In the latter

study the increase was significant in one of eight subjects on acetaminophen and two of nine subjects on the same dosage schedule of phenacetin. This effect was considerably less than that seen in subjects taking similar doses of aspirin.

Edwards, Edwards, Huskisson and Taylor (Ref. 61) found only a minor impairment of urine concentrating ability in 6 of 13 patients after their intake of 2 to 30 kg acetaminophen over a period of 2 years. Batterman and Grossman (Ref. 7) noted no blood, liver or kidney disturbances in human subjects receiving 3.6 g daily for up to 116 weeks.

In an experiment on dehydrated dogs, Bluemle and Goldberg (Ref. 62) found a high concentration of acetaminophen in the papillae of the kidney after a single dose of phenacetin, and a similar concentration of the drug in the renal papillae was observed after a single dose of acetaminophen. However, in this study, no concentration of acetaminophen was found in nondehydrated dogs.

Acetaminophen has not been reported to produce effects on the central nervous system like those produced by phenacetin, variously described as euphoria, stimulation, sedation, depression, etc. These effects of phenacetin are considered to constitute the basis of the potential for abuse of analgesic preparations containing this drug: In comparing the subjective effects of phenacetin and acetaminophen in 20 healthy male volunteers, Eade and Lasagna (Ref. 63) found that phenacetin "depressed mood, energy and mentation," while acetaminophen in the same dose, 28 mg/kg, had no such effects and did not differ from aspirin or placebo. However, Nakra et al. recently reported that some patients, especially housewives, have used acetaminophen as a "pick-me-up" and raises the possibility that some will abuse it (Ref. 64).

No comparison has yet been made with regard to the relative abuse potential of analgesic mixtures of phenacetin and similar mixtures of acetaminophen. A longer history of use of acetaminophen combinations, especially those with aspirin, will be required before this question can be answered. However, considering the lack of effects of acetaminophen on the sensorium similar to those of phenacetin it is justifiable to conclude that acetaminophen, as a single entity or in analgesic mixtures, does not have the abuse potential demonstrated for analgesic mixtures containing phenacetin. Reports from Australia (Ref. 59) showing that established abusers of phenacetin-containing drugs continued to abuse acetaminophen combinations after the removal of phenacetin from proprietary products, do not indicate a primary abuse potential of acetaminophen or of its analgesic mixtures.

The Panel concludes from observations reviewed above that acetaminophen may be taken in recommended doses without undue risk.

The Panel has examined the regulations of the Poison Prevention Packaging

Act of 1970 as set forth in 21 CFR 1700.15 (a), (b) and (c), that provide for poison prevention packaging standards for aspirin-containing products in a dosage form intended for oral administration. The standards for child-resistant safety closures required on the containers of these products are intended to protect children from intentional or accidental ingestion without hampering the adult use effectiveness of the products. The Panel concurs with these standards and is of the opinion that the standards for child-resistant safety closures should apply to the containers in which acetaminophen oral products are packaged as well as to aspirin-containing products.

The Panel further concludes that the restrictions on the maximum number of tablets permitted in containers of aspirin products for child use should also apply to acetaminophen products formulated for use in children only. Therefore, acetaminophen products containing 80 mg (1.23 gr) tablets intended for oral use in children should contain no more than 36 tablets to reduce the hazard of accidental poisoning, as set forth in 21 CFR 201.314(c)(2) for products containing 80 mg (1.23 gr) tablets of aspirin for pediatric use.

The Panel concludes that the OTC packaging requirements for safety closures and the restriction on the maximum number of tablets in the containers of aspirin products for pediatric use should also apply to acetaminophen products for use in children.

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- (3) **Dosage.** (i) *For products containing 325 mg (5 gr) per dosage unit.* (a) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.
- (b) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.
- (ii) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days.
- Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.
- (iii) *For products containing 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is 500 mg (7.69 gr) to 1,000 mg (15.38 gr) initially, followed by 500 mg (7.69 gr) every 3 hours or 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.
- (4) **Labeling.** The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) **Warnings.** (a) "Do not exceed recommended dosage because severe liver damage may occur". (b) "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".
- (ii) **Standard acetaminophen dosage unit.** In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of acetaminophen per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing acetaminophen differs per dosage unit from the established standard of 325 mg (5 gr) acetaminophen per dosage unit. (See part II, paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)
- The Panel recommends that all products containing acetaminophen be clearly labeled as containing acetaminophen on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of acetaminophen per dosage unit.
- (a) *Products containing the standard acetaminophen dosage unit.* The Panel recommends that products containing only 325 mg (5 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.
- (b) *Products containing acetaminophen in an amount different than the standard acetaminophen dosage unit.* While the Panel recommends that products contain only 325 mg (5 gr) aceta-

minophen per dosage unit, if the Food and Drug Administration is unable to implement this recommendation the Panel recommends that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard dosage unit of 325 mg (5 gr). The Panel recommends that products containing 500 mg (7.69 gr) of acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

J. c. Calcium carbaspirin. The Panel concludes that calcium carbaspirin is a safe and effective OTC analgesic when taken in the recommended dosage of 414 to 828 mg every 4 hours while symptoms persist not to exceed 4,968 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Calcium carbaspirin is a complex of calcium acetylsalicylate and urea (Ref. 1). This compound is also frequently called soluble calcium aspirin. This nomenclature has produced some confusion with another preparation which consists of aspirin, calcium carbonate, and citric acid, which occasionally is also referred to as "soluble" calcium aspirin. Because calcium carbaspirin is a larger molecule than aspirin, a larger amount (414 mg) will be required to produce the same pharmacological effect as that produced by 325 mg of aspirin. Levy and Hayes have reported that the dissolution rate for this compound is faster than that for aspirin (Ref. 2). However, Beaver noted that the rate of absorption into the bloodstream was similar to that of aspirin (Ref. 3). Bonica and Allen have reported that "there is no evidence that it offers a clinically significant advantage (over aspirin) in the rate in which analgesic effects are achieved" (Ref. 4).

The previous discussion in this document with regard to effectiveness of aspirin including the limitations on maximum daily and total intake are applicable here with a slight modification based upon potency (414 mg instead of 325 mg). In addition, the previous discussion on aspirin dose-response relationship regarding the lack of correlation between blood levels and threshold levels of analgesia, rapidity of onset of analgesic action, intensity of analgesia, and duration of pain relief, are equally applicable to calcium carbaspirin. (See part III, paragraph B.1.a.(1) above—Effectiveness.)

(2) *Safety.* Evidence indicates that calcium carbaspirin is as safe as aspirin when taken in equivalent doses (Ref. 5). It is a complex of urea and calcium acetylsalicylate which is hydrolyzed (broken down) in the gastrointestinal tract to aspirin, calcium and urea. While calcium carbaspirin has a more rapid dissolution rate than aspirin, the amounts of calcium and urea formed from the breakdown of therapeutic doses of calcium carbaspirin would not be ex-

pected to have any pharmacological effects. It is assumed that calcium and urea are not absorbed in significant quantities. Thus the severity and incidence of adverse reactions either prior to or after absorption of calcium carbaspirin would be comparable to the incidence of adverse reactions discussed previously in this document for aspirin. (See part III, paragraph B.1.a.(2) above—Safety.)

The only studies which show that the side effects of calcium carbaspirin may be different from those of aspirin are the following: Muir and Cossar (Ref. 6) in a study with patients undergoing gastrectomy summarized their finding as follows: "Soluble calcium aspirin has shown no significant signs of gastric irritation in 95 gastrectomy specimens. Standard aspirin has shown potentially serious gastric lesions in 8 out of 102." These authors also found that calcium carbaspirin produced significantly less gastric bleeding than aspirin in 20 patients (aspirin 65 percent with bleeding, calcium carbaspirin 5 percent with bleeding) with no previous history of dyspepsia.

One article reported a series of studies using radioactive labeled chromate to determine gastrointestinal blood loss when aspirin and calcium carbaspirin were ingested (Ref. 7). The authors concluded that gastrointestinal bleeding occurred for both drugs, but the quantities of blood lost were less with calcium carbaspirin than with aspirin preparations for the same subjects (Ref. 7), and this difference was highly significant (p is less than 0.01).

In an unpublished study submitted by the manufacturer (Ref. 5), 20 patients with known intestinal ulcers and 20 patients with arthritis were followed for 9 months. Stool tests for blood using the testing reagent guaiac were used. A comparison between aspirin, placebo and calcium carbaspirin revealed guaiac reagent-positive stools in all three situations, and no difference could be observed between the three treatments. The data are difficult to assess; the results were not presented in tabulated form and the data were not statistically analyzed.

The Panel concludes that while slightly less gastrointestinal bleeding may result from the use of calcium carbaspirin, not enough evidence exists to differentiate this effect quantitatively from that of aspirin. Consequently, all cautions required for aspirin should be required for calcium carbaspirin.

(3) *Dosage.* Adult oral dosage is 414 to 828 mg every 4 hours while symptoms persist not to exceed 4,968 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 621 mg every 4 hours while symptoms persist not to exceed 3,105 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 517.5 mg every 4 hours while symptoms persist not to exceed 2,587.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 414 mg every 4 hours while symptoms persist not to ex-

ceed 2,070 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 310.5 mg every 4 hours while symptoms persist not to exceed 1,552.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 207 mg every 4 hours while symptoms persist not to exceed 1,035 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (a) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(b) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(c) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of calcium carbaspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing calcium carbaspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin. (See part II, paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing calcium carbaspirin be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 414 mg calcium carbaspirin per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg (5 gr) per tablet of the established standard of 325 mg (5 gr) aspirin per tablet".

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d. Choline salicylate. The Panel concludes that choline salicylate is a safe and effective OTC analgesic when taken in the recommended dosage of 435 to 870 mg every 4 hours while symptoms persist not to exceed 5,220 mg in 24 hours for not more than 10 days.

(1) **Effectiveness.** Choline salicylate is one of several nonacetylated salicylates reviewed by the Panel. Choline salicylate is highly soluble and may be administered as a stable, palatable liquid. It should be noted that an advantage of this drug is that it is the only liquid salicylate preparation that is currently available on the OTC drug market. It is said to be absorbed 5 times faster than aspirin (Ref. 1). Beaver (Ref. 2) has stated that "While choline salicylate may prove more palatable than an equivalent dose of aspirin, the analgesic effectiveness of the two drugs has never been adequately compared, and experience with sodium salicylate suggests that from the standpoint of analgesia at least, simple salicylates are less than equianalgesic when compared with equivalent doses of aspirin."

While no well-controlled clinical studies for the assessment of the analgesic activity of choline salicylate have been found, the Panel's review of the scientific literature has produced sufficient evidence of its analgesic activity. Broh-Kahn (Ref. 3) conducted a study in which 80 physicians throughout the U.S. and Canada gave this drug to 1,200 patients. Attempts were made to compare the effectiveness of choline salicylate to that of aspirin. This was accomplished in several ways. In some cases, patients had been treated with aspirin, and when its effect was assessed, it was discontinued and replaced with choline salicylate. In other cases in which the effect of aspirin was not previously ascertained, a crossover study was performed. Physical differences in the appearance of both drugs precluded the use of a double-blind technique. Finally, in some cases the physician compared the effects of choline salicylate in some patients with the known effects of aspirin in his patient population at large. The author concluded that "choline salicylate displayed a more favorable effect than aspirin." No adequate statistical analysis is presented to support this conclusion.

Leary (Ref. 1) has also reported that salicylate concentration in the blood of man rises faster and to a considerably higher level after the administration of choline salicylate than after the administration of aspirin.

Levy, Gumtow and Rutowski (Ref. 4), in a study with 12 healthy male volunteers, assessed the blood plasma levels obtained after the administration of a solu-

tion of choline salicylate with those of two product formulations of aspirin tablets, aspirin tablets combined with aluminum glycinate and magnesium carbonate and an aqueous solution of sodium salicylate. The authors concluded that the two aspirin formulations produced significantly lower absorption rates than choline salicylate solution. There was no difference in absorption between the several types of salicylates administered in solution (Ref. 4).

Wolf and Aboody (Ref. 5) have also shown that choline salicylate is more rapidly absorbed than aspirin.

Broh-Kahn (Ref. 6) in a study with normal volunteers who acted as their own controls has shown that choline salicylate is absorbed approximately 5 times more rapidly than aspirin.

The significance of faster absorption has not been determined, since there is no evidence that faster absorption also indicates a faster onset of analgesic effect. Besides, as stated by Beckman (Ref. 7), "it is absurd to claim advantages for compounds that may at best advance the advent of relief no more than a few minutes."

2 Safety. The Panel finds that choline salicylate is about as safe as aspirin, because the side effects are similar to aspirin and those of the other salicylates. Yet unlike aspirin and the other acetylated salicylates, choline salicylate has not been reported to be associated with reactions causing asthmatic attacks in susceptible people. In addition, choline salicylate, as well as the other nonacetylated salicylates, do not affect the platelet adhesiveness involved in the clotting mechanism. However, choline salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect. Therefore, the caution concerning bleeding should be addressed to that population which is exposed to large doses of choline salicylate.

There have been many reports assessing the occurrence of gastrointestinal bleeding associated with the use of choline salicylate. Watson and Pierson (Ref. 8) measured gastrointestinal bleeding in 90 normal volunteers who had ingested various salicylate compounds. The subjects were injected with radioactively labeled red blood cells and the daily stools were checked for blood loss. The average loss was 4.8 ml for the patients taking aspirin. Ten percent showed a loss of over 10 ml daily for aspirin. Choline salicylate resulted in an average daily loss of 0.5 ml.

Lange (Ref. 9) selected 19 patients who had shown signs of occult (unseen) or manifest (noticeable) bleeding under ordinary salicylate treatment. He concluded that there was less incidence of blood in the stool with the use of choline salicylate. In a crossover study 73 percent of patients who took aspirin versus 36 percent of those using choline salicylate showed occult blood loss.

Rider et al. (Ref. 10), using the gastroscope studied 30 patients soon after ingestion of choline salicylate. He found no evidence of irritation of the mucous

membrane of the stomach, hyperemia, hemorrhage, or ulcer.

In another study using radioactive Chromium-51 tagging of cells, Pierson, Holt, Watson and Keating (Ref. 11) demonstrated that 73 percent of 148 patients had significant bleeding with aspirin. When choline salicylate was used, no intestinal bleeding was noted. Croft, Cuddigan and Sweetland (Ref. 12) using Chromium-51 labeled red blood cells reported the same amount of bleeding after choline salicylate or soluble aspirin administration.

A submission summarizes ten uncontrolled or partially controlled clinical studies involving approximately 1,500 patients (Ref. 13). There were no serious untoward reactions reported. The most significant of these reports was that of Broh-Kahn (Ref. 2) which included a collection of the results of a cooperative study by 80 physicians of 1,200 patients using aspirin as a reference standard. The conclusion was stated in general terms. There evidently was a lower incidence of gastrointestinal distress, and choline salicylate was better tolerated in higher doses than aspirin.

The labeling in this submission (Ref. 13) includes claims for choline salicylate such as "Taken on an Empty Stomach, Starts Acting 5 Times Faster Than Aspirin" and "Provides Gentle-To-The-Stomach Action". Other claims made for this product have been discussed by the Panel elsewhere in this document. (See part III, paragraph B.2. below—Category II Labeling.) As for the claims mentioned above, the Panel concludes that its remarks regarding the claims of rapid absorption and the consequent rapid onset of analgesia made for highly buffered aspirin products also apply to choline salicylate products. (See part VI, paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

In the case of choline salicylate, the Panel notes that although choline salicylate may not contain buffering ingredients as highly buffered aspirin does, it is, like highly buffered aspirin, taken in a solution dosage form and therefore may, for this reason, have similar performance action. In addition, the Panel concludes that regarding the claims for choline salicylate and its effect on the stomach, further testing is required to substantiate such claims, and therefore, will only permit the following claim which may be included in the principal display panel and which it classifies as Category III labeling: "May be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The Panel further concludes that any other statement(s) are classified as Category II.

(3) **Dosage.** Adult oral dosage is 435 to 870 mg every 4 hours while symptoms persist not to exceed 5,220 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 652.5 mg every 4 hours while symptoms persist

not to exceed 3,262.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 543.8 mg every 4 hours while symptoms persist not to exceed 2,719 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 435 mg every 4 hours while symptoms persist not to exceed 2,175 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 326.5 mg every 4 hours while symptoms persist not to exceed 1,632.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 217.5 mg every 4 hours while symptoms persist not to exceed 1,087.5 mg in 24 hours for not more than 5 days. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) **Warning.** "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) **Analgesic equivalence value.** In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of choline salicylate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing choline salicylate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See Part II, paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing choline salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 435 mg choline salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per tablet of the established standard of 325 mg sodium salicylate per tablet".

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Magnesium salicylate. The Panel concludes that magnesium salicylate is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) **Effectiveness.** This ingredient has been used since 1888 when it was first cited in an editorial of *Pharmazeutische Post* and was used for therapy of typhoid fever (Ref. 1). The same year Caldwell (Ref. 2) in a review article reported on its use as an "intestinal antiseptic" and therefore useful in typhoid fever. This product was still found in the *Merck Index*, 1930 Ed., where it was described as antiseptic, antirheumatic and anti-diarrheic and still listed among its uses "typhoid fevers and typhus" (Ref. 3).

In a report published in the late 1930's, analgesia is mentioned for the first time by Joseph (Ref. 4). That report consists of the experience of a single physician with ten of his patients in which magnesium salicylate produced a marked analgesic effect. In 1967, Stern (Ref. 5) compared aspirin with magnesium salicylate and found no statistically significant differences in the levels of analgesia using these two agents. This study was double-blind and analgesia was evaluated in 22 patients with several types of arthritis. They concluded that magnesium salicylate was preferable to aspirin in conditions requiring long term therapy since it produced less gastrointestinal irritation than aspirin.

In an unpublished study performed by F. W. McCoy (Ref. 6) in 1964, aspirin, magnesium salicylate and aspirin plus magnesium aluminum hydroxide were compared on the basis of salicylate blood levels. Although it is known that salicylate blood levels do not directly correlate with analgesic effects it is interesting to note that magnesium salicylate, in spite of a greater solubility than aspirin, gave "somehow" lower blood levels of salicylate than aspirin. The blood levels of salicylate obtained with magnesium salicylate were greater than those ob-

tained with aspirin plus aluminum and magnesium hydroxides. This is most likely due to the buffering of the aspirin formulations by aluminum and magnesium hydroxides. In another unpublished study, the analgesic effectiveness of magnesium salicylate was evaluated in 42 elderly patients with degenerative bone disease. In this double-blind crossover study, magnesium salicylate was compared to aspirin and placebo. The data were analyzed statistically, and the conclusions obtained from this study were that magnesium salicylate and aspirin were equally effective in relieving the pain of patients with osteoarthritis and that both drugs were superior to placebo (Ref. 7).

Batterman (Ref. 8) reported the use of magnesium salicylate in 34 patients with rheumatoid arthritis and 27 patients with degenerative joint disease. In this study, analgesic and not antirheumatic effect was assessed. The data suggest the effective value of this drug as an analgesic in the patients tested.

The Panel concludes that while the number of well-controlled clinical studies are few and mostly unpublished, the studies and the other data reviewed by the Panel indicate that magnesium salicylate is an effective analgesic and that it is comparable to aspirin. However, the claim that magnesium salicylate might be indicated when aspirin cannot be tolerated, remains to be proven.

(2) **Safety.** At the present time, there is evidence which indicates that magnesium salicylate is as safe as aspirin, although it has side effects similar to aspirin and the other salicylates. Unlike aspirin and the other acetylated salicylates, magnesium salicylate has not been associated with reactions causing asthmatic attacks in susceptible people. In addition, magnesium salicylate, as well as the other nonacetylated salicylates, are not known to affect the platelet adhesiveness involved in the clotting mechanism. However, magnesium salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect. There is evidence of gastric mucosal bleeding and irritation similar to aspirin.

Unpublished studies on magnesium salicylate, utilizing the gastroscope, revealed some variation between aspirin and magnesium salicylate when irritation of the stomach walls was assessed. Irritation to the mucous membranes of the stomach did occur in the presence of both drugs (Ref. 9). Other submitted studies used radioactively-labeled sodium chromate Cr⁵¹. These studies indicated that bleeding also took place in a significant number of subjects. There was evidence that the amount of bleeding might be less with magnesium salicylate than with aspirin (Ref. 10). One study that determined magnesium concentrations in the blood indicated considerable individual variations which were neither consistent nor significant (Ref. 11).

The Panel has reviewed the possible systemic toxicity of magnesium ions with

recommended doses of magnesium salicylate. Unless renal insufficiency is present, toxicity due to the absorption of magnesium is unlikely in the recommended dosages of 325 to 650 mg magnesium salicylate every 4 hours not to exceed 3,900 mg in 24 hours for not more than 10 days (Ref. 12). Absorbed magnesium is rapidly excreted, so that hypermagnesemia is difficult to achieve by the oral route in the presence of normal renal function. In renal dysfunction, however, hypermagnesemia toxicity may occur and a warning is therefore necessary (Ref. 13). The Panel concludes, based on the available evidence, that a restriction on the intake of magnesium salicylate for normal persons in the recommended daily dosage is not necessary because there is no evidence of possible systemic toxic effects due to magnesium. The amount of magnesium in the recommended maximum daily dosage of 3,900 mg magnesium salicylate is 26.2 mEq magnesium which does not pose any safety problem. However, for any product containing magnesium in which the maximum daily dosage exceeds 50 mEq of magnesium, the labeling should contain the warning: "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(3) *Dosage.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed 2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persist not to exceed 1,625 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing more than 50 mEq of magnesium in the recommended daily dosage.* *Warning.* "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(iii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of

magnesium salicylate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing magnesium salicylate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See Part II, paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing magnesium salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 325 mg magnesium salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per teaspoon of the established standard of 325 mg sodium salicylate per tablet".

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f. Sodium salicylate. The Panel concludes that sodium salicylate is a safe and effective OTC analgesic when used in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Sodium salicylate had already been in use for about 25 years when aspirin was introduced into therapy in 1899. Aspirin was introduced on the basis that it was more palatable and caused less gastrointestinal disturbances than sodium salicylate (Ref. 1).

It has been demonstrated that aspirin (acetylsalicylic acid) is hydrolyzed to salicylic acid. It has been suggested that the latter is the active compound (Ref. 2). However, the therapeutic effect of aspirin as an analgesic is generally recognized as being superior to an equal dose of sodium salicylate (Refs. 1 and 2).

Some researchers using patients with cancer pain as well as post partum patients, have found aspirin superior to sodium salicylate when given in equimolar doses (Refs. 3 and 4).

Frey has reported that aspirin was more effective than sodium salicylate in the treatment of the common headache (Ref. 5).

The *AMA Drug Evaluations* (Ref. 6) mentions sodium salicylate as an analgesic and states that " * * * it is less effective than equal doses of aspirin in relieving pain and reducing fever * * * "

Woodbury (Ref. 7) cites sodium salicylate as one of the two most commonly used preparations for analgesic effects, the other one being aspirin.

The Panel concludes that the few well-controlled clinical studies, the long clinical history of this ingredient's use and acceptance in most basic medical and pharmacology texts, indicate that sodium salicylate is an effective analgesic.

(2) *Safety.* The Panel concludes that sodium salicylate is as safe as aspirin, although it has side effects similar to aspirin and the other salicylates. Yet unlike aspirin and the other acetylated salicylates, sodium salicylate has not been associated with reactions causing asthmatic attacks in susceptible people. In addition, sodium salicylate, as well as the other nonacetylated salicylates, are not known to affect the platelet adhesiveness involved in the clotting mechanism. However, sodium salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect.

Comparison between aspirin preparations and sodium salicylate in various studies reveals some differences of opinion in the conclusions drawn by the authors. However, it would seem that some bleeding from the gastrointestinal tract does indeed take place.

Grossman et al. reported that sodium salicylate, aspirin, and calcium aspirin all gave a significant increase of blood in the stools as compared to the controls. This was determined using the radioactively-labeled red blood cell technique (Ref. 8). Stubbe, Pietersen and Van Heulen after studying 130 patients found that there was much less blood found in the stools when using sodium salicylate as compared to aspirin (Ref. 9). Scott et al. in 1961 also reported decreased bleeding with sodium salicylate as compared to aspirin (Ref. 10).

Leonards and Levy (Ref. 11) have shown that 325 mg sodium salicylate

tablets caused a gastrointestinal blood loss of 1.2 ml daily above control values but the blood loss produced by 325 mg aspirin tablets was appreciably greater, 5.6 ml daily above control values.

Furthermore, the effects of prolonged salicylate administration on the carbohydrate metabolism of rheumatic fever patients ranging in age from 5 to 18 years have been studied. Glucose or other carbohydrates were given orally at a dose of 1 g/kg after measuring the fasting blood sugar. It was found that although the fasting blood sugar was lower than normal, sugar concentrations determined 30 and 60 minutes after the carbohydrate administration remained abnormally high. The single ingestion of 0.6 g of sodium salicylate did not produce these changes in glucose metabolism (Ref. 12).

These latter reports are not sufficiently clear to permit any definitive conclusion to warrant a labeling warning.

The Panel has reviewed the relationship between sodium intake and hypertension and found that it is generally accepted that sodium intake is one of several factors contributing to the pathophysiology of hypertension. In experimental animals, sodium salts may precipitate marked hypertension in the presence of certain endocrine and/or renal disturbances. Even in the absence of abnormalities, blood pressure increases with sodium intake. However, in the presence of normal renal function, the rise in pressure is moderate (Ref. 13). The doubling of salt and water intake raises the mean blood pressure in man by 10 mm Hg (Ref. 13). Apart from hypertension, edema may develop in persons with occult heart failure or renal disease with high salt intake. The prevalence of these conditions increases with age (Refs. 14, 15, and 16). The recommended maximum daily dosage of 4,000 mg sodium salicylate contains 25 mEq sodium which is sufficiently high to warrant a warning in the labeling. Therefore, the Panel concludes that the labeling for sodium salicylate shall contain the warning: "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician" (Ref. 17). It would seem prudent for individuals on sodium restricted diets to take another Category I OTC analgesic, antipyretic or anti-rheumatic product instead of sodium salicylate to avoid any increase in sodium intake.

(3) *Dosage.* (i) *For products containing 325 mg per dosage unit.* (a) *Standard schedule.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed 2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persist not to exceed 1,625 mg in 24 hours for not more than 5 days.

Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Nonstandard schedule.* Adult oral dosage is 325 mg to 975 mg initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing more than 325 mg but not more than 421 mg per dosage unit.* Adult oral dosage is more than 325 mg but not more than 842 mg initially, followed by more than 325 mg but not more than 421 mg every 3 hours while symptoms persist not to exceed 3,789 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing more than 421 mg but not more than 485 mg per dosage unit.* Adult oral dosage is more than 421 mg but not more than 970 mg initially, followed by more than 421 mg but not more than 485 mg every 4 hours or 842 mg but not more than 970 mg every 6 hours while symptoms persist not to exceed 3,880 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *For products containing more than 485 mg but not more than 500 mg per dosage unit.* Adult oral dosage is more than 485 mg but not more than 1,000 mg initially, followed by more than 485 mg but not more than 500 mg every 3 hours or 970 mg but not more than 1,000 mg every 6 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) *For products containing more than 500 mg but not more than 650 mg per dosage unit.* Adult oral dosage is more than 500 mg but not more than 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(iii) *For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage.* *Warning.* "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

The Panel recommends that all products containing sodium salicylate be clearly labeled as containing sodium salicylate on the principal display panel.

(a) *Products containing the standard sodium salicylate dosage unit.* The Panel recommends that products containing only 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(b) *Products containing sodium salicylate in an amount different from the standard sodium salicylate dosage unit.* While the Panel recommends that products contain only 325 mg sodium salicylate per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of sodium salicylate other than 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

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(a) *Aspirin*. There is no recommended dosage except under the advice and supervision of a physician.

(b) *Calcium carbaspirin*. There is no recommended dosage except under the advice and supervision of a physician.

(c) *Choline salicylate*. There is no recommended dosage except under the advice and supervision of a physician.

(d) *Magnesium salicylate*. There is no recommended dosage except under the advice and supervision of a physician.

(e) *Sodium salicylate*. There is no recommended dosage except under the advice and supervision of a physician.

§ 343.20 Permitted combinations of active ingredients.

(a) *Active ingredients*. The active ingredients of the combination product consist of any two of the following at the dosage limit established for each ingredient:

(1) Aspirin 325 mg (5 gr) per dosage unit.

(2) Acetaminophen 325 mg (5 gr) per dosage unit.

(3) Calcium carbaspirin 414 mg per dosage unit.

(4) Choline salicylate 435 mg per dosage unit.

(5) Magnesium salicylate 325 mg per dosage unit.

(6) Sodium salicylate 325 mg per dosage unit.

(b) *For analgesic combination products*. Adult oral dosage is 1 dosage unit every 4 hours while symptoms persist not to exceed 6 dosage units in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *For antipyretic combination products*. Adult oral dosage is 1 dosage unit every 4 hours while fever persists not to exceed 6 dosage units in 24 hours for not more than 3 days.

(d) *For combination products containing nonanalgesic and/or nonantipyretic active ingredients*. (1) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective antitussive active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(2) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective expectorant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(3) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of nasal congestion due to the common cold (cold)".

(4) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective antihistamine active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and to alleviate, decrease, or temporarily relieve running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(5) Any single active ingredient identified in § 343.10(b), or § 343.12(b) may be combined with antacid active ingredient(s) which meet the requirements of § 331.10 of this chapter provided the product is labeled for the concurrent indications identified in § 343.50(a) and § 331.30(a) of this chapter.

(6) Aspirin identified in § 343.10(a) or § 343.12(a) may be combined with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided the product is identified as highly buffered aspirin with labeling only as identified in § 343.50(a).

(7) Aspirin identified in § 343.10(a) or § 343.12(a) may be combined with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided the product is identified as buffered aspirin with labeling only as identified in § 343.50(a).

Subpart C—[Reserved]

Subpart D—Labeling

§ 343.50 Labeling of analgesic and antipyretic products.

(a) *Indications*. The labeling shall identify the product pursuant to the appropriate definition(s) established in § 343.3 and shall contain the following:

(1) For products containing analgesic ingredients identified in § 343.10 or § 343.20 if applicable under the heading "Indications," the labeling shall state

"For the temporary relief of occasional minor aches, pains and headache."

(2) For products containing antipyretic ingredients identified in § 343.12 or § 343.20 if applicable under the heading "Indications," the labeling shall state "For the reduction of fever."

(3) For products containing analgesic-antipyretic ingredients identified in §§ 343.10 and 343.12 or § 343.20 if applicable under the heading "Indications," the labeling shall state "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever."

(b) *Directions for use*. The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 343.10 and 343.12, followed by "or as directed by a physician."

(c) *Warnings*. The labeling of the product contains the appropriate warnings under the heading "Warnings" which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable as follows:

(1) For products containing any analgesic ingredient identified in § 343.10:

✓(i) "Adults: Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician".

✓(ii) "Children under 12 years: Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

✓(2) For products containing any antipyretic ingredient identified in § 343.12: "If fever persists for more than 3 days (72 hours), or recurs, consult your physician".

✓(3) For products containing any analgesic or any antipyretic ingredient identified in §§ 343.10 and 343.12 other than acetaminophen identified in §§ 343.10(b) and 343.12(c):

✓(i) "Take this product for the treatment of arthritis only under the advice and supervision of a physician".

✓(ii) "Stop taking this product if ringing in the ears or other symptoms occur".

✓(iii) For products intended for oral administration as a solid dosage form, e.g., tablets: (a) "Adults: Drink a full glass of water with each dose".

✓(b) "Children under 12 years: Drink water with each dose".

✓(iv) "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

✓(v) "Caution: Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

(4) For products containing any analgesic or any antipyretic ingredient identified in § 343.10 (a) and (c) or § 343.12 (a) and (c) or § 343.20 if applicable:

✓(i) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

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(ii) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(iii) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(5) For products containing acetaminophen identified in § 343.10(b), § 343.12(b) or § 343.20 if applicable:

(i) "Do not exceed recommended dosage because severe liver damage may occur".

(ii) "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

(6) For products containing any analgesic or any antipyretic ingredient identified in § 343.10(d), (e), (f), § 343.12(d), (e), (f), or § 343.20 if applicable: "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(7) For products containing magnesium salicylate identified in § 343.10(e), § 343.12(e) or § 343.20 if applicable in an amount more than 50 mEq of magnesium in the recommended daily dosage: "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(8) For products containing sodium identified in § 343.10(f), § 343.12(f) or § 343.20 if applicable:

(i) For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit: The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(ii) For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage: "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

(d) *Statement on dosage unit.* (1) For products containing the standard aspirin dosage unit identified in § 343.10(a)(1) or § 343.12(a)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(2) For products containing aspirin in an amount different than the standard aspirin dosage unit identified in § 343.10(a)(3), (4), (5), (6) or § 343.12(a)(3), (4), (5), (6) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the

established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(3) For products containing the standard acetaminophen dosage unit identified in § 343.10(b)(1) or § 343.12(b)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(4) For products containing 500 mg (7.69 gr) acetaminophen identified in § 343.10(b)(3) or § 343.12(b)(3) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(5) For products containing the standard sodium salicylate dosage unit identified in § 343.10(f)(1) or § 343.12(f)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(6) For products containing sodium salicylate in an amount different than the standard sodium salicylate dosage unit identified in § 343.10(f)(2), (3), (4), (5) or § 343.12(f)(2), (3), (4), (5) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(e) *Statement on analgesic equivalence value.* (1) For products containing calcium carbaspirin identified in § 343.10(c) or § 343.12(c) shall be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(2) For products containing choline salicylate identified in § 343.10(d) or

§ 343.12(d) shall be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(3) For products containing magnesium salicylate identified in § 343.10(e) or § 343.12(e) shall be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

§ 343.80 Professional labeling.

The labeling of a product provided to health professionals (but not to the general public) containing active ingredients identified in § 343.14 may contain any of the following indications: "For rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis."

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before October 6, 1977. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before November 7, 1977. Received comments may be seen in the above office between the hours of 9 a. m. and 4 p. m. Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107.

Dated: June 7, 1977.

SHERWIN GARDNER,
Acting Commissioner of
Food and Drugs.

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