FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

8:07 a.m

Thursday, June 12, 2003

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

COMMITTEE MEMBERS: (Continued)

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ATTENDEES (Continued)

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ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

JONCA BULL, M.D.
TIA FRAZIER, R.N.
CHARLES GANLEY, M.D.
CURTIS ROSEBRAUGH, M.D., M.P.H.
ARLENE H. SOLBECK, M.S.

ALSO PRESENT:

KATHERINE McCOMAS, PH.D.
ROSE ANN SOLOWAY, R.N., MSEd, DABAT
ARMOND M. WELCH, B.S. PHCY

C O N T E N T S

CONTINUE OVER-THE-COUNTER STATUS OF
IPECAC SYRUP

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P R O C E E D I N G S

(8:07 a.m.)

DR. CANTILENA: Good morning everyone, and welcome to the June 12, 2003 meeting of the Nonprescription Drugs Advisory Committee. My name is Dr. Lou Cantilena, head of clinical pharmacology at the Uniformed Services University. I'll be chairing today's meeting.

We would first like to introduce the committee, and what we'd like to do is actually start on this end, and if you can introduce yourself and say who you are and where you're from. How about if we start over on this end and then hopefully we will straighten your mike out.

DR. BULL: Good morning. Jonca Bull. I'm the Director of the Office of Drug Evaluation V at the Food and Drug Administration, the Center for Drug Evaluation and Research, Office of New Drugs.

DR. GANLEY: I'm Charlie Ganley, Director of the Division of Over-the-Counter Drugs.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy Director of the Division of Over-the-Counter Drugs.

DR. LAM: Francis Lam from the University of Texas Health Science Center in San Antonio. I'm a member of NDAC.

DR. PATTEN: Sonia Patten. I'm the consumer representative on NDAC. I'm from Minnesota and I'm an

anthropologist teaching at Macalester College.

DR. UDEN: I'm Don Uden from the University of Minnesota, College of Pharmacy, and a member of NDAC.

DR. WOOD: I'm Alastair Wood from Vanderbilt University.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. DAVIDOFF: I'm Frank Davidoff. I'm an internist, formerly editor of the Annals of Internal Medicine, and I'm a member of the committee.

DR. WILLIAMS: I'm Henry Williams, Howard University, Department of Community Health and Family Practice. I'm a member of NDAC.

DR. TONG: Good morning. I'm Ted Tong. I'm from the University of Arizona, College of Pharmacy. I'm an invited consultant to the committee this morning and afternoon. I'm a professor of pharmacy practice, pharmacology, toxicology, and public health at the University of Arizona, and I'm also the Executive Director of the Arizona Poison Information Center.

DR. JOHNSON: Hi. My name is Julie Johnson. I'm from the University of Florida and I'm a member of the Nonprescription Drugs Committee.

DR. CLAPP: Leslie Clapp, pediatrician, Main Pediatrics in Buffalo, New York, and I'm a member of NDAC.

DR. BLEWITT: George Blewitt, acting industry liaison representative for NDAC.

DR. CANTILENA: Thank you.

We'll now have the reading of the conflict of interest statement by Dr. Somers.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to the meeting and is made a part of the record to preclude even the appearance of such at the meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

We would like to note that Dr. George Blewitt is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Blewitt would like to disclose that the Consumer Health Care Products Association is paying for his travel expenses and honorarium for his attendance at the meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves

from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

Dr. Katherine McComas of the University of Maryland would like to address you for a few minutes.

DR. McCOMAS: Thank you and good morning.

I'm here today conducting a study on public attitudes and understanding about the conflict of interest procedures that the FDA uses to monitor and manage real or potential conflicts of interest of its advisory committees and its members. This is a study that's being conducted across multiple advisory committee meetings, across multiple centers.

For those of you in the audience, there's a questionnaire which I've distributed on your chairs. It takes about 15 minutes to complete. If you have a chance to complete it today, there's a box outside the door you can drop it in. Otherwise, there's a business reply envelope that you can mail it back to me at no cost to yourself.

I've also distributed questionnaires to the

advisory committee members. Again, I greatly appreciate your time in completing it and sending it back to me. The more responses we get, the more reliable and valid the results will be, and it will help us to offer feedback to the FDA on what the public knows and understands about its conflict of interest procedures.

If you have any questions, I'll be around to answer them, and please feel free to contact me if you'd like a summary of the results. Those will be freely available to all and any who are interested.

Thank you very much.

DR. CANTILENA: Thank you.

We'll now have Dr. Curt Rosebraugh introduce the topic for discussion today.

DR. ROSEBRAUGH: Good morning. I'm Curt Rosebraugh, the Deputy Director of the Division of Over-the-Counter Drug Products, and on behalf of the division, I'd like to welcome the members of the Nonprescription Advisory Committee to today's meeting regarding the over-the-counter status of ipecac syrup.

By way of introduction, I'd like to briefly give some background and describe the purpose of the meeting, outline our agenda, introduce the speakers for the morning session, and review the discussion points for the afternoon session.

Ipecac syrup has been available as an over-the-counter drug product since 1965. Prior to regulations that allowed OTC marketing, whether ipecac syrup should have OTC status was controversial because it was felt that it should only be used under medical supervision. At the same time, it was recognized that its use in poison emergencies necessitated easy and quick access.

At that time, during its deliberations, the FDA sought expert recommendations from poison experts and medical societies. It was the unanimous recommendation of the American Academy of Pediatrics, the American Association of Poison Control Centers, the American Medical Association, and the Medical Advisory Board to the FDA that ipecac syrup should be sold without a prescription so that it would be readily available for emergency treatment of poisoning. However, that recommendation did come with a caveat that it would be labeled such that it stated, before using, call a physician, the poison control center, or hospital emergency room.

I think it's probably safe to say that since that time ipecac syrup has been thought of as a vital component in the strategy for preventing childhood poisoning deaths.

Now, however, the OTC status of ipecac syrup has been called into question by some medical societies and

poison experts. These societies and experts suggest that there are several factors that merit a reevaluation of the current nonprescription status of ipecac syrup. These factors that they cite include that the use of gastric emptying has been declining significantly over recent years, and that there is in their view insufficient evidence of the benefits of therapy, and that this is coupled to a possibility of mortality and morbidity from adverse events and abuse and misuse issues associated with the ready availability of ipecac syrup.

So with that as a background, the purpose of the advisory committee meeting today is to provide a public forum for discussion and review of the over-the-counter status of ipecac syrup. There will be several presentations from distinguished speakers for the committee to consider during its deliberations.

The first speaker will be Arlene Solbeck from within our Division of Over-the-Counter Drug Products. Arlene will be reviewing the regulatory history of ipecac syrup.

This will be followed by three guest speakers, Drs. Tenenbein, Manoguerra, and Robertson. They will be giving us their review of the published literature regarding the use of ipecac syrup as a treatment for poisoning.

This will then be followed by Dr. Silber who will give us his review of abuse and misuse issues associated with ipecac syrup.

During the presentations, the NDAC committee members should consider the information and use the question and answer session immediately after each speaker's presentation to prepare to address the following discussion points.

First, the committee will have a general discussion over the role of gastrointestinal decontamination and poison management. This will be followed by three questions, the first of which is, is the availability of emergency medical treatment, rural versus urban setting, clinically relevant to whether ipecac syrup is used for gastrointestinal decontamination in poison management? Second, is the evidence available in the literature of adequate quality and quantity to establish the risk/benefit ratio of ipecac syrup for over-the-counter use? And finally, should ipecac syrup retain OTC status for use by consumers to treat accidental poisoning?

And now that the stage is set, I'd like to introduce the next speaker. Arlene Solbeck is an interdisciplinary scientist within the Division of Over-the-Counter Drug Products. She is the lead reviewer and primary author for the OTC Poison Treatment Rulemaking, and

she will present the regulatory history of ipecac syrup. Arlene?

MS. SOLBECK: Thank you, Curt, and good morning. This morning I'm going to provide you with some regulatory history on FDA's review of the safety and effectiveness of ipecac syrup, an OTC poison treatment drug.

What I'm going to discuss includes, first, an overview of the OTC drug monograph process. Then the regulatory history for ipecac syrup beginning in 1965 and leading up to the current 1985 rulemaking, a tentative final monograph or proposed rule, and I will show some proposed labeling from that rulemaking. I will also mention some of the issues from the public comments that we have received back about the 1985 TFM that are guiding us in our preparation of the final monograph and conclude with a summary.

The OTC drug review, which was begun in 1972 to evaluate the safety and effectiveness of all OTC drugs, is commonly referred to as the monograph process. It is an active ingredient-based review. Rather than evaluate each specific product, FDA determined that it would be more practical to determine products by class and to review each class by their active ingredients. For example, ipecac syrup is an ingredient in a class of products for poison

treatment.

The final monograph or final regulation states the conditions for marketing a product containing these ingredients for a specified use or uses and also states the required labeling. Ipecac syrup under discussion today is regulated as part of the monograph process.

This slide provides a little more information about the monograph process. There are generally three phases. First, a panel or panels with experts in specific drug area is convened to discuss safety and effectiveness data and to hear presentations from the agency, industry, and other interested parties in a public meeting like this one. Then the panels present a report to the FDA with their recommendations. The FDA then publishes the panel's report, and this is the advance notice of proposed rulemaking, or the ANPR.

After public comment, comments from industry and other interested parties, and any new data that is submitted is evaluated, the agency proposes a tentative final monograph or proposed rule which contains the FDA's proposed position for regulating that particular class of OTC drugs.

Finally, after another comment period, the FDA follows the same process in reviewing the new information that has come in and develops a final monograph, or final

rule, which is the final regulation for that particular drug class. At this point in time, FDA is developing the final monograph for ipecac syrup, and so today's discussions will be considered in developing that rulemaking.

Now we'll move to some regulatory history beginning with FDA's 1965 regulation. Ipecac syrup has been available as an over-the-counter drug product in an emergency treatment for use in poisonings under 21 C.F.R. 201.308 since October 27, 1965. Note that 1965 was before the OTC drug review began. Although controversy existed about whether ipecac syrup should be OTC, because it was felt that it should be only used under medical supervision, it was also recognized that the immediate availability of ipecac syrup for use in poisoning emergencies necessitated quick and easy availability for consumers. So the FDA obtained the views of medical authorities, and it was the unanimous recommendation of the American Academy of Pediatrics, the American Association of Poison Control Centers, the American Medical Association, and the Medical Advisory Board of the Food and Drug Administration that ipecac syrup be available for sale without a prescription in 1 fluid ounce containers. And so the Commissioner of Food and Drug determined that it was in the public interest to put ipecac over the counter.

The recommendations made in 1965 are shown in this slide. The ruling said that the label must have in a conspicuous manner boxed and in red letters the following: Before using, call physician, the poison control center, or hospital emergency room immediately for advice. It also recommended that the usual dosage be 15 mls in persons over 1 year of age, that it not be used in unconscious persons, and that it not be administered after certain kinds of poisons, particularly strychnine, corrosives, and petroleum distillates.

Following the 1965 regulation, as part of the OTC drug review, the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products, which is the LAEA Panel, reviewed ipecac syrup, and in its report published in the Federal Register in 1975, classified it as a category 1 safe and effective emetic to induce vomiting in case of poisoning.

The panel added to the 1965 rulemaking a dosage for infants under 1 year and some further warnings and directions, and put a package limitation size of more than 30 milliliters on the product.

But then in 1978, FDA published a tentative final monograph with the tentative conclusions on comments submitted in response to the 1975 panel's report. The recommendations from this rulemaking, which differed from

the 1965 rulemaking, are shown on this slide. For instance, the dosages were expanded to include one for infants under 1 year and one for infants over 1 year, children, and adults. The rulemaking also included the kinds of liquids and the amount of liquids that should follow the ingestion of ipecac and also what liquids not to drink after ipecac, particularly milk or carbonated beverages. Also the directions included to administer a second dose after 20 minutes if vomiting hadn't occurred and not to administer in semiconscious or unconscious persons. The directions also included a drug interaction precaution, not to administer activated charcoal before successful vomiting had been produced by ipecac syrup.

And the warning about not using after contraindicated poisons were ingested remained the same as the 1965 rulemaking, as well as the labeling of the principal display panel with the instructions to definitely call a health professional for advice before using.

In 1982, the FDA published the recommendations of another advisory review panel, the OTC Miscellaneous Internal Drugs Panel, or the MI Panel. It is not usual procedure to have another advisory panel review an ingredient, particularly after a tentative final monograph has already been issued, but in this case a kit containing ipecac syrup needed to be reviewed and was given to the MI

Panel for review. The Miscellaneous Internal Drugs Panel was given this assignment. The MI Panel concurred with the Laxative Panel about ipecac syrup and proposed that activated charcoal, as well as ipecac syrup, be classified as safe and effective to treat acute toxic ingestion.

And this brings us to the 1985 tentative final monograph. Because of the overlap between the emetic tentative final monograph and the Miscellaneous Internal Drugs Panel report, the agency decided to combine the two rulemakings and to publish a single TFM. So in 1985, FDA published the tentative final monograph, Poison Treatment Drug Products for Over-the-Counter Use, containing FDA's tentative conclusions and proposed labeling on both ipecac syrup and activated charcoal as poison treatment drug products.

And here are some highlights from the 1985 TFM. FDA was concerned that the label be brief enough to read and understood in emergency situations, yet contain adequate warnings and directions for the consumer in case professional emergency help could not be reached quickly. Therefore, FDA proposed to devise the label into two distinct sections.

First, as shown in this slide, the FDA proposed that the principal display panel contain the following directions in red letters, boxed in a conspicuous place to

read: If possible call a poison control center, emergency medical facility, or health professional for help before using the product. Also, if help couldn't be reached quickly, follow the directions. Of note here, is that the agency recommended calling for professional help first, particularly if ipecac is contraindicated for certain poisonings and for use in certain situations.

However, the agency proposed that for times when professional help cannot be contacted, the consumer should go ahead and use the drug according to the directions and not delay treatment.

The TFM also stated that labeling should provide space for consumers to write down emergency telephone numbers.

The second part of the label contains the warnings and directions, as shown in this slide. The agency recommended that companies use a wraparound label to provide more label space for larger print, but said that a package insert would not be acceptable because it might become separated from the product.

The proposed dosages, as shown in this slide, were expanded to place adults and children 12 years and older in one category and children 1 year and under 12 years in one category, children 6 months to under 1 year in another category. And the drug is not recommended for

children under 6 months. You can see that the recommended dosages have been expanded from the earlier proposals in which there was only one dosage for children and one dosage for adults.

The rulemaking also recommends the amounts of liquid to be administered after each dose. The rest of the directions state to drink water or clear liquids after ingesting ipecac. Milk should not be given. To repeat the dosage if vomiting doesn't occur within -- and this time it was changed from 20 to 30 minutes -- and to keep patients active and moving to maintain the consciousness of the patient.

This slide contains a list of the suggested warnings. Do not use in persons who are not fully conscious replaces the old do not use in people who are unconscious or semiconscious. Also, do not use if certain contraindicated poisons have been ingested, such as turpentine, corrosives, and petroleum distillates, and also do not administer milk.

In 1985, the TFM also proposed directions for use of poison treatment kits in which ipecac syrup is first used to cause vomiting, and then after vomiting has occurred, activated charcoal was given to help absorb any remaining toxic substance. So a drug interaction precaution was included to read: Do not give activated

charcoal until after the patient had vomited, unless directed by a health professional. And this is because simultaneous use of these products reduces their effectiveness and may also pose a safety problem.

Now, this is a typical label for ipecac syrup. This product was purchased recently at a local pharmacy and I reproduced the label for this slide. The label does not have to be in drug best format until May 16, 2005. So you notice that it isn't in drug best format. Even though manufacturers do not have to comply with panel recommendations before completion of the rulemaking, this manufacturer has labeled their product according to the 1985 TFM with all the instructions, directions, and warnings that were shown in the prior slides.

Well, what happened after the TFM was published? FDA received comments from poison control centers, hospitals, medical centers, medical schools, trade associations, manufacturers, law firms, and individuals. The FDA received a number of comments that supported OTC availability of ipecac syrup for treating accidental poisonings and stated that OTC availability of ipecac is in the public interest medically and financially.

However, there were some concerns about the safety aspects of using ipecac syrup that were included in some of those comments and are shown on this slide. FDA

received comments expressing concern that consumers know exactly what to do in what order so the poisoning is properly managed, things such as exactly how to use the poison treatment drug, in what order, how many times to repeat them, what are the maximum dosages, when to give charcoal after ipecac, and so on so that consumers act in a responsible manner.

Several comments expressed concerns about the use of ipecac in babies between ages 6 months and 1 year. The primary concern was the aspiration and dehydration that can be caused after the vomiting. Similar concerns were also expressed about the elderly.

And finally, FDA also received comments that called for strong warnings against misuse and abuse, and this related to prolonged or repeated use in eating disorders.

Currently the labeling for ipecac syrup clearly states that it is for the treatment of poisoning and OTC marketing is limited to 1 ounce containers. But although the labeling clearly states the purpose of the product, there is a concern about misuse by individuals who are seeking a way to control their weight to stay thin.

In addition to the issues raised in the comments to the 1985 TFM, the medical literature and some poison control and clinical toxicology societies have

indicated that the safety and efficacy of ipecac syrup for the use as an over-the-counter emetic in the management of poisoning should be reevaluated. There have been clinical studies since the 1985 TFM which have raised questions about whether ipecac is of any benefit as a poison treatment drug.

And here are some examples of some organizations with differing recommendations on the use of ipecac syrup. The American Academy of Clinical Toxicology and the European Association of Poison Centers & Clinical Toxicologists issued a position statement in 1997 after reviewing the scientific literature and stated that the data are lacking to demonstrate that ipecac improves the outcome of poison patients. This position has been endorsed by the American Board of Applied Toxicology and the Canadian Association of Poison Control Centers.

However, the American College of Emergency Physicians and the American Medical Association, among others, still recommend keeping a 1 ounce bottle on hand in the event of an accidental poisoning.

So in conclusion, FDA is in the process of completing the final monograph for poison treatment ingredients. Ipecac syrup and activated charcoal are the only two ingredients classified as category 1 for poison treatment and both are regulated by the monograph process.

One of the important questions for us today is whether, in light of recent data and information, ipecac syrup should remain OTC.

Thank you.

DR. CANTILENA: Thank you, Ms. Solbeck.

We'll now go into the presentations, and Dr. Rosebraugh will introduce the speakers. Our plan will be to have ample time for you to question each speaker at the completion of their talk. Dr. Rosebraugh?

DR. ROSEBRAUGH: We're going to have a little schedule change. The first speaker will be Dr. Anthony Manoguerra. Dr. Manoguerra is Professor of Clinical Pharmacy and Associate Dean for Student Affairs at the UCSD School of Pharmacy and Pharmaceutical Sciences and Director of the San Diego Division of the California Poison Control Center at UCSD Medical Center.

He received his Pharm.D. degree from the University of California, San Francisco in 1971 and has been actively involved in poison research since that time. He's a diplomat of the American Board of Applied Toxicology and past President of the American Association of Poison Control Centers.

He is widely published on poison therapy and is the lead author on a new guideline due for release soon regarding the use of ipecac syrup in out-of-hospital

management of ingested poison. The development of this guideline is a joint project of the American Association of Poison Control Centers in collaboration with the American Academy of Clinical Toxicology and the American College of Medical Toxicology.

Dr. Manoguerra?

DR. MANOGUERRA: It's a real honor to be invited to speak with you today.

As Dr. Rosebraugh mentioned, I came to the attention of the FDA as a result of co-authoring a guideline that is currently in its final draft phase, and I wanted to initially talk about that guideline's project.

It's a joint project of the American Association of Poison Control Centers, the American Academy of Clinical Toxicology, and the American College of Medical Toxicology. And it's funded by a project grant from the Maternal and Child Bureau of the Health Resources and Services Administration of the Department of Health and Human Services.

These are the members of the panel at the present time. It was put together to be representative of the interdisciplinary nature of toxicology, as well as the representatives from across the country.

The panel's charge is to review literature evidence, to develop a draft guideline. That guideline is

then circulated for secondary review, and I believe that is how the FDA became aware of the ipecac guideline, through the secondary review process. The committee then incorporates the review comments from that secondary review, then develops a final guideline representing consensus of the panel for approval by the boards of the sponsoring organizations.

The purpose of the guideline is to produce consistency in patient management between poison control centers across the country, and the project is to be based on the best interpretation of the available literature. And public policy decisions are to be left to the sponsoring organizations.

Now, I make a point of that because in the draft guideline on ipecac, the consensus panel made a recommendation that OTC status of ipecac be reviewed by the FDA. On secondary review and on further discussion, the consensus panel felt that they probably overstepped their charge in making that recommendation and that policy decisions should be left to the sponsoring organizations. So the final draft of the document will not contain that statement.

We have completed one guideline, and the ipecac one is the second guideline that we're currently working on, and we're working on three additional ones. The goal

is to have about a dozen guidelines completed by the end of this next year.

As I said, the ipecac guideline is not yet complete. The final draft is currently being written for approval by the panel, and I want to point out that my comments today are based on the review of the literature, the initial drafts of the guideline, the panel discussions that were held, and my personal experience over the past 30 years. And I want to point out that my statements do not represent the official policy of any of the sponsoring organizations at this time. I'm hopeful that the sponsoring organizations will accept the consensus panel's recommendations, but that hasn't occurred yet.

Pediatric exposures reported to poison control centers over the last 16 years have increased substantially. This is from the American Association of Poison Control Centers national toxic exposure surveillance system, and you can see that from 1986 -- I didn't go back all the way to 1983, but you can extrapolate those numbers back even further from when the system began. In 1986, there were about 700,000 cases reported to poison control centers, and that has now, in the last few years, grown to approximately 1.5 million cases a year.

If you contrast that with the use of ipecac by U.S. poison control centers over that same time period, you

can see that the use of ipecac has declined substantially. In 1986, there were about 150,000 uses of ipecac by U.S. poison centers, and in the latest year for which we have data, it was about 16,000 uses of ipecac by poison centers.

I need to point out that these are cases in which ipecac was used. I've not seen the data yet, although I've requested it and I'm told that it was e-mailed to me yesterday, as to whether the poison center recommended the use of ipecac in these cases or if health professionals or individuals used ipecac without the poison center's recommendation. So I hope to have that data very soon.

One of the questions that I was asked to address is what is the role of gastrointestinal decontamination in poison management, and I have to admit that this is one of the most controversial topics in clinical toxicology over the past 10 to 15 years. I began my work in poison centers in 1974, and at that time, I can tell you that this was not a controversial topic. It was generally agreed that any procedure that we did to remove stomach contents was going to benefit the patient. And it wasn't until about the last 15 years that this attitude was questioned, and as the work has been done, I think my attitude has changed and I think the attitude of many in the poison center world and the clinical toxicology world

has changed as well. I have to point out that there is not complete agreement but that there is general consensus that has been developing in recent years.

In general, emesis and lavage are now rarely being used. Gastric lavage is rarely being used in emergency room situations and the use of emesis, as I've shown, has declined substantially. More activated charcoal is being used in the hospital situation. The use of activated charcoal in the home situation has not been very successful. The use of cathartic agents, which was also something else that we recommended at that time, has just about totally been abandoned. These trends are supported by the bulk of the literature evidence that's available, although highly rated evidence is lacking on all of these areas of discussion.

Numerous studies have demonstrated that activated charcoal appears to be superior to ipecac-induced emesis or gastric lavage in reducing the absorption of ingested materials in experimental situations. However, there is no convincing evidence in my opinion and I believe in the opinion of many others that emesis, gastric lavage, or activated charcoal positively affect patient outcome. I'll review some of that data for you in just a minute.

The problem that we're faced with, though, when we review this literature, if we apply the standard rating

systems that are being used for evidence-based medicine, such as the Oxford Rating System, for example, none of this work has very high evidence ratings. And some of that has to do with just the design of the studies that are used in this work is classically thought not to be the highest level of evidence. It's very difficult to do a double-blind, controlled study in this area. So the studies don't come out with very high evidence ratings.

Most of the studies are animal studies, retrospective case series, or volunteer studies that use low doses of marker materials, and then measure the amount of material that's either been removed or the amount of material that's been absorbed after the induction of emesis or gastric lavage or the use of activated charcoal.

I'd like to summarize, though, the information that is available on the effectiveness of ipecac syrup. Ipecac does make approximately 85 percent of people given the drug vomit after the first dose, and of those given two doses, the number increases to 95 percent. So it was stated earlier that the standard recommendation has been to give a dose of ipecac along with 4 to 6 ounces of water, and if the patient doesn't vomit in 20 to 30 minutes, then the dose of ipecac should be repeated. These are the numbers that result from following that recommendation.

The onset of emesis is typically within 20 to

30 minutes of that first dose administration. If a patient requires a second dose, it's typically been within 5 to 10 minutes of the administration of that second dose.

The amount of material removed by ipecac has huge inter-subject variability. If given within 5 minutes of ingestion, which is how most of the volunteer studies have been conducted, either ipecac has been administered simultaneously with a marker agent or within 5 minutes of the administration of the marker agent. If given within 5 minutes, it removes somewhere between 0 and 80 percent of the administered material, with a mean of about 25 to 30 percent. So a huge inter-subject variability.

There is a rapid reduction in removal of materials with ipecac with time such that in the studies that if the ipecac is not administered within 30 minutes of the marker material, it's no better than the control subjects.

There are seven papers that have been published that examine the impact of emesis, gastric lavage, and activated charcoal on the outcome of poisoned patients. Most of these authors concluded that there was no difference between the treatments and that activated charcoal was the most effective -- excuse me. They either reported that there was no difference between the treatments or that activated charcoal was more effective

than either emesis or gastric lavage. If you examine each of those studies closely, just about all of them had significant methodological flaws that make interpretation and applicability of the results difficult.

My conclusion is that there's no conclusive evidence that ipecac or any of the other decontamination procedures, gastric lavage, or activated charcoal, positively affect patient outcome.

So that leaves us with two camps that look at this data. There's the glass is a quarter full camp, which says, if I give ipecac, I can get 25 to 30 percent of whatever my patient has ingested out, and that's really good. And then there's the glass is three-quarter empty camp which says, if I give someone syrup of ipecac, I can only get out 25 or 30 percent of ingested substance at best. And you will find people in the poison center world that are in both of these camps.

You'll probably get the impression, after hearing my presentation, that I'm in the three-quarter empty glass camp. After having been for many, many years in that first camp, I have done a complete turnabout in my position on ipecac, as my experience has grown over the last 30 years.

What are the risks of ipecac syrup use? It's another issue that this committee must address.

Considering the thousands of doses of ipecac that have been administered over the past 30 or 40 years -- I talked about in 1986 there were 150,000 doses administered by U.S. poison centers. We don't know how many total doses were used that poison centers didn't hear about. So if you look at the large numbers of doses that have been administered and the occurrence of adverse events that have been reported, we can say that ipecac is safe when used therapeutically. The numerator of adverse events is low. The denominator of use is very, very high. So I think we can conclude that it is a safe agent.

Some of the adverse events that have been reported, however, include -- and what I've done is I've summarized these percentages from a number of different studies that have looked at adverse events. Sedation and drowsiness occurs in about 12 to 25 percent of patients given ipecac. Diarrhea occurs in about 17 to 30 percent of patients given the drug. Prolonged and repeated emesis, defined as vomiting beyond 1 hour after administration, occurs in about 10 to 18 percent of people given the drug.

Some less common adverse events that have been reported in the literature, and these are primarily case reports. Aspiration pneumonitis from aspiration of stomach contents following vomiting. There are Mallory-Weiss tears and esophageal and gastric perforations that have been

reported. Pneumomediastinum, gastric rupture, diaphragmatic rupture, a case of intracranial hemorrhage in an elderly patient given the drug, and there are a few cases of allergic reactions manifested as rash and urticaria following the administration of ipecac. As I want to emphasize, these are case reports and these adverse reactions are extremely rare.

As far as dose-related acute toxicity from ipecac, it has not been reported following the single use of ipecac syrup or even multiple use -- short-term use of ipecac syrup.

Acute toxicity with ipecac has only been reported following the ingestion of the fluid extract of ipecac, which is no longer available. The best I could determine is that production of this agent ceased in 1970, and its removal from the market occurred following a number of deaths that were reported with the use of this agent. It was intended to be diluted by pharmacists into the syrup form before it was administered, and the cases of acute toxicity occurred when the fluid extract was given instead of the syrup form.

Chronic dose-related toxicity. I understand we're going to have a presentation on abuse of ipecac later on. Emetine is one of the alkaloids in ipecac. The two major ones are emetine and cephaeline. There are at least

a half a dozen other alkaloids that have been identified in the preparation as well. Emetine has well-documented, chronic, dose-related effects on both skeletal and cardiac muscle leading to myopathy. The pattern of myopathy seen with chronic ipecac syrup administration is similar to that seen when emetine is used therapeutically, and the assumptions have been made, therefore, that the toxicity that you see following chronic ipecac use or abuse is related to the emetine content. But there are other alkaloids such as cephaeline, psychotrine, emetamine, and others whose contribution to the toxicity is not really known.

Now, we do know that these alkaloids in ipecac do get absorbed, and I'll just quote one study here for you that looked at this in 1984 where they measured the absorption of emetine and cephaeline in 10 adult patients given a 30 milliliter dose of ipecac syrup, and they measured the alkaloids in the emesis that was recovered, and they measured alkaloid levels in the plasma of the volunteers. The recovery of the alkaloids in the emesis averaged 45 plus or minus 33 percent, huge variability in the amount that was removed in the emesis. And alkaloid levels were measured in the plasma of all of the subjects in varying amounts. There was also a huge variability. That correlated with the amount that was recovered. Those

patients that vomited up the majority of the alkaloids had the lowest absorbed levels, and vice versa. The conclusion of this study was that all patients given ipecac will absorb the alkaloids, but that the extent of absorption is highly variable.

Emetine is excreted totally by the kidney, and unchanged emetine can be detected in the urine 40 to 60 days following the administration of a single dose of ipecac. There have been several papers published, one very dramatic one in a child who was accidentally administered a larger than normal dose of ipecac, several doses acutely, and emetine levels were detected in that child's urine 62 days after administration of that single acute use of ipecac.

Ipecac has also been used in a condition called Munchausen syndrome by proxy where a child has been used as the mechanism for unusual and use of medical care by an adult. There are nine published papers describing 13 cases where ipecac was used in this fashion by caregivers. 6 of the patients did not develop myopathy and had resolution of their gastrointestinal symptoms which was the primary reason why they were taken in for health care. However, 2 patients developed skeletal muscle myopathy and recovered. 5 developed skeletal and cardiac myopathy, and 3 recovered and 2 of the children died.

As far as ipecac syrup abuse is concerned, there are 17 papers in the United States literature that report 20 cases of patients with eating disorders who developed cardiac and skeletal muscle myopathy following use of ipecac syrup, and I need to emphasize that this was not single use of ipecac syrup or even short-term use of ipecac syrup. This was multiple administrations daily for periods of months. There were 4 deaths in the literature from ipecac syrup abuse in this fashion.

But I need to point out that there are other deaths that have been reported in the news media that are not in the medical literature. For example, one of the most famous ones was Karen Carpenter, the singer back in the 1980s, who died from ipecac abuse. Her case is not included in the cases that are reported in the medical literature, so that are a number of cases that have been reported in the lay press that never made it into the medical literature.

There are two papers that attempted to quantify the extent of ipecac abuse in patients with eating disorders. One is a paper that looked at 851 patients attending an eating disorders clinic. On questioning of those patients, 7.8 percent had used ipecac at least once, 4.7 intermittently, and 3.1 percent on a chronic basis.

In another study, 622 patients in an eating

disorder clinic reported that .09 percent of patients between the age of 9 and 19 years of age reported the use of ipecac, and 3.8 percent of women between the ages of 20 to 46 years of age had used ipecac.

Another thing that has been questioned in the literature is when ipecac is readily available, is it ever used inappropriately. I was only able to find one paper that looked at the appropriateness of use of ipecac by physicians, and the author concluded that the use of ipecac was inappropriate in 20 percent of the cases where physicians initiated the use of ipecac prior to the contact with the poison center. Their conclusion was that these uses were inappropriate because the drug was used in situations where the drug was contraindicated, and if you go further into the paper, most of those contraindications were the use of ipecac in patients who had ingested drugs where the loss of consciousness could be anticipated during the time period when the patient would be vomiting from the ipecac.

I was not able to find any papers that did a systematic examination of the appropriateness of the use of ipecac by the general public. As far as I know, that work has not been done. However, there are a few case reports of children who had ingested corrosive agents where the caregiver administered ipecac to those children.

I think before you can talk about when ipecac might be used, I think you need to talk about when it should not be used. So I'd like to spend just a few minutes discussing that as well.

When is ipecac syrup contraindicated? And this goes actually beyond the contraindications that are on the label of ipecac, and I think these are generally accepted contraindications in the poison center world. It should not be given when patients are comatose, when they're lethargic, when they're having convulsions, or when they're unable to protect their airway and aspiration of stomach contents may occur as a result of their inability to protect their airway.

It should not be used when the substance ingested is a corrosive agent.

It should not be used when the substance ingested is a petroleum distillate of low viscosity with a high aspiration risk. Now, there is some controversy in this area. There are some people who feel that the use of ipecac in petroleum distillates is acceptable. I happen to be one of those people who feels that it is not an acceptable risk considering the fact that absorption of petroleum distillates from the gastrointestinal tract is not a significant route of toxicity. The toxicity occurs primarily by aspiration, and therefore why risk an

additional aspiration by inducing vomiting in these particular situations?

It is also contraindicated when the substance is likely to cause a loss of consciousness or coma, or convulsions are likely to occur while vomiting is taking place. So vomiting typically begins about 20 to 30 minutes after the administration of ipecac, and typically occurs three or four times over the next 30 to 60 minutes after vomiting ensues. And if the substance is likely to cause the loss of consciousness or the onset of convulsions in that time period, then the risk of aspiration of emesis is significant. Some of those materials are some of the tricyclic antidepressants, isoniazid, some of the older antihistamines. There's a large number of materials that are ingested that fit into this category.

And lastly, when emesis may interfere with the administration of an oral antidotal therapy, and the example that's commonly used is the administration of N-acetylcysteine in acetaminophen ingestions. If the patient is vomiting from the administration of ipecac, it obviously would be more difficult to get the patient to take oral N-acetylcysteine.

So when might ipecac be used? We spent quite a bit of time in the consensus panel discussions talking about when might there be situations when ipecac would be

considered. First of all, it would be used when it's not contraindicated. I think that is obvious. It can be used when it could be administered soon after ingestion and no later than 30 minutes after ingestion based on the evidence that's in the literature. When removal of 25 to 30 percent of an ingested dose may have a significant influence on patient outcome because, in general, 25 to 30 percent is what typically is seen as far as removal. And it also might be used when there is a long delay in the anticipated arrival of the patient at a health care facility, for example, greater than an hour.

Now, when the consensus actually sat down and tried to come up with examples that fit this scenario, we couldn't come up with very many examples that fit this. The only one that we were able to come up with was an acetaminophen ingestion in a very remote environment, very rural environment with poor emergency medical services support where it would take a significant amount of time for an EMS provider to get to the victim and a significant amount of time for that victim to get to a health care facility. Then we said, how often do you see severe acetaminophen ingestions in children? And the answer to that is we don't. So the net result is that the situations where ipecac actually may be used are little to none in our opinion.

What have we specifically done in San Diego? I arrived there in 1977. Prior to that, I was director of the poison center in Minneapolis, and there we used ipecac extensively. We administered it, probably on average, 10 to 15 times a day. And we did that as well in San Diego when I arrived there. As I said, I was a strong advocate of the use of ipecac.

From 1977 through 1990, we had protocols that specifically told the staff when they should use ipecac. For example, we had one that said if a child ingested less than 150 milligrams per kilogram of acetaminophen, we could observe that child at home without any intervention. If they took between 150 and 200 milligrams per kilogram of acetaminophen, we would induce vomiting with ipecac, and we would observe the child at home. And if the child ingested more than 200 milligrams per kilogram, we would send the child to an emergency department. This was standard procedure in poison centers across the country to have protocols that resembled these.

In 1990, we decided to completely eliminate the use of ipecac. Since 1990, the poison center has not recommended the use of ipecac to any caller into the poison center. What we did with those children that we were giving ipecac to, we put those into our "observe at home" category. What we have found is that we have had no change

in the number of children that we had to send to the emergency room as a result of eliminating the use of ipecac. It's our feeling that what we ended up doing to those children is that we were taking children who were probably going to be asymptomatic or have very mild symptoms and we were making them symptomatic by administering syrup of ipecac to them and that we were providing no benefit in their ultimate outcome because those children were going to do fine anyway. As a result of that, we have been strong advocates for eliminating the use of ipecac by other poison centers as well.

I was also asked to address what are the alternatives to the use of ipecac. One of the alternatives is the use of activated charcoal in the home. There have been a number of studies that attempted to look at how useful the administration of activated charcoal would be in the home situation, and in each of those situations, it was discovered that administering charcoal to children by caregivers is an extremely difficult thing to do. It's not a very appetizing substance. It's very difficult to get children to accept it even when a trusting parent administers it, let alone a caregiver that the child doesn't know very well. If you add on top of that the data shows the proof of long-term benefit to the outcome of the ingestion is lacking, we have not been strong advocates of

home use of activated charcoal.

You can restrict ipecac to prescription, and that's one of the issues before the committee today. That will decrease the availability of the material to public for abuse and misuse, but it also reduces the availability for use within that 30-minute time window where it may have some effectiveness.

It will allow physicians to prescribe it for specific patient situations. So if there is a physician who has a patient in a rural environment where that physician feels strongly that that patient should have ipecac, the availability on a prescription basis at least allows the physician the option of making it available to that patient. I'm not a strong advocate of that, but I think that's an alternative.

And it will also allow emergency medical services providers to have it available in situations where they think it may be useful. Again, I'm not a strong advocate of that as well.

So what do I feel are the ultimate questions that need to be addressed? The first one is, does the benefit that accrues to poisoned patients through the use of ipecac syrup outweigh the potential adverse events that may infrequently occur? And does the benefit that accrues to poisoned patients from the over-the-counter availability

of ipecac syrup outweigh the potential adverse events that result from the improper use of the drug and the abuse of the drug by patients with eating disorders?

You will get different opinions from different people, some of which will follow me in my discussions here this morning. I need to close my presentation by saying that my answer to both of these questions is no. I don't believe that there's enough benefit that accrues in either of these situations to continue the over-the-counter availability of ipecac.

That concludes my presentation.

DR. CANTILENA: Thank you, Dr. Manoguerra.

I would like to actually open this up to questions from the committee, if you'll stay there please.

DR. MANOGUERRA: Sure.

DR. CANTILENA: Perhaps I can just start with a couple of clarifying questions.

The studies that you talk about with comparative efficacy between ipecac and charcoal are all done in the setting of an emergency department in general. Is that true?

DR. MANOGUERRA: The ones that looked at the --

DR. CANTILENA: The seven studies.

DR. MANOGUERRA: -- at the outcome, yes, they're in emergency departments. That's correct.

DR. CANTILENA: Then charcoal I think generally, if I heard you correctly, is not really a viable option for the home use, especially in the toddler.

DR. MANOGUERRA: We have not been able to successfully administer it to a child in the home. Probably the best study that looked at that was one that was done in Massachusetts where they actually sent people out to the home with charcoal, had them give it to the parent, and then observe the administration of it to children, and they were unsuccessful in doing that as well.

DR. CANTILENA: Then just about the protocol that you used in San Diego where you studied that. I can imagine like an IRB you would say, well, what are the risks and what is your safety net. But your safety net, I guess, in that study as the investigator was that you would be observing them and if they got into trouble, they would be able to come into the emergency room.

DR. MANOGUERRA: That's correct.

DR. CANTILENA: So really in terms of the safety net side of the protocol, if you're out in rural America where you're an hour-plus away, then that probably wouldn't have flown from a protocol standpoint.

DR. MANOGUERRA: The only thing that we changed was that we eliminated the use of ipecac, and we took that group and put it into our "observe only" category. All of

our follow-up procedures were the same. We do routine follow-up procedures for all patients that we leave at home.

I have to tell you that we have very rural areas in our service area. If you get out of metropolitan San Diego County, there are mountains and desert all the way to the Arizona border, and our service area includes all of southern California except Los Angeles. So there are areas where there are 2- to 3-hour drives to the closest medical facility, and we found that even in those situations, eliminating the use of ipecac did not adversely affect the patient.

DR. CANTILENA: Thank you for those clarification points.

Questions from the committee. Dr. Uden?

DR. UDEN: Also the safety net for that study is that children who ingest acetaminophen between 150 and 200 milligrams per kilo sulfate the drug versus glucuronidate the drug, and there's very little risk anyway. So why would you give ipecac when there's very little risk of anything happening? I think that was your biggest safety net by making that decision.

DR. MANOGUERRA: It wasn't just for acetaminophen. I used that as my example, but we had protocols for cough and cold preparations. We have

protocols for any ingestion that a child would get into where we had cutoffs for observation and cutoffs for ipecac. The acetaminophen was an example. It's actually a bad example because we can probably leave all the kids at home and nothing bad is going to happen to them. We have learned that over the years.

DR. UDEN: I have a couple other follow-up questions. On your graphs where you looked at the pediatric exposures reported to U.S. poison centers, over the years that are in that graph, are the substances that pediatric patients are exposed to relatively the same and so the substances they're exposed to have not changed over those 14-15 years?

DR. MANOGUERRA: We didn't do a breakdown of that. My experience has been that the substances, if anything, have gotten safer over the last 15 or 20 years and not more toxic.

DR. UDEN: And then my final question is about the seven outcome studies. Did they really look at the substances which were ingested in those studies? My question is, were the substances in general that were taken were taken in too low amounts and were really not toxic? Therefore, the outcomes would not be any different than doing nothing.

DR. MANOGUERRA: First of all, they were all

adult studies. They were not pediatric studies. I think that's an important thing to point out. No. Excuse me. There may have been one pediatric study.

I talked about the methodological flaws. One of the problems with some of the studies that have been pointed out as the best examples actually are that the patients who were the least sick patients were in either the emesis group or the activated charcoal group, and the sicker patients were in the gastric lavage group. And so they really weren't comparable groups that were looked at. That's why my conclusion is that there's really no evidence that any of them provide positive benefit because you really can't tell the difference between the different groups. They're not comparable groups.

DR. UDEN: Thank you.

DR. CANTILENA: Dr. Tong, then Dr. Davidoff.

DR. TONG: Thank you.

Dr. Manoguerra, thank you for a very thorough review of what the data shows. I'm interested in your issue about the syrup of ipecac abuse. In the cases that you looked at, were there details on how the syrup of ipecac was obtained? Was it through the usual channels? Was it stockpiled? Was it through the OTC distribution of syrup of ipecac at pharmacies and health centers?

DR. MANOGUERRA: I don't recall in any of the

case reports there being any description of how the patient obtained it.

DR. TONG: So these are large amounts of ipecac. We're not talking about unit doses of 30 mls.

DR. MANOGUERRA: Well, the only form that's available, as far as I know, is the 1 ounce bottle of ipecac. So I would assume that the patients obtained it as 1 ounce bottles. But in all of those cases, they were people who ingested it multiple times a day for months to years.

DR. TONG: The gastric emptying is an intuitive reaction of a parent when a child has ingested something. Is there a concern that if syrup of ipecac were not available with all the prerequisites that's placed on it when it's given on the label, that inappropriate use of other materials that are out there, salt water, peroxide, foreign objects, will become more of a problem for us in the poison control centers to deal with?

DR. MANOGUERRA: I really can't say. It has not been a problem in San Diego for the last 12 years that we've been not using ipecac. We haven't seen a single case of salt water administration as an emetic in that time period. We have had people trying to gag their kids with their fingers during that time period, maybe 20 or 30 cases in 12 years.

DR. TONG: So in your teaching of clinical toxicology to your medical pharmacy and nursing students about poisoning, gastric emptying in the home following ingestion is no longer part of the discussion?

DR. MANOGUERRA: That's correct, and we don't advocate emesis or lavage in the emergency department at all. We still do advocate activated charcoal administration in the hospital.

DR. TONG: One other comment. In Arizona, we also have great distances in terms of patients and homes, and when they call the poison center -- and we receive 70,000 calls a year for information and treatment referral and assistance. We too also are experiencing a limited use of syrup of ipecac, but we don't have people give ipecac and then get in the car because during that trip, when the child is vomiting, it could create a serious problem. So we do find syrup of ipecac, limited use in an extended distance from a health care facility, to actually keep them in a home and do exactly what you're doing, managing at home. So perhaps your panel might consider at least the Arizona experience there. We do not put people in cars after they've given children ipecac.

Good job, and thank you.

DR. MANOGUERRA: Actually we did have a case of a mother who got into an automobile accident while she was

attempting to catch the emesis in a basin driving the car with her child sitting next to her on the car seat.

DR. TONG: And given what you said, the child would have been better off at home.

DR. MANOGUERRA: Right. The child now had an ingestion and an accident, rather than just an ingestion.

DR. TONG: Because we do have homes in Arizona without cars. So that is a limitation for us also.

Thank you.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Thanks.

Yes, I was also impressed that these controlled studies were primarily done in emergency rooms, which makes it really difficult to extrapolate to home use, as you point out. But that raised the question in my mind as to whether there was any evidence, which will obviously have to be case-controlled sort of evidence, looking at the patients who do present to emergency rooms or, if possible, if they could be followed at home, with the cases being those that had received ipecac and the controls obviously being the ones that had not, to look at the outcomes in that fashion, but the ipecac having been administered at home rather than in the emergency room setting. Are there any data of that sort? I would think that would be useful.

DR. MANOGUERRA: No, I don't believe there are

any studies like that in the literature.

DR. CANTILENA: Dr. Clapp, then Dr. Johnson.

DR. CLAPP: Several questions. For the 16,000 cases that were reported as having used ipecac, perhaps not under the advisement of the poison control, but it came to the awareness of the poison control, of the 1.5 million that you said in the recent study, do you have any idea of the nature of the ingestion of those patients?

DR. MANOGUERRA: I had requested that data and I was informed that it was e-mailed to me last night. So I don't have a breakdown of that information.

DR. CLAPP: I thought you might know the nature of the ingestion. I thought you just didn't know who advised it.

DR. MANOGUERRA: No.

DR. CLAPP: So the second question I have is, of course, it's a dose-related phenomenon when you talk about a 25 to 30 percent reduction in the toxic burden that the patient who ingested the toxic substance has with ipecac if they use the ipecac within 5 to 30 minutes, presumably, of the ingestion. But you addressed acetaminophen, and I think as a pediatrician, we all pretty much accept that acetaminophen toxicity is not as worrisome as we thought maybe 15 years ago. But how about salicylates or iron, and would you find that to be

something that would be an indication for certainly home use?

DR. MANOGUERRA: If you're in that one-fourth glass full category, those are the arguments that people use. If you get 25 to 30 percent of a potentially lethal dose of a salicylate out of a child, then that may make it a sublethal ingestion.

DR. CLAPP: Or iron as well.

DR. MANOGUERRA: Well, I'll talk about iron in just a second. My feeling with salicylates is that I would rather that parent spend the time getting that child to the hospital where we could do more definitive treatment than giving ipecac at home because I think that actually slows the parent down from getting the child to the hospital. By administering the ipecac at home, the child is vomiting. That time period -- and then like Dr. Tong mentioned, you have a vomiting child in a car on the way to the hospital, I think it actually makes the whole scenario much more difficult to deal with. I would just rather they put the child in the car, go to the hospital where we could do more definitive care.

I used to be a strong advocate -- when we started to eliminate the use of ipecac, iron was the one thing I advocated its use in until we had two deaths with iron poisonings, both of which had been given ipecac and

both of which had significant amounts of iron remaining in their stomach after being ipecaced, after being lavaged. Both children went on to die. It convinced me that I would rather have spent that time getting the child to the hospital and doing more aggressive things such as whole bowel irrigation, for example, which I will admit the efficacy has not been proven as well, but I would rather do more vigorous methods of trying to move that iron through the GI tract and begin the treatment process than to administer the ipecac at home.

DR. CLAPP: How about lavage in that circumstance? You say it didn't help.

DR. MANOGUERRA: None of us use lavage tubes large enough to remove iron tablets from a child's stomach.

DR. CLAPP: Thank you.

DR. CANTILENA: Dr. Johnson?

DR. JOHNSON: I'm just curious about what it was in 1990 that caused you to basically change your protocols that included ipecac and remove those.

DR. MANOGUERRA: The medical director and I sat down and we said to ourselves it really looks like ipecac does not seem to be providing us with any benefit. Why don't we stop using it for a while and see what happens? And so that's what we did. We stopped using it and we've never reinstated it back in again. It was just a matter of

us sitting down and looking at some of the outcomes that we had observed and making that decision.

DR. JOHNSON: And was that a fairly controversial move at that point in time?

DR. MANOGUERRA: In 1990, I would say it was very controversial. I think if we did it today, it would not generate as much controversy.

The staff were very resistant to it because the use of ipecac -- it's just intuitive. Someone ingests something. You give them something to make them vomit it back up again. It's got to be working. That was the general feeling that everyone had. And the data was starting to come out, some of those early studies were starting to come out questioning the effectiveness. So we just decided not to use it anymore at that point.

DR. CANTILENA: Yes, we have a follow-up from Dr. Clapp and then from Dr. Tong.

DR. CLAPP: Have there been studies done about accessibility? Because that's my greatest concern with the ipecac perspective, is those who live in remote or rural areas. You say you have it represented in your patient population in San Diego. What's your level of confidence that those who absolutely don't have emergency medical services available within an hour's drive or have absolutely no accessibility by car, who have clinics set up

on a revolving basis in rural places in the United States? I'm very concerned about that population and their accessibility to health care after having an ingestion.

DR. MANOGUERRA: Well, I don't know if we're unique compared to the rest of the country, but even in the rural areas, we have very good ambulance and emergency medical services that can get to patients usually within 30 minutes to an hour, even in the very remote areas. There are volunteer ambulance services where there aren't paid ambulance services. So that has not been an issue for us even along the Colorado River area where it could be a 3-hour drive to a hospital. We're able to get paramedics to them usually within 30 to 45 minutes. And if they need transport right away, we can get a helicopter to them very quickly as well.

DR. CANTILENA: Dr. Tong, then Dr. Blewitt.

DR. TONG: Dr. Manoguerra, Ms. Solbeck described the statement, the gastrointestinal decontamination statement, that the Academy of Clinical Toxicology and the European poison centers had approved, and that was in 1997. It did not say that ipecac could not be used or should not be used in the home. Did it not actually say ipecac is a more practical agent if home decontamination was to be administered?

DR. MANOGUERRA: I don't remember the exact

wording, but I believe it said that there was no evidence for or against the effectiveness of ipecac on patient outcome is I believe exactly what it said.

DR. TONG: The question was impact on outcome, although everything that you did say about its efficacy, safety, adverse reactions were in the statement. I just was curious because it did not say not to use, but it was just pointing out what you point out.

DR. MANOGUERRA: I think Dr. Tenenbein, when he gives his presentation, may be a better person to ask because he was involved in the development of that statement.

DR. TONG: Thank you.

DR. CANTILENA: Dr. Blewitt, then Dr. Wood.

DR. BLEWITT: Yes. Thank you for that very detailed presentation. I appreciate it.

I had three questions, the first of which is related to the 25 to 30 percent removal based on the clinical pharmacologies that were performed. Your quarter-full statement.

DR. MANOGUERRA: Right.

DR. BLEWITT: And that is that I wondered how you derived that statement because I looked in the package at a number of clinical pharmacology studies which showed varying results, some of which were very good. I agree

there was a fair amount of variability even within the studies. But I also felt that a lot was related to study design, as well as the substrate that was used. I was wondering whether using the 25 to 30 percent figure wasn't putting a lot of apples and oranges together to come up with that number.

DR. MANOGUERRA: Each of the studies did look at a different substance. Most of them were volunteer studies, and the ranges varied between 0 percent recovery and 80 percent recovery, if you look at the individual volunteer recoveries. If you look at it overall and you put all of the studies together, you come out with a figure that's in that 25 to 30 percent range. Now, whether that's apples and oranges or a fruit basket, it's just the way you want to look at it, and that's the way I looked at it.

DR. BLEWITT: Is that a mean or is it a median?

DR. MANOGUERRA: I don't think any of the studies on average showed more than about 40 percent recovery.

DR. BLEWITT: I'd have to go back, but I thought some were much more.

DR. MANOGUERRA: I don't believe there were any that were more than about 40 percent, and many of them were less than that.

DR. BLEWITT: My second question concerned the

rural environment and whether the emphasis on the rural environment isn't to the exclusion of other situations that could even happen in an urban environment or suburban environment where there would be inadequate access or the inability to access emergency care, if there's a snowstorm or if you're in New York City at rush hour and can't get a cab at that time, and whether it isn't more broad-based than simply the rural areas.

DR. MANOGUERRA: That may be the case. I think the issue is whether you believe the benefit that you're going to get from administering it outweighs the risk. I've given you my opinion and you'll get other opinions this morning as well.

DR. BLEWITT: Okay, sure.

Then the final point was that in your slide on alternatives you mentioned restricting ipecac to prescription. You mentioned that it would decrease the availability for abuse or misuse, but it would also reduce the availability for use within 30 minutes of ingestion.

DR. MANOGUERRA: Yes.

DR. BLEWITT: So aside from other issues, even making it a prescription product on that basis would create some difficulties.

DR. MANOGUERRA: Yes, it would. If you believe that it should be given within 30 minutes, it would reduce

the availability in those situations.

DR. BLEWITT: And then the question becomes, if that's the case, is the real issue whether the ingredient should be available at all in the marketplace. Does it not take you there?

DR. MANOGUERRA: I wasn't ready to take it that far, but if you want my opinion, I think we could get along very well without it.

DR. BLEWITT: Don't you believe that there are situations where in certain instances the ability to have it in the home could potentially save a life?

DR. MANOGUERRA: I personally don't believe that that's the case. But it occurred to me when you were mentioning what I had on my slide, putting it on prescription would not necessarily decrease the availability in that first 30 minutes because if somebody doesn't have it, whether they bought it over the counter or got it by prescription, they're still not going to have it in 30 minutes. So limiting it to prescription does not change whether it's available in 30 minutes. A physician could prescribe it for them and give it to them so that they have it in that 30-minute time period.

DR. BLEWITT: It potentially limits whether people are going to go through the trouble of having it in their house if they have to go through a physician to have

it. But that raises a different issue.

DR. MANOGUERRA: Right. There was a paper just recently published that looked at if a patient didn't have it in the home and were sent to a pharmacy to get it, how long it took them to get to the pharmacy, administer it to the child, and then for vomiting to take place. The conclusion of that paper was it's not worth the time to send them to the pharmacy.

DR. BLEWITT: It's too long.

DR. MANOGUERRA: It's too long. Right. But that was a procedure that poison centers did for a number of years, and I think something that most of them have now abandoned.

DR. BLEWITT: Thank you.

DR. CANTILENA: Thank you.

Dr. Wood, and then Dr. Lam.

DR. WOOD: I guess this question probably should be addressed to the FDA. What data do we have on the sales of ipecac and the trend line of the sales?

DR. CANTILENA: I think they're looking for that now, Dr. Wood.

DR. ROSEBRAUGH: We're all looking at each other, but I think we have something here for you.

DR. CANTILENA: How about if we come back to that? Perhaps we can have Dr. Lam, and then we'll come

back to Dr. Wood.

DR. LAM: In the study that you reviewed from the literature, in terms of a certain amount of the ingestion being vomited by the patients and the general feeling that ipecac is not very efficacious, is there any data on the time frame of presentation to the emergency room? Is it more than 30 minutes, more than an hour, and more than 2 hours? Because the longer it takes for the patient to go to the emergency rooms, obviously the lower will be the efficacy. And if a patient intentionally overdosed, why would he or she want to get to the emergency room earlier?

DR. MANOGUERRA: A couple of issues there. First of all, the emergency room studies were not -- the percent recovery were not done in patients in emergency rooms. The outcome studies were done in emergency room patients. The percent recovery studies were done in volunteers in a controlled experimental environment where they were given a marker substance and then the ipecac was given at a time interval after the substance was administered. In those studies it showed that beyond 30 minutes, the amount that was recovered was about equivalent to control patients that were not given ipecac at all. That is kind of an unusual way to say it.

They weren't measuring the amount vomited back

up. They were measuring the blood levels achieved when they were given the marker substance. So the blood levels achieved in patients in the control groups, if ipecac was given more than 30 minutes after ingestion, those blood levels were similar. Is that clear?

DR. LAM: And I would assume that there's no pediatric data in terms of the recovery?

DR. MANOGUERRA: No. It's all adult volunteer data.

DR. CANTILENA: Dr. Wood, are there other issues that you want to -- there aren't. Usually we have a sponsor here and they usually have that information at their fingertips.

DR. WOOD: There is a response from industry. Are they here?

DR. CANTILENA: That's going to be handled at the open public.

Dr. Tong, did you want to ask one more?

DR. TONG: I don't have an answer to Dr. Wood's question, but I'm a pharmacist and I've been in poison centers for 30 years. I've given out cases of ipecac but have never sold one. So I'm not sure sales really is an indication of what's out there because I'm imagining some of the ipecac that I gave out are now second generation children that are still in the medicine cabinets of homes.

So I'm not sure what sales might specifically reflect.

DR. WOOD: Well, I don't agree actually. I think it's critical to know that because if you look at the slide that was shown on the use of ipecac by U.S. poison centers, if we find the sales are increasing and at a time when the slide on page 2 of the talk shows that the decrease from 14,000 down to virtually 0, then I think that speaks volumes to where that ipecac is going. It's going to abuse. So that is a critical piece of data to have and I think we need that.

DR. CANTILENA: Dr. Rosebraugh, are we going to have that information soon, or should we --

DR. ROSEBRAUGH: We can't release exact numbers, but what we can say is over about the last 4 years unit dosages have decreased by about half.

DR. CANTILENA: All right.

I think actually what we'll do, because of the schedule, is why don't we take our break now and resume in 15 minutes with our next speaker.

(Recess.)

DR. CANTILENA: If the committee can take their seats please, we'll get back to the program.

Dr. Rosebraugh will introduce our next speaker.

DR. ROSEBRAUGH: Our next speaker will be Dr. Milton Tenenbein. Dr. Tenenbein is Professor of Pediatrics

and Pharmacology at the University of Manitoba. He is the Director of Emergency Services for the Children's Hospital in Winnipeg and Director of the Manitoba Poison Control Center. Both positions he has held since the late 1970s.

He received his undergraduate and graduate education, including pediatric residency, all at the University of Manitoba.

He has been the former chair of the section of Pediatrics with the Canadian Association of Emergency Physicians, is on multiple pediatric and emergency medicine editorial boards and is widely published on the field of emergency medicine and poison control. He has received numerous awards, including the American Association of Poison Control Center's Micromedex Award in 1991 for outstanding research in the field of toxicology. Dr. Tenenbein is currently the immediate past President of the American Academy of Clinical Toxicology.

DR. TENENBEIN: Well, thank you very much, indeed, for that kind introduction.

First, I would like to apologize to the chair and the committee and the audience for my late arrival. There was an unfortunate problem with my hotel reservation, and as someone just commented to me, my life is now complete because I know that there is a place called Gaithersburg.

(Laughter.)

DR. TENENBEIN: I wouldn't call it a rural setting, apropos of some of the discussion that I heard as I entered the room regarding Dr. Manoguerra's presentation. But I found the comment about getting a taxi in Manhattan from one of the panel quite interesting, having visited there many times because my brother lives there. You can't get a taxi in suburban Gaithersburg.

(Laughter.)

DR. TENENBEIN: It took a half an hour for it come, and then it was a handicap, wheelchair access vehicle. And he found out where I wanted to go, and he refused to take me because he had to be somewhere in a half an hour to transport someone in a wheelchair.

So much of my trial and tribulations. I'm sure you're probably bored by them by now. So it's time to start my presentation.

I've entitled it Syrup of Ipecac, OTC or not OTC? Because this is this committee's concern. So that is the question I guess. If I try to go to the bard and say whether 'tis nobler in mind to suffer the slings and arrows of home ipecac, or by opposing them, end them, it might be a way to go about it, but I don't think my English lit teacher would appreciate that.

My objectives then are to discuss the need for

OTC status of syrup of ipecac, which is this committee's charge and specifically to discuss four specific questions that were posed to me by the committee. These questions were: what is the role of gut decontamination?

What is the role of ipecac in gut decontamination? And question two had three subquestions to it. 2a, what are the benefits and risks of ipecac? What is the literature assessment of these benefits and risks? And what about remote populations?

Question 3 is what is the abuse potential of syrup of ipecac. I'll just touch on that in passing because I know there's another speaker who will be dealing with that in detail.

And what are the alternatives to ipecac?

I think it is best to start with the burden of disease for the population under discussion, which is children under the age of 6. The most recent data available is the American Association of Poison Control Center's annual report of 2001 in which they reported 1.2 times 10 to the 6th -- that's 1.2 million -- exposures in children under the age of 6. This is a reasonably steady figure that this organization reports annually. Note the term "exposures" because immediately there's this perception that these are poisonings. These are not poisonings. These are exposures. They're potential

exposures. These are telephone calls to poison control centers.

Poisoning death is unusual under the age of 6. There were 500 per annum in the 1940s, which is the chief impetus for the formation of poison control centers in the 1950s. There were 25 or so in 1997, and annually there are less than 25 per year. That's been the experience for the last decade or two. So we're not dealing with a major disease. In fact, most of these phone calls to poison control centers involved exposures to subtoxic doses.

But, nevertheless, with this fall-off of 500 to 25, poison prevention is a success story. I'd like to review the reasons for the success because it's important. Why has it gone down from 500 to 25? Could ipecac be responsible for that?

Well, certainly one of the most important reasons is child-resistant closures on the medications and consumer products. There are all sorts of data to support this intervention as effective published over the last 20 years or so.

Constituent reformulations. Both industries, the pharmaceutical and the consumer product industry, have an impetus to remove poisonous substances from their products for obvious reasons, if only for risk management other than altruistic reasons.

Anticipatory guidance which we as pediatricians and family practitioners are charged to do, and of course most of us do do during well-patient visits.

Public education. Certainly an activity of poison control centers, public health nurses and other agencies with the mandate to provide public education.

Legislation. There is some very important legislation that, over the last 30 years or so, has resulted in decreased toxicity of pharmaceuticals and consumer products, not just the requirement for child-resistant closures, but limiting the amount of acetaminophen in children's products and also of aspirin in children's products are good examples of legislation.

Poison control centers certainly have contributed to this decrease in morbidity and mortality.

Product formulation and poison treatment databases. When we started in poison control -- when I say "we," just all of the speakers and some of the panelists -- we recall the pre-Micromedex POISINDEX days where our information databases were not databases. It was just a patchwork quilt of information on 5 by 7 recipe-size cards in file drawers. The database, which is now a standard internationally, has certainly resulted in improvements in care to poison patients.

Sophisticated medical treatment resources.

When I began my career in pediatrics, there were no per se pediatric emergency departments or pediatric intensive care units. So the ability to deliver specialized care to the very sick poisoned children certainly has improved over the past three decades.

New antidotes have contributed to the decreased morbidity and mortality, but only to a minor degree.

And finally, safer medications. Dr. Manoguerra made that comment in one of the answers to the question regarding, over the years, have the medications stayed the same. No, they're safer. Indeed, I'll give a few examples. One of the major problems for morbidity and mortality in the '40s and '50s were non-barbiturates sedative hypnotics. That was replaced by the benzodiazepine family in the late '60s and early '70s, and it's virtually impossible to die after an overdose of an oral benzodiazepine. Aspirin was a serious problem in children in the '50s and '60s. With the advent of acetaminophen, that solved that particular problem. Other medications that have come and gone include theophylline. Tricyclic antidepressants are certainly on the wane because of SSRI medications.

So in summary, the two most important reasons for decreased morbidity and mortality in young children from poisoning are child-resistant closures and safer

medications. This indeed is responsible for the decreased morbidity and mortality.

It's also important to know that morbidity and mortality figures in other countries in the western world, be it Canada, the United Kingdom, or Western Europe, for poisoning of small children are really no different than the USA, and this is the only country in the world that has ipecac in the home.

Poison treatment then. Gastrointestinal decontamination is a cardinal principle in the management of the overdose patient. It has been for decades and decades, actually for generations and generations. The traditional hospital management has been a so-called gastric emptying procedure. I actually have a lot of difficulty with this term. I never use it except in presentations such as this because it's giving more credit to this procedure than it is due because it does not empty the stomach. One of the questions that Dr. Manoguerra received began with the term "gastric emptying." Studies have very clearly shown that whether you're doing a gastric lavage or a syrup of ipecac-induced emesis, immediately after the ingestion in adults -- and there are pediatric data available actually, young children, pediatric data available -- that they do not empty the stomach. Indeed, the 25 to 30 percent that was quoted is the best that we

can expect according to pediatric data.

Having said that, the traditional hospital management consisted of either syrup of ipecac-induced emesis or gastric lavage, followed by a toxin adsorption procedure, which was typically activated charcoal plus or minus the administration of a cathartic. Research over the past two decades or so has changed this.

I should say, though, that poison treatment in the home -- ipecac became an obvious intervention. It became an intuitive intervention, not based on any research. In the 1960s, it was thought to be a good idea and it was promoted. Indeed, as everyone in this room knows from the material that was circulated, ipecac was granted OTC status by the FDA in 1965. Indeed, of course, that was controversial at that time. It's become a standard. Now the shoe is on the other foot. It's controversial to relinquish that status.

Ipecac in the home became a policy of the American Academy of Pediatrics earlier than was stated here, but that's the last reaffirmation that I could find in their literature. It's a mainstay of their anticipatory guidance and poison prevention. TIPP is the injury prevention program which is offered to all pediatricians in the USA, and ipecac in the home is promoted in that. It's promoted in other injury prevention publications of the

academy and in poison prevention brochures of the academy and other agencies. It's also an official policy of the American Association of Poison Control Centers.

Support for ipecac in the home, though, is under review, I think as this committee knows. Both the American Academy of Pediatrics and the American Association of Poison Control Centers are reviewing this policy, and it's anticipated by me and by many others that these two groups will rescind this recommendation in the near future.

Now, how did this all change? The hospital treatment. How did that change where the so-called gastric emptying procedures, ipecac-induced emesis and gastric lavage, are no longer recommended? The research, as I said a moment ago, has really been going on since the early 1980s addressing the treatment of poisonings in the emergency department. This culminated in a consensus statement which was published in 1997, as Dr. Tong mentioned. There were five papers and this was a consensus of the American Academy of Clinical Toxicology and the European Association of Poison Centers and Clinical Toxicologists.

I should give the following advice, that I was one of the panel of these papers. So if people disagree with it, they may indeed feel that I'm not exactly being objective about this.

These five position papers were on ipecac, gastric lavage, charcoal, cathartics, and whole bowel irrigation. Taken together, these five position papers retired ipecac, lavage, and cathartics from the armamentarium of treatment of poisoning in the emergency department, and it advocated charcoal as first-line therapy. The importance of all of this is it certainly set the stage for the discussion of ipecac in the home.

Having said all this, all of the material that was reviewed in these five position papers are not relevant to treatment in the home because treatment in the home, at least in theory, can begin immediately after the ingestion. Treatment in the hospital in practice begins considerably later. The mean time for arrival of a young child to an emergency department after an ingestion is approximately 1 hour. The mean time for arrival of a teenager or an adult is anywhere between 2-and-a-half and 4 hours, depending on which study you look at.

Indeed, the AACT/EAPCCT position papers deal with the treatment of poisonings within the first hour for the effectiveness of GI decontamination. They make the point that beyond 1 hour, that GI decontamination is probably not effective.

The specific paper dealing with ipecac of these five -- and I quote -- "its routine administration in the

emergency department should be abandoned." There was no definitive statement on ipecac in the home, and I can tell the committee and the audience that was done on purpose. It was difficult enough to get consensus for the emergency department treatment in one document. Therefore, we chose the politically expedient path of not dealing with ipecac in the home in this statement.

Nevertheless, this statement generated considerable thought, discussion, and debate regarding ipecac in the home for obvious reasons. If we're saying it doesn't work in the hospital, it's a reasonable question to ask, does it work in the home?

This thought, discussion, and the debate is not new. In 1981, Dershowitz wrote, "The ipecac story is but another example of a seemingly sensible preventive health strategy being universally recommended and widely accepted before its efficacy and validity has been established." It's efficacy and validity has never been established. So we're dealing with a treatment that intuitively seems sensible, for which there's no data to support its use, and essentially treating, in many cases, a non-disease because most of these children do not have a toxic amount on board.

What can we say about the efficacy? There are no data that support benefit for the patient from ipecac in the home. I recognize quite well, as do most people in

this room, that a lack of evidence doesn't mean that there is no evidence.

There are data that support lack of benefit for the patient treated with ipecac in the hospital. I got the feeling that Dr. Manoguerra reviewed those clinical studies. Unfortunately, I was not present for that review. But again, as I said a few moments ago, those clinical data in emergency departments are not relevant to this discussion.

But what can we say about ipecac performance? There are, indeed, data available in young children under the age of 5. This is the study that was done in the 1960s which was a very interesting study. The mean amount removed from these children, after ipecac-induced emesis, was 28 percent. The range was 0 to 78 percent. This was a small group of children, 13 done in a hospital in Texas.

The way that this was done was very interesting. These were children who had all ingested aspirin and were in the emergency department because of an overdose of aspirin. Immediately before giving the ipecac, they were given a measured dose of milk of magnesia. All of the emesis was collected from these children, and the amount of magnesium was quantified in the emesis. So what we have is essentially the model of treatment in the home. So these data are very relevant. Obviously, the

limitation to these data is the small sample size.

Other data that I could present are data that I published specifically relevant to iron, and that came up in the previous question period. Iron is a unique poison because it shows up by x-ray. I've published several cases of children who have ingested iron. When they presented to the emergency department, we took an x-ray, counted the iron pills in the stomach, then gave the patient ipecac, counted the iron pills after they finished vomiting, and the same number of pills were still there.

We went farther than that. We then did gastric lavage in these patients and have x-rays to show the same number of pills are still there. None of these pills were stuck or adhering to the gastric mucosa. Some people might wonder. Nor were there any bezoars or concretions.

Finally, we went on to whole bowel irrigation for these patients.

Again, more evidence that ipecac does not empty the stomach. What ipecac actually does is it brings up mostly the supernatant, the liquid where the solid material stays in the stomach. This has been shown by radionucleotide scan studies in humans, and there's all kinds of animal research that, of course, you have to take with a grain of salt, dogs given barium and x-rayed before and after ipecac. Clearly ipecac does not empty the

stomach. This is where this 25 to 30 percent figure comes from.

So in this study, there's obviously a poor and unreliable performance. In adults, the human volunteer studies -- and we've contributed several of these to the literature, as have many other people, including several people in this room. At 5 minutes, there's anywhere from 51 to 83 percent removal in adults. In 30 minutes, anywhere from 2 to 59 percent removal.

Again, there was a question about apples and oranges, but I think that's very important actually because you want to look at a wide breadth of different substances to get a better feeling. In other words, you want to have, as Tony mentioned, a fruit basket to look at all of these different substances to get a general feeling for performance, not just for one test marker substance such as acetaminophen or aspirin, but for many. So we have this variability and unreliability.

What are the adverse effects? Well, it's an understatement to say that emesis is unpleasant. All of us have experienced emesis I'm sure, and it's no fun. If taken in the context that it's therapeutically beneficial to a young child, then we can justify this particular adverse effect, but if there is no benefit to the child, then the commonly used epithet "can't hurt/might help"

should be viewed in a different context.

Persistent vomiting -- and that's defined as emesis longer than 2 hours -- has been shown to occur in 13 to 17 percent of subjects.

Diarrhea in 8 to 13 percent of subjects.

Lethargy in 12 to 21 percent of patients receiving ipecac. This is important because one of the things we do as clinicians to monitor patients is their level of consciousness. So if we're in a situation where a patient's level of consciousness is decreasing, it might be confounded by our intervention, the ipecac. In other words, it might be iatrogenic rather than as a complication of the poisoning. So it complicates, in that context, the management after the ingestion.

Then there's an inability to tolerate subsequent therapies such as activated charcoal which there is consensus now that activated charcoal is more effective than ipecac, and we wouldn't want to delay the administration of activated charcoal. N-acetylcysteine in this country is -- the only FDA-approved route of administration is orally. And whole bowel irrigation is important for a very small, limited number of poisonings, with iron being the most important one.

A word about iron. Another intervention that has really decreased the morbidity and mortality from iron

is, again, a simple, primary prevention intervention and that's with iron now mandated in the United States to be available in blister packs. The data collected by the American Association of Poison Control Centers has shown a rapid falloff in iron poisoning deaths in young children.

What about inappropriate use? It's frequently used when not indicated in two contexts, by lay persons who do not follow the directions on the bottle, do not use unless consulting with a poison control center or a physician, but also there are data in the poison control literature where poison information specialists or physicians, upon finding out that there is ipecac in the home, decided, well, you might as well use it because it can't hurt, it might help. Again, if it wasn't in the home, it wouldn't have been used kind of a thing. So those are the two types of inappropriate use. I should say the two types of frequently used when not indicated.

It's occasionally used when contraindicated such as a caustic ingestion or what have you. The literature to support this is very sparse. It's anecdotal. It's case report. But indeed, these types of scenarios need to be considered if we're questioning the role of ipecac in the home to begin with.

What about misuse? Again, you'll be hearing a lot more about bulimia and eating disorders. That's well

documented. There's really no argument about that, that it occurs and that this is not rare. Unless the presenter has some specific data regarding either incidence or prevalence data, I certainly don't have those data. So I'm not aware of being able to quantify that, and I think it would be unlikely that we could quantify that.

And very rarely there are reports in the literature of Munchausen syndrome by proxy, which I think you all are aware that's the caregiver, typically the mother administering ipecac to the child and then taking the child to the hospital saying there's persistent vomiting to get attention and care for the family unit. This, I'm sure, is quite uncommon. I've actually reviewed that literature and found several case reports.

What can we say about the use of ipecac? These data on this graph are the figures published in the annual reports of the American Association of Poison Control Centers, and they are the percentage of phone calls for which they've recommended ipecac. The data were first published in 1985 and the last available report is 2001. I think this graph speaks for itself. Our experts are no longer recommending it. In the first year, they were recommending it for 15 percent of all poisonings, and in 2001 -- you can see every year it has gone down -- .7 percent. So quite clearly, this is becoming a therapy of

the past.

I can't help but wonder the few times that it is being recommended -- and I know this will translate to 15,000-25,000 cases, which seem like a lot, but in the context of 1.2 million cases, it's just a drop in the bucket or in the ocean perhaps.

Another purported benefit of ipecac in the home is that if you use it in the home, you'll prevent a visit to the emergency department. In other words, you do the entire treatment in the home. That will prevent a visit to the hospital, the time, the expense, the anxiety, the stress, and what have you. This is often cited as an advantage of ipecac in the home. It is indeed an assumed benefit that there would be decreased hospital visits.

There are data which are soon to be published. These data are in press so I can't give you the specifics of these data. They will be published in the Journal of Pediatrics within the next few months. The conclusion from this study, which is a study of the American Association of Poison Control Center's database, looking at several hospitals and poison control centers across the United States, that home use of ipecac was very weakly associated with increased, not decreased, referral to the emergency department. Now, this increase in referral was not statistically significant, so it would be fair to say that

there was no effect in decreasing emergency department visits. So like many other things in medicine, when a purported benefit is finally studied, it's found not to be true.

The author of the study was Randy Bond, who's in Cincinnati, who is a medical toxicologist and a pediatric emergency medicine physician.

So what are the alternatives to ipecac in the home. The obvious one that comes to mind is charcoal in the home. The shortcomings of charcoal in the home is that it is poorly accepted by young children. In the emergency department for children under the age of 5, almost always it's administered by nasogastric tube. I've had 27 years of experience of treating these children myself in emergency departments, and I've never been able to give -- and that's completely never -- the full oral dose of charcoal to a child. I've been confronted on many occasions by a nurse who said, let me try, I can do it, and he or she has failed on each occasion. When I make this comment during presentations, I will always get some comment from the audience saying that they've done it, they can do it. I remain to be convinced on that point.

The other issue is that ipecac sediments during storage over long periods of time, and we can anticipate that the storage in a home would be much longer than an

emergency department. Having said that, when I give ipecac in my emergency department, the nurse knows that she'll receive the wrath of Tenenbein if I don't see her shaking that bottle before she gives it. It can take on the consistency of a briquette suitable for use in your barbecue.

It's messy. What about caretaker acceptance or other issues? These are issues that I speculate about. Having said that, there is published experience. Tony referred to some of it I believe; at least, it seemed that he did in the answer to one of his questions. But there are three full articles and three other abstracts that haven't been published as articles in the literature. The therapeutic dose was not given in greater than 50 percent of the children. The mothers couldn't get the charcoal into the child. I should say if we have trouble with an experienced emergency nurse, who is cool, calm, and collected, who's tried to do it in an emergency department and can't -- we have to give it by the tube -- in a crisis situation, a mother with the perception that if I don't get this antidote into my baby, he'll die, this poor performance is not unexpected.

Tony did refer to a study done in Massachusetts, which was one of these abstracts that never saw the light of day as an article, quite a long time ago.

I call it the SWAT team study. If the travel time from the poison control center to the home was short enough, an experienced nurse went to the home, taught the mother how to give the charcoal, gave the charcoal to the mother, and she administered to the child, and the mother was not able to get the therapeutic dose into the child.

The other point is that when they looked at the home versus ED administration of charcoal, they were able to get the charcoal into the -- it took 35 minutes from the time of ingestion to get the charcoal into the child. And the most critical time is the first 30 minutes. In the hospital they can do it in 65 minutes. So the question that has to be asked but, of course, we can't answer is, is there a clinically important significance to the patient for this extra 30 minutes of delay when the rapid falloff has already occurred from the experimental studies and data that are available to us?

So what can we say of charcoal in the home? This was reviewed in an article in Clinical Pediatric Emergency Medicine in the year 2000. They reviewed most of the data that I've described. Some of the data that I've described was published since that time. And the conclusion of that review is that it's premature to recommend this intervention.

So what are my conclusions then? My

conclusions are, in fact, to discontinue ipecac in the home, as has been done in several areas, as we've heard earlier, and that it's premature to use charcoal in the home. We're in the same situation with charcoal where we were when Dershowitz made that 1981 quote that this is a seemingly sensible intervention, but the efficacy and adverse effects are far from characterized.

So now I'd like to try to answer the four questions that were posed to me. Question 1, what is the role of gut decontamination in general? It's very limited and it's really confined to the first hour after ingestion for there to be any benefit. Serious poisonings then presenting to the hospital within 1 hour would be the role of gut decontamination.

Question 2, what is the role of ipecac in gut decontamination? In my view it has no role in any environment.

The subquestions of question 2, 2a, what are the benefits and risks of ipecac? The speculated benefit is removal of the poison, but as I hope I've shown you from the data available to us, it does not remove the poison. It at best removes 25 to 30 percent of the poison if given immediately afterwards. I guess I could say if a child has ingested two times the lethal dose of a poison, taking out 25 percent will not benefit that child. Surely everybody

in the room can come up with a hypothetical situation of a child on the bubble, so to speak. The problem is that we cannot define these children. The histories are inaccurate in all cases, and how wide or narrow that bubble is is open to speculation as to whether we would save a life. That would mean that we would have to have someone who perhaps has taken barely one lethal dose, and if we reduce that by 25 percent, the patient would still be pretty sick, perhaps requiring intensive care in a tertiary care institution. We have so few of those. As I said, there are less than 25 deaths per year in this country, and most of those deaths are deaths discovered long after the event when ipecac would not have meant a difference anyway.

The risks I've already characterized. We've quantified the vomiting, diarrhea, and lethargy. We cannot quantify the poor tolerance of subsequent oral therapies and the inappropriate use and frank misuse.

2b, what's the literature assessment of the benefits and risks? There's no literature at all demonstrating benefit, as I've said earlier, and as I've just said, we've quantified the adverse effects. All the other effects are just anecdotal reports in the literature.

Question 2c, what about remote populations? Again, I don't like to use the word "rural" either. Perhaps the best term is "access to care." In my practice

situation in my catchment area, I manage the care of children in remote Indian villages. We call them reserves. You call them reservations. They are 700, 800, 900 miles away, and the only access to them is by airplane. We don't use helicopters because they're inefficient. We use jets, air ambulance jets. We don't keep ipecac in those locations. There are nurses there. We just don't feel that it's useful at all.

The point being again, it's counterintuitive to say that ipecac doesn't work, but quite frankly, it doesn't. So whether you're next door to a hospital or you're 3 hours away from the hospital, for whatever reason, traffic jams in Manhattan or in a place where there's only access by an airplane, it's not going to work there either. So to me this whole argument is a non-argument. Efficacy does not improve with distance from care is my point that I wish to make regarding question 2c.

Question 3 is, what is the abuse potential of syrup of ipecac? Again, we're going to hear a lot more from a person more expert than I. There certainly is occasional use for eating disorders in people with bulimia, and there's rare abuse of ipecac in a Munchausen syndrome by proxy scenario.

And finally, question 4, what are the alternatives to ipecac? In the hospital, it's activated

charcoal. At home it's to call the poison control center for care.

So my summary and conclusion is since the use of ipecac in the home will no longer be recommended and since there is a potential for its misuse and abuse, it makes no sense for it to remain as an over-the-counter drug.

Thank you for your kind attention.

DR. CANTILENA: Thank you, Dr. Tenenbein, for an outstanding presentation.

I would like to just start with one clarifying question and then open it up to the committee. The study that you quoted, your study with iron where you used the radiologic endpoints to examine the efficacy of ipecac -- how long after ingestion did you administer the ipecac, and were there any other endpoints in that study in terms of amount of iron absorbed, et cetera or clinical outcomes?

DR. TENENBEIN: Well, the time after the ingestion of iron is not important because the iron we documented, objectively documented, as being present in the stomach. So the goal of ipecac is to remove the iron from the stomach. So the time since ingestion in this particular situation is not relevant, with respect.

The reason why you want to give the ipecac in the home is to get it out of the stomach. As long as you

know that the stuff is still in the stomach and you're administering the ipecac, that's the desired endpoint. It's not a surrogate endpoint.

The second question is were drug levels done. All of these patients that we described had a series of gastrointestinal decontamination procedures done because several of them had lethal amounts of iron on board. So we did other interventions following it, the gastric lavage, as I've indicated, which incidentally we also showed to be not effective. And then we did a procedure called whole bowel irrigation. Actually that was the thrust of the study. It was the original study to demonstrate that whole bowel irrigation had a potential role in iron poisoning. Indeed, we followed the serum iron levels in that scenario, and of course, they didn't go up because we got the poison out of the gut. That was the thrust of the study. The study was not to specifically to study the efficacy of ipecac, but the study of the efficacy of whole bowel irrigation.

DR. CANTILENA: Right. But I guess you would that as you increase the time from ingestion of any tablet, including iron, the probability of efficacy from ipecac would go down? Are we in agreement on that point?

DR. TENENBEIN: Not necessarily. If you're in a situation that you can demonstrate that the iron is in

the stomach, the role of ipecac is to get it out of the stomach. So that's independent of time.

DR. CANTILENA: Right. But other studies have shown that if you wait more than 30 minutes or 60 minutes, the chance of success from ipecac is extremely low as opposed to giving it like if you're in the home, Johnny gets into mom's iron, and you give the ipecac within 5 or 10 minutes. The prior probability of success would be decreased. So that in your study if it had been an hour or more since the iron was ingested, you would not expect the ipecac to really work anyway. Is it true?

DR. TENENBEIN: No. No, I wouldn't agree with that at all actually. Again, I'll go back to the point. The role of ipecac, the goal of ipecac is to get the poison out of the stomach. All you need to be confident of is the poison is in the stomach, and then you can test whether the ipecac is working.

I think it's important to separate -- we were talking about apples and oranges and fruit baskets earlier. The data that showed ipecac loses its effectiveness after a half an hour are not based on iron. They're based on acetaminophen. Acetaminophen is specifically designed to have a rapid dissolution. Iron is not designed to have a rapid dissolution. So the tablets dissolve. They pass from the stomach into the intestine much quicker. Indeed,

what we're really showing here is that there's a different dissolution rate.

But I think we're kind of getting mired down between these two specific poisonings. But I think the important point of my x-ray data is to show that if a poison is in the stomach in a tablet form, ipecac is not that effective. So I would generalize that to say if acetaminophen is present in the patient's stomach 5 minutes after ingestion and you give the ipecac then, it's reasonable for me to conclude, I believe, that it would be relatively ineffective getting those tablets out as well.

DR. CANTILENA: I understand your point. I guess what I'm trying to sort of get at is the fact that iron is a known substance for concretions. Unless you really have endoscopy, you're not really sure what's actually there. You can see the shape of tablets, if you will, in a concretion unless they're spread out throughout the gastric pouch.

DR. TENENBEIN: Indeed, we demonstrated a lack of concretions by x-raying these patients in three different planes and changing the orientation of the tablets to each other. We clearly demonstrated that concretions were not present.

DR. CANTILENA: Okay.

Questions from the committee? Dr. Wood?

DR. WOOD: I'd like to change the conversation a little bit about the way we're thinking about this. The putative indication for ipecac is to improve the outcome in poisoning, and the evidence that it does that is nonexistent. So it doesn't improve the outcome in poisoning.

When we say it like that and you also have to recognize this is by orders of magnitude the most toxic substance available over the counter, and when we talk about it and we show slides of the side effects of ipecac, we should include the fact that 85 percent of the patients who receive this -- maybe 95 percent of the patients who receive this -- had the adverse effect of severe vomiting.

Now, the reason I say it's an adverse effect is the goal is to improve the outcome of poisoning. If it doesn't do that, then the vomiting becomes an adverse effect. So the risk/benefit ratio here is, by any other over-the-counter drug, appalling. We've got a drug for which there's no evidence it works, and uniformly produces severe vomiting.

So I think we need to avoid stepping into the trap of assuming that because its putative mechanism of action is by causing vomiting that we shouldn't count the vomiting as an adverse effect. The therapeutic goal that we're aiming for is improved outcome, not vomiting. If we

fail to achieve the therapeutic goal of improved outcome, then the vomiting becomes an adverse event.

Getting into speculation about where or when or in what circumstances it might work seems to me to beg the question. If somebody has good data that it does work in some specific geographic or therapeutic area, then we ought to see that. In the absence of that, we should assume, as we always do, that that means it doesn't work.

DR. CANTILENA: Other questions from the committee?

So what you're saying, Alastair, is vomiting is an adverse event even though it's the mechanism of action.

DR. WOOD: Let's take acetaminophen, for example. The options in therapy are to give N-acetylcysteine or a syrup of ipecac. N-acetylcysteine, if it produced vomiting in 95 percent of patients, we'd view that as an adverse event. We certainly have excellent data on the efficacy of N-acetylcysteine. We have no data -- at least I'm unimpressed by data of the efficacy of ipecac.

So I think we have to examine that in the same way as we would with any other drug. If someone came in here and said there's a drug that can control arrhythmias by producing vomiting, which is not so outrageous an idea as one might think, we wouldn't accept that the vomiting

shouldn't be counted as an adverse event in its therapy. And that's not as facetious a suggestion as you might think. There's plenty of data to support an increase in vagal activity as a means of controlling some arrhythmias.

DR. TENENBEIN: Indeed. If I am allowed an interruption. You're quite correct. Dr. Robertson will recall that ipecac was a recommended treatment for supraventricular tachycardia in young infants because of its vagal effects. So for those of us pediatricians who go back that far, indeed it was used in that fashion, and the vomiting was -- as questioner says, it's not just speculation. It's indeed true.

DR. WOOD: That was my point actually, yes.

DR. CANTILENA: Any other questions? Dr. Blewitt?

DR. BLEWITT: This isn't a headache or an upset stomach. This is an overdose. In this case, we get caught up in semantics. The adverse effect is the intended effect. So I don't think we should be confused by that.

DR. WOOD: Well, but we need to be careful. This is not a drug which works in deliberate overdose. That's important to remember that. If it were to work at all, the time it would work would be in the immediate post-ingestion period. People who deliberately take drugs to poison themselves usually don't present to receive ipecac

in that immediate period. That is why we've slipped into this discussion about children, because the assumption there is that the child doesn't take it with the self-destructive intent, but ends up with taking it and is observed, and then an intervention can be made.

Now, we know what the mortality is from that situation in this country. Some years ago it was 50 children. So 150,000 children ended up vomiting from ipecac and 50 died from overdoses, and there's no evidence that that number would have been -- we know that number has gone down as the use of ipecac has gone down with it. So I don't think the data supports that.

DR. CANTILENA: Any other questions?

DR. BLEWITT: Well, I'll just make one final point. I still think that the database is lacking in terms of efficacy in the home use situation. And how you're going to accomplish that I don't know because the amount of usage is so low at this point. It would be very difficult to conduct a study that would give you any reasonable endpoints given the limited amount of use at present.

DR. CANTILENA: I think that's really the essence of the questions for this afternoon. We're really looking at a very small segment of the population, and children and settings that we've been talking about. So I think that actually, for me anyway, is really the essence

of the whole argument. There's no question that we should not be using this in the setting of emergency rooms and the like, but it really comes down to those issues that I think everyone has framed. And I look forward to that discussion this afternoon.

Any other questions for the speaker?

(No response.)

DR. CANTILENA: Very good. Well, then thank you very much, Dr. Tenenbein. It was a very enjoyable talk.

Dr. Rosebraugh, who is our next speaker?

DR. ROSEBRAUGH: The final presentation of the day, at least regarding the use of ipecac syrup in poisoning, will be given by Dr. William Robertson. Dr. Robertson is a professor with the Department of Pediatrics at the University of Washington in Seattle and is the Medical Director of the Seattle, Washington Poison Center.

He received his medical degree from the University of Rochester in New York, completed his pediatric residency at Yale University prior to moving to the University of Washington where he has been since 1963.

Over his career at Washington, he has twice served as acting Chairman of the Department of Pediatrics, spent a decade as the Associate Dean of the University of Washington School of Medicine, and was the Chair of the

American Association of Poison Control Centers from 1988 to 1990.

He is also widely published in the area of poison therapy, including authoring the chapter on poisoning in the 18th Edition of the Merck Manual of Diagnosis and Therapy.

Dr. Robertson?

DR. ROBERTSON: Thanks very much, Curt.

With reference to this particular topic, I must begin with a disclaimer that it's been kind of a hobby for almost 50 years, and those 50 years, I couldn't help but think, as Dr. Wood raised an important question, and that is, is emesis itself an adverse reaction? Of course, it is. It's just like the adverse reaction when we used mercurial diuretics. The adverse reaction was it paralyzed the kidneys' ability to absorb water, but we used it therapeutically.

The emesis response had been extensively used, not for the supraventricular tachycardia but for routine treatment of croup. The kid who has croup who vomits, instantaneously after the vomiting, the croup will temporarily disappear. Now, the question is, which do you like least? The vomiting or the croup? And until we found Hemophilus epiglottitis to confuse us on this, we used it routinely.

I'm going to go and show you some slides -- I hope everybody can see them -- and make a couple of points and give you some food for thought. I would say that some of the figures that my predecessors have given, you can look them up and you'll see that the 28 to 30 percent is a selected choice. Many of the choices in those five guidelines that were set up and approved by two groups were a little bit subjectively selected. I'm going to subjectively select some things too. So what's fair in war is fair all the way around.

The second thing is I'd call your attention to the fact that neither the American Association of Poison Centers nor the American Academy of Pediatrics ever endorsed those five guidelines. So we have now reached a stage of maturity in the field of toxicology where we have groups of competing guidelines like everybody else has, and I think we have to be careful about that.

I'd make the point that it wasn't until the late 1700s when chemistry, as we know it today, got started. Only in the 1820s could you measure that iron was there. If you haven't read the book about mauve, you've got to read it because that's the origins of organic chemistry when they took coal tar, spilled some phenol and some other things on it and inadvertently came up with purple dye. That was the start of the dye industry, the

nutritional industry, the pharmaceutical, the plastics, and the petroleum industries, all beginning in the 1860s.

When I began in the poison center business -- and it began roughly 50 years ago -- there were 1.2 million chemical entities known to man and a couple of years ago, the American Chemical Society's register showed it's more than 47 million. Despite all those terrible chemicals that are out there -- and think about this because of its implications for the general public -- notice that the mortality rate from accidental poisoning has gone down. I pride myself with being pretty good on three and maybe four of these 47 million, but it's access to information that we've become more reliant on.

A poisoning episode has several things: a susceptible host, a toxic chemical. And I mention the toxic chemical with quotes around it, and this will come up in a few minutes in another setting for you to think about really the use of the word "toxic." You've got to have a sufficient dose. There's no question that you have to have a sufficient dose. If the dose gets cut to 50 percent of what it was that the child -- and here I'm primarily talking about children -- took, it's going to be less toxic on a probability basis than it would if he had the whole thing. And that's really what we're talking about, is potential probability. You've got to have a route of

exposure, meaningful absorption, and an intact response mechanism.

If you look at some of the things we know, we take for granted. For some of you, I apologize but I think it's important to think about it. The susceptible host. You can alter the susceptibility, for example, to diphtheria toxin, by immunizing the host. For other toxic chemicals, you can precipitate them, and they will change the chemical format and they're not toxic anymore. With sufficient dose, you can ban and outlaw it. PCBs. They're a dead issue. They're gone. They're not being manufactured anymore.

You can limit exposure with supposedly gastrointestinal decontamination. We'll come back to that.

Curtail adsorption, diatomaceous earth or charcoal, or Mount St. Helen's ash -- no, no. Mount St. Helen's ash is the perfect non-adsorptive agent. We thought we had money in the bank out there in Washington and it doesn't work.

And the last one is you can block the response system with various receptors.

Now, one of the things that Dr. Wood also asked -- and this relates a little bit to Milt's talk about using iron. Iron, as far as I'm concerned -- he probably couldn't have picked a worse substance to try and measure

or estimate efficacy of treatment. But he did choose it. I would make the point that a number of chemicals are now being put in slow, not like acetaminophen, but release tablets. And this, for example, Prozac. You don't have to take it three times a day. You can take it once a week. And Aterol and other things for my attention deficit disorder. I don't have to take it three times a day. You don't have to give it in school. You can take it once a day and some of the slow release occurs in the gut. Some of the slow release occurs after it's been absorbed. So there may be a reason for thinking, yes, the urgency of immediate treatment is important, but there may be some instances where other treatments have been used.

There's one adult -- and a number of these testimonials before Medline went into a search -- that was 1966. One adult vomited 210 aspirin tablets. He or she changed their mind after they took too much aspirin. It's possible. It's only anecdotal. I just mention it.

Now, these are the things that people have been talking about, the garden hose lavage. And I use garden hose as a negative term. I would mention people have agreed it's not used anymore, but then they added one other thing, and they use a nasogastric tube. That's a garden hose lavage tube, that after the child arrives in the emergency department, you can't persuade them to drink the

charcoal there either, so you stick a tube down his throat, and then you stick the charcoal in that way. Whether that's an adverse response, the uncomfortableness of that procedure, or not, I'm going to leave up to you.

The other things you've heard a lot of talk about it. The whole bowel lavage. Those who would purge us who led to the evolution of homeopathy 200 years ago are still anxious to purge us periodically.

Now, the question was posed before, what about the drugs, the chemicals that are eaten by kids? And these are the leading exposures of kids for the last 15 years or so. This came out of the 2002 data. Cosmetics, cleaning stuff, analgesic agents, foreign bodies, topicals, goos that you put on, plants, and cough medicines. Virtually nobody wastes their time with any GI decontamination for cosmetics. You don't do it for cleaning stuff because it might be dangerous. You don't do it for foreign bodies because it's not going to help. And you don't do it for the topicals, and nowadays you don't do it for the plants. We don't do it for hoards of things that back in the 1950s we didn't know was it toxic or wasn't it toxic. And those espousing the precautionary principle said, if you can't be sure, try to decontaminate the stomach or make them throw up. That was the mission that the early treatment of use of decontamination -- that was the question that was trying

to be addressed.

Now, let relate a little story about ipecac and me, and it's true. And it's in publication. You can go read it in 1993. I began as an intern in 1949. That may seem like eons ago, and I may appear like Methuselah, but I wasn't here at the turn of the century. The first day I was assigned to work in a clinic and in that clinic you covered the emergency department because there were no physicians assigned to the university hospital emergency department. At 8 o'clock I got called to go down there. Some poor little kid had licked an ant cap, an ant cap being a bottle cap that was impregnated with some stuff called plastic wood and the plastic wood was impregnated with arsenic, and the child licked it.

Well, if I knew then what I know now, I would have forgotten it and given him a hit in the head and told him don't do it again, go home. But the precautionary principles said and the boss said wash out his stomach. We did gastric lavage which entailed wrapping him up, hanging his head over the edge of the table backwards and sticking a gastric tube down him, and rinsing his stomach out. I got through, talked to the parent. Everything seemed fine. Went home.

11:30 that morning, I get called to go down there again. Same kid, same problem, same treatment.

And believe it or not, at 5:00 he was back for a third time. Now, you say what was the matter with the mother. The mother was a reasonable person. He went up a ladder and got it out of a cupboard the third time. He apparently didn't make an association between what he was doing and what we were doing.

He fought like a wounded eagle the first time. The second time he gave a fair fight. The third time he just looked at me, and I see people looking at me that same way today and I'm always wondering, is he going to come up behind me and get even? I just don't know.

That was my original contact. That same day in an adjacent crib, two kids were being treated with ipecac to make them vomit for the croup, and I said to the boss, why don't we make them vomit to empty the stomach out? He says, it doesn't work. I said, what do you mean it doesn't work? They don't vomit. I said, well, how come those kids vomit and the ones who ingest don't? He said, I don't know, but the books say they don't vomit. And the books said that they didn't vomit at the time.

It took me about seven years before I could get an agreement that we could look at this particular question. I had to go to three different institutions, and we were finally able to do the study, an experiment on children no less -- and, you know, we like children as

pediatricians -- back in Columbus, Ohio. And that was the first documentation, not that 85 percent of the kids vomit, but that 97 percent of the kids vomit. And the other studies that have been done show it's between 95 and 99 percent, not the 85 percent. This is of the kids. Of the adults, the same thing.

I should also remind people nobody, absolutely nobody, in their right mind ever said you should routinely use either ipecac at home or in the emergency department. Using it on 100 percent of patients who overdose is psychosis, but it's a popular thing. You say, well, we're not going to use it routinely. I hope you never did.

If you look here, it says that "do something" mentality was important. Harry Shirkey, a pharmacist and a physician, was the one who led the charge back in 1965 that got the use of ipecac endorsed. Prior to that time, the fluid extract was being used, and if you look at the toxicity of the fluid extract, that had some associated with it, and the mistakes made in mixing it up led to three of the deaths that I published about. So I've seen the down side of the fluid extract, and we've had the only documented case of the syrup leading to a death. The syrup was administered because a child ate a flower of a plant. The precautionary principle is what tripped the treatment, and he had a negative outcome. That I'm just stressing.

Finally, I would be remiss if I didn't mention this. In the early 1970s, helicopter transport of emergency patients became popular. It was pushed by the regional medical program, the Debakey program, and what was going on in Chicago and in Baltimore got a lot of publicity, and the specialty of emergency medicine began. The specialty of emergency medicine for very good reason made first class citizens out of emergency physicians. Prior to that time, it wasn't a group, and usually in most communities it was the youngest person in town who was moonlighting because he needed to make some money while he built up the practice.

One of the first things the emergency physicians understandably and justifiably did was said they don't practice telephone medicine. The poison centers practiced telephone medicine. Ipecac is telephone medicine. Charcoal is not telephone medicine. You've got to come into my institution and let me feed it to you or stick it down a tube. So I see a conflict of interest in the backgrounds of some of the studies, and if you look at those charcoal studies done in emergency departments, it was ipecac plus charcoal versus charcoal alone. No difference. Ergo, use the charcoal until finally somebody said, how about ipecac plus charcoal versus charcoal versus nothing?

In the last two years you haven't heard much about it, but it's been publicized nothing does just about as much good in the emergency department as does the charcoal. The reason is simple. We studied ipecac back in 1960 and 1961. It took then 69 minutes on average for 214 children to get to the emergency department. That same study was replicated in Tacoma, in Spokane, and in Seattle in 1989. Not in the boonies. In cities. The mean time in 1989 was 71 minutes. So it's an hour to get to the hospital.

We just completed another study in the State of Washington, as well as in the Spokane region, that found after you get there, to get the activated charcoal into stomach is an additional hour. So as an alternative, it's not the best alternative, and it costs a lot of money.

I put down the last thing here is looking at the non-poisons, ranging from plants to hormones to botulinus toxin. The nicest thing that's happened to me in my 50-year career happened last year when more than a million people paid in excess of $500 an injection to have the worst biological toxin known to man stuck into their foreheads, and nobody got sick.

This has implication for what the American Chemical Society has found that when you use the word "chemical," 92 percent of the population says it's toxic,

it's bad, it's hazardous, it's waste, when it's really not. I'm a bag of chemicals. You're a bag of chemicals. They're usually pretty good, and we're finding more and more are not all that toxic.

Now, here's the data that I would simply repeat. The mean time till delay with children in emesis has been 15 to 20 minutes. The recovery for markers and using different markers makes a difference -- that 13-person study that Colonel Corby and his charcoal advocates down in Texas did -- they used magnesium. And magnesium, unfortunately like aluminum and calcium, has some adsorptive characteristics to gastrointestinal mucosa which makes it a lousy marker because it's stuck there. It can't come out. So the 25 percent, you've got to be a little bit cautious about. The 85 percent was done with radioactive substances, and you may have to be a little bit cautious about that.

Four people now have looked at groups of children and made an assumption that they are in one large group. Some of them were treated with ipecac at home because the parent had it. Some of them weren't because the parent didn't have it. After these kids all got into hospitals, they compared the blood levels of the ones who got the ipecac with the ones that didn't get the ipecac. On average, there was about a 50 percent reduction between

the ones who didn't get the ipecac and the ones who did get the ipecac. So it wasn't 25 percent. It was closer to 50.

DR. WOOD: A 50 percent reduction or a 50 percent difference?

DR. ROBERTSON: 50 percent reduction, 50 percent lower level. 33 down to 16.

DR. WOOD: In the two groups.

DR. ROBERTSON: In the two groups.

DR. WOOD: So a 50 percent difference, not a 50 percent reduction.

DR. ROBERTSON: Well, how do you look at it? It's not a 100 percent reduction. 16 is 50 percent of 33, or 50 percent difference. It went down.

The complications relatively rare, and yes, there are some. But I would just say -- and I checked it out again last week -- we in the Seattle area used ipecac for an entirely different purpose and that was to treat the chronic alcoholic to go through Pavlovian conditioning. And you were admitted for 14 days to the Shick Shadel Sanitarium. Six times a day you went into a little bit of a cubicle. It was glass-lined with your favorite booz. You sniffed it. You looked at it. You sipped it, and then you were given ipecac, and you'd throw up into the basin. And you did this six times a day for 14 days. By the end of the 7th day, 50 percent of the people who walked into

that room threw up. By the end of the 14th day, when they got near their stuff, they threw up. And it was pretty effective. They had a surprisingly high recovery rate. This was done to take care of people within industry, not the poor people on the street, but within industry where they wanted to get people really off the stuff.

Then two people didn't wash their hands when they went to lunch over in Austria, and antabuse came along, and antabuse made chemical conditioning as opposed to Pavlovian conditioning the thing to do.

If you look at the total number of doses, they had adults treated with ipecac more than 300,000 times. Several of the people did have some emesis with bleeding, but they've had some portal changes anyway. Nobody had any severe problems. What I'm saying is that the rate of complications is remarkably low.

Now, let me talk a little bit about some evidence-based medicine issues. Remember in 1949 75 percent of the children in the United States got Calomel, mercurous chloride, for teething. Calomel is a dangerous poison. Teething is a nonexistent entity, and some people will argue with me about that. But that was a very popular thing to do. Look at all the treatments we've used from A to Z for constipation and the other types of ointments that we've used for diaper rash. You can use almost anything

that you want for infantile colic, and I have treated four kids within the last month who have been given a grandparent's medication by mistake instead of some anticholinergic that was prescribed in a tablet form before they were 3 months of age for colic, and we made them throw it up.

Dilution for poisoning was the treatment used last year for more than a million patients treated on the telephone by the Association of Poison Centers. I haven't heard anybody anytime talk about the efficacy or the worthwhileness of dilution as a treatment from the poison center that feels it has to do something. It's probably not harmful, but I don't have the slightest evidence that it does any good.

And I already mentioned the terrible botulinus toxin.

So let me conclude with my thesis. I keep it simple stupid program. 80 percent of toddler ingestions -- that's 18 months to 3-and-a-half years of age -- are recognized -- two different studies -- in less than 10 minutes by the parent. If they call the poison center, it takes 5 minutes, and if they then have to find the ipecac they have in the home -- and in some of the promotional campaigns, we've been able to get better than 75 percent of the homes to claim that they have the ipecac there. We've

had two pharmacy students go out to the home and find remarkably high compliance. They're going out to the home. They ask could they see the bottle to see if the bottle had passed the expiration date. We've studied that. True, the expiration is not a valid one about emesis. It still produces emesis as long as 24 years after it's been bottled. Anyway, that's going to take you that time.

You're going to then have a choice: stay home or go to the hospital. If you vomit at home, or if you vomit in the car, assuming there are two adults there -- and you've got to be psychotic to drive with the kid. It's like a kid who's having a seizure in the death seat beside you. I don't want to be on the road when that person is there. So if there are two adults or a teenager, they can hold a bucket in front of the kid. Anybody here who has had kids -- we had five of them. Emesis is a common occurrence in 2- to 3-year-olds, and they know how to hit the bucket. And observe in either location, and you don't have to do anything else.

The final one is a hypothetical thing to think about. Assume there are 4 million toddlers in the United States every year, and assume, as we did a study, that each of those toddlers puts more than 12 non-food items in his or her mouth every day. Make that assumption. You calculate that 360 days a year. That's 17 billion

exposures per year, ingestions, not exposures through the skin, but ingestions. Assume that only 1 in 100,000 of those would qualify for ipecac at home. That's 17,000. Assume that no ipecac was available and therefore they had to go to the hospital. They go to the hospital at $400 apiece, you're talking about $6,800,000.

In contrast, assume that you put a $2 bottle of ipecac in everybody's home and they are one-kid families. That's $8 million. Pretty close in terms of expenses. If the prior sibs had it, you don't have to repeat it for this. So it's going to be less expensive. And I would urge you think about the cost/benefit implications as well as not just the benefit/risk implications.

On that point, I think I'll shut up and would be glad to answer any questions, or try to.

DR. CANTILENA: Thank you very much, Dr. Robertson. A very nice presentation and summary.

Open for questions from the committee. Ted?

DR. TONG: Dr. Robertson, you're one of the leaders in poison control center development, and I know in Seattle the tremendous success with getting ipecac into the homes. What about the issue of misuse and inappropriate use of ipecac? Is that an issue in your community? Is it's something that's addressed? Because there's so much ipecac being promoted. Much of your ipecac in fact, I

think, are given out and not sold at pharmacies.

DR. ROBERTSON: The hospital pays for it, but the hospital then gives it out.

In the past, both the profession of pharmacy, as well as a number of the physicians and a number of the institutions, did join with us in alerting the public. We used a sticker, a "Mr. Yuk" sticker. We used the syrup of ipecac, and we use other things, all aimed at getting compliance with child-resistant containers. Our board of pharmacy monitors this compliance, and we've been able to get a very low noncompliance of the requirements of the board. You've got to sign a specific statement if you don't get a --

DR. TONG: I was curious about the abuse and the complications.

DR. ROBERTSON: We've not been able to find any difference in the relative frequency either of the Munchausen's -- and one of our people is one of the authors in that area, and he's looked at it -- and/or the teenagers. Yes, we do have teenagers, but they don't get the ipecac from the bottle that their parents took home 14-18 years before.

It's a major problem. Our ephebiatricians, the adolescent medicine people, our psychiatrists, and we in the poison centers are attempting to try and do something

about it, but you and I know what's the epidemic of the '90s and 2000. Obesity. It makes SARS look like nothing.

DR. CANTILENA: Dr. Uden?

DR. UDEN: Dr. Robertson, you were here for Dr. Manoguerra's presentation, and in his he had referenced seven studies where apparently these seven studies are what the poison control center organizations are using and maybe the Academy of Pediatrics is going to be using to disavow any knowledge of ipecac in the future.

DR. ROBERTSON: It never existed.

DR. UDEN: Okay. So given those seven studies, are any of those studies in your mind worthwhile to support not giving ipecac as we are discussing it here?

DR. ROBERTSON: Two of the studies were done and warrant a careful look at them, a man named Curtis and another one named Albertson.

The ones by Kulig and the group at Rocky Mountain didn't document the time expiration between the overdose and when they did their various entities. And if it's been more than 2 hours, it couldn't possibly show any significant differences, and they didn't run any controls against nothing.

I don't think he alluded to Dr. Manoguerra's two studies, the most recent one from last year, that looked at a large number of patients where there was a

control of no treatment, not just no treatment in the asymptomatic patients, but no treatment at all, and couldn't find any benefit of the charcoal.

I would add one other one that he didn't talk about, and that was published in Pediatrics a year ago in January, published in Pediatrics, 115 administrations of charcoal at home and then followed by 229 after the study was done. And the kids ate the charcoal every single time. I can't get 30 kids to eat a bar of chocolate. And the 300-plus kids would take charcoal at home says that journal, in my opinion -- and I've said it in print -- ought to have its review process carefully analyzed.

DR. UDEN: So I guess the bottom line for where you're standing on this situation, are you still going to recommend that every household with a baby in it, an infant in it, have a bottle of ipecac in the cupboard for a potential exposure?

DR. ROBERTSON: If this group and the other clubs come out and say that's not a good idea, I'm not going to recommend it anymore. I want you to think I think it's probably on a risk/benefit basis a worthwhile thing to try to do. We're down to 25 deaths a year among kids. We're having awful problems with teenagers. What we're doing probably isn't doing a thing for the teenagers, and I don't think the ipecac will either. So it may not be a

major issue.

DR. UDEN: Thank you.

DR. CANTILENA: Any other questions from the committee? Dr. Lam?

DR. LAM: Dr. Robertson, the previous two speakers basically have said that for patients or parents living in a remote area, delaying it for them to actually get to the emergency room is not an issue, and they cannot put a finger on what particular medication would that be a problem. I would like to get your opinion on that.

DR. ROBERTSON: The rural areas -- they're nice places to visit. I wouldn't want to live there. The rural areas are not going to be the first to follow technological advances that go out there. They do pay attention to health care warnings.

As you saw from the data I presented, we didn't test the rural area. We tested the urban area and the delay time until they get into hospital and until treatment gets started is 2 hours. And McGuigan has shown the same thing, and that was referenced up there.

Seven out of seven studies in children, all of them, it was more than an hour after the kids got there that they got the charcoal. Now, if I go in with a heart attack, the emergency docs do something in 3 minutes. If I go in with asthma, they've got a puffer in my face in less

than 2 minutes. As a group they haven't really addressed the question how do they expedite the usage of charcoal.

I hope that answers your question. It reveals a little bias up here. I thank everybody for their attention.

DR. CANTILENA: Thank you, Dr. Robertson.

We have one speaker remaining. Dr. Rosebraugh, would you please introduce our final speaker for this morning?

DR. ROSEBRAUGH: Our final speaker is Dr. Silber, and he will now address abuse and misuse issues associated with ipecac syrup.

Dr. Silber is a professor of pediatrics with George Washington University and is the Director of Education and Training of the Section of Adolescent Medicine at the Children's National Medical Center. He received his medical degree from the University of Buenos Aires and completed a pediatric residency at Thomas Jefferson University in Philadelphia and a fellowship in adolescent medicine at Children's National where he has been since 1973.

He is a member of the board of directors of the Society for Adolescent Medicine, is an adolescent medicine health consultant to the Pan American Health Organization and a panel member of the Adolescent Health Section of the

World Health Organization.

He's also widely published and is focused on the areas of adolescent health with a particular interest in eating disorders.

DR. SILBER: Thank you very much for giving me this opportunity.

What I'm going to be discussing is the issue of ipecac abuse, and if we look at what we're going to do today, the review of ipecac syrup for over-the-counter status, we have been dealing with the role in gastrointestinal decontamination, risk/benefit ratio, role in the treatment for populations with limited access, abuse of ipecac, and alternative therapies. So it's abuse of ipecac that I'm going to be discussing now.

As a definition, one could define ipecac abuse as consistent with the repeated use of the syrup for the sole purpose of self-inducing emesis as a method of weight control.

It's actually synonymous in a way with an adolescent and young adult population. People who have used this consist of experimenters, people who already have developed an eating disorder, the most common one being the eating disorder not otherwise specified, those patients with anorexia nervosa who have developed the purging type complication, and patients with bulimia nervosa.

There are some characteristics that appear in relationship to this. First of all, of course, the behavior is secret, it's hidden. Nobody is to know about it, last of all, the physician. It's addictive. Once they have gotten into the cycle, it's difficult for them to break it. There is denial. This is just something that I do when my stomach is full and I don't feel well to help me vomit, but I'm really not abusing this. And there's plain lying about it when confronted with findings that are suggestive of it. So it's a powerful event.

We don't know the epidemiology of self-induced vomiting for all those reasons. We do know that in anorexia nervosa, there is a lifetime prevalence of 0.1 to 1 percent. And we know that according to studies, between 8 percent of the lower end and 41 percent on the higher end of individuals with anorexia nervosa will develop bulimia nervosa. And the higher end is probably the most correct one because they have the longest time of follow-up study. The lifetime prevalence of bulimia nervosa is estimated to be 3 percent. So between experimenters, eating disorders that are beginning, anorexia and bulimia, you have a high number of patients, or persons actually -- they often don't become patients who self-induce vomiting.

The majority of them have no difficulties in doing so, but there is a minority of patients -- and we

don't know the number -- that simply has difficulty in inducing with a gag self-induced vomiting, and they just can't do it. Yet, they feel a tremendous urge to do so and discover that ipecac makes the difference.

One of the concerns we, of course, have is that if they already have difficulty with vomiting, they may not vomit all the ipecac. They take it repeatedly. A lot of it gets absorbed, and of course, it's a poison.

So looking at the adverse events relating to the use of ipecac, it's terribly difficult to know this. Over-the-counter preparations do not require submissions of adverse events to the FDA, and so the data are very limited. However, those reports that we do have are consistent with characteristic effects of ipecac that are very well known and have been described.

Signs and symptoms of this ipecac poisoning, as it accumulates, have been described recently by Lee and reviewed by Karowski in Post-Marketing Safety Review, May 6th of 2003. These effects include recurrent vomiting, diarrhea, abdominal cramping, muscle pain and stiffness, muscle weakness, myopathy, erythema, urticaria, edema, cardiomyopathy, cardiac insufficiency, cardiac arrhythmias. And in their report, they report about 6 deaths. 4 of those were due to ipecac abuse.

Now, we have reasons to think that many of

these patients with difficulties and problems will never be reported. I have in my hand a letter sent to us that I think really gives the feeling for this very sad situation. The author of the letter says, on March 9 of this year, I awoke to find that my 22-year-old daughter had died in her sleep. She had been anorexic for three years and had been holding her own. Approximately 6 to 8 weeks before her death, she was introduced by a college classmate to ipecac and was hooked. After her death, I found many bottles of ipecac in her room, all bought at the local drugstore. And she tells a bit more about the story. But you get the feeling.

Do we know if this death was related to ipecac use? We don't know. We do know that people that are malnourished and take ipecac can get sleepy, can get somewhat obtunded. There may be an aspiration or any of the other complicating events. So that's what's haunts us. There is out there something going on and it's being hidden very well from us, and it's difficult to ascertain.

However, I think it's worthwhile to go over each one of the side effects and problems a bit more in detail.

Recurrent vomiting dentists will tell you will certainly induce dental abnormalities. There's tooth enamel that gets dissolved. Teeth become sensitive.

Cavities increase. There's periodontal disease. Teeth can get lost, and parotid gland enlargement can occur.

Gastrointestinal abnormalities certainly have been described, esophagitis, reflux, Barret's esophagus. That is a dysplastic disorder that may predispose to cancer of the esophagus. And, of course, lots of symptoms, dysphagia, odynophagia, esophageal strictures can occur. Mallory-Weiss tears have been described with hematemesis and aspiration pneumonitis.

There are metabolic abnormalities, metabolic alkalosis really being the most common one and one of the ways that one can to suspect this issue. There's hypokalemia which is fatigue, muscle weakness, polydipsia, nocturia, abdominal pain, constipation, headaches, palpitations, and renal pathology like in Barter's. They can become dehydrated. They can get to be in shock. They can have sudden death. This can occur with anybody who is in this cycle, but of course, it can also occur in those that get into this cycle with ipecac.

Diarrhea can lead to dehydration. Secretory diarrhea has been described. Hemorrhagic colitis, pseudo melanosis coli, and intestinal pseudo-obstruction are all in the literature related to ipecac.

Myopathy. There's progressive weakness in the proximal muscles. There's often myalgia. Patients can

lose deep tendon reflexes, can have swallowing difficulties, and may have even slurred speech, all things that can make one suspicious. In evaluating this, there can be a persistent increase in phosphokinase and aldolase. Electromyographic features of toxic myopathy can be discovered with people who are abusing ipecac. And muscle biopsy has been done in patients that astute clinicians identified, and they have shown severe disruption of sarcomeres sarcotubular lesions, and in electron microscopy they have found foci of Z-band degeneration. And what's most interesting and that really indicts ipecac in this is that with cessation of the use of ipecac, these findings were reversible and disappeared.

The cardiac abnormalities are, of course, those that alarm the most. Cardiomyopathy has been identified. Cardiomegaly has been shown, as well as tricuspid and mitral valve insufficiency, decreased cardiac ejection fraction, hypotension, arrhythmia, and as mentioned, death as an outcome is a possibility, an unpredictable one.

If one suspects this and one does EKG studies, there are a variety of findings. Sinus tachycardia, T wave depression and inversion, prolonged PR interval and QTc, atrial tachycardia, atrial premature beats, ventricular tachycardia, and ventricular fibrillation are all described in the literature.

When echocardiography has been done in these patients, one has found ventricular dysfunction and reduced ejection fraction, and even electron microscopy of the myocardium has been done and showed zones of myofibrillar lysis, fragmented fibers, irregular alignments or clumps of Z bands here too.

Rare things that have been described, pneumomediastinum, pneumoperitoneum, intestinal perforation, hepatic toxicity, cerebral hemorrhages and seizures, extremely rare.

A word about Munchausen syndrome by proxy. It shares with the abuse, which is my theme -- but as a pediatrician I can't forget this -- the secrecy, the intention to obscure the facts, and an addictive tendency to repeat it, but this is not abuse of ipecac. This is really child abuse by poisoning. It's a criminal behavior, and it is reported more, but it's probably under-recognized. It's a severe recurrent pathology, and it certainly has ended in some cases by causing the death of the child.

Detection of this abuse really requires a high index of suspicion. Many of the findings, symptoms, signs that I described to you can be attributed to another cause and be treated as if this is something else. We see this all the time in our adolescent medicine program as patients

come to us in consult. So one has to have a very high index of suspicion which I don't think we have yet in our country, and perhaps events such as this may help to publicize that. Yes, the laboratory can confirm the suspicion, lead us, EKG, CPK-aldolase, and there is confirmation methodology which is high performance liquid chromatography to detect this. It can be detected in serum. It can be detected in urine, and it has been detected in tissues by pathologists.

So I have some recommendations.

The first one is that studies are needed to determine the incidence and prevalence of ipecac abuse. We don't know that.

We need to promote professional education about ipecac abuse to facilitate early detection and treatment.

We have to develop prevention of this. Depending on this risk/benefit ratio, this may include a status change from over-the-counter to prescription medication. And that's not my area of expertise, so I'll let the body use some of the elements that I have presented and balance them.

But another possibility is to have warnings about the danger of abuse to be included. It may be helpful that labeling indicate the maximum total dose or maximum number of times the dose can/should be repeated,

which is not included in the labeling.

These are some examples of warnings. Use of ipecac to repeatedly self-induce vomiting is hazardous to your health. Prolonged use of ipecac is poisonous and can induce, among others, muscle weakness and pain secondary to muscle destruction. Ipecac toxicity can lead to cardiac damage, electrolyte imbalance, and death. And if you are or have abused ipecac, seek professional advice, or a variant thereof.

Thank you very much.

DR. CANTILENA: Thank you, Dr. Silber.

Questions from the committee? Dr. Blewitt?

DR. BLEWITT: Dr. Silber, is it possible to, just for the moment, separate cardiac abnormalities in patients who have persistent vomiting or chronic vomiting versus those who have taken ipecac?

DR. SILBER: Yes, it's possible.

DR. BLEWITT: In other words, do you see that in both situations, or is it confined specifically to ipecac? Cardiac abnormalities.

DR. SILBER: You can see cardiac abnormalities in the people who self-induce vomiting because you often have metabolic alkalosis with hypokalemia, and that type of arrhythmia can be seen without the use of ipecac. However, the myocarditis is never a complication of self-induced

vomiting.

I forgot to mention that the same way as the devastating muscular illness disappears when ipecac stops being used, the myocardial damage has been shown to reverse when patients stop using ipecac.

DR. BLEWITT: Now, does that also occur with chronic vomiters who don't take ipecac?

DR. SILBER: Myocarditis? No, it does not.

DR. BLEWITT: And the skeletal muscle changes.

DR. SILBER: Do not occur in patients who self-induce vomiting without ipecac. It's a clear toxic effect of the drug.

DR. BLEWITT: Thank you.

DR. CANTILENA: Dr. Davidoff, then Dr. Tong.

DR. DAVIDOFF: Yes. Dr. Silber, thanks for the presentation, which was very enlightening.

But you did make the point that in your view there was not really any quantitative evidence on the prevalence or frequency of the use.

DR. SILBER: No. That needs to be studied.

DR. DAVIDOFF: But we heard earlier from Dr. Manoguerra about two papers, and I'll just mention briefly what he said on his slide. Two papers attempted to quantify the extent of ipecac abuse in patients with eating disorders. The first showed that out of 851 patients in an

eating disorders clinic, 3.1 percent used ipecac chronically and 4.7 percent intermittently. And there was another paper in which of 622 patients in an eating disorders clinic, 3.8 percent of the women age 20 to 46 years of age used ipecac. Are you familiar with those data and do you think they're relevant?

DR. SILBER: Yes, I think they're relevant, but I think they are the tip of iceberg. That's really a small number. But there's a large number of people with eating disorders that will not see a doctor, and there are many people who come to the clinician with symptoms that clearly would indicate either an eating disorder or ipecac toxicity but who don't admit to an eating disorder. So those that come to an eating disorders program are a self-selected group where people have already had the wisdom of identifying them and referring them. Many are being treated not in eating disorders programs but in the community, and there's less sophistication there.

DR. DAVIDOFF: Well, if I may, I actually had the opposite the impression, that is, that these are actually quite large numbers. I mean, if 3 percent of the population has experienced an eating disorder in their lifetime and 3 percent of those are abusing ipecac -- and there are how many million women in this country? It's mostly a disease of women.

DR. SILBER: Yes.

DR. DAVIDOFF: That multiplies out to, in my view, a very large number of people relatively speaking.

DR. SILBER: But my point is probably it's more, but we don't know. And it really deserves to be studied.

DR. CANTILENA: Dr. Tong.

DR. TONG: Dr. Silber, thank you for bringing your experience to this group here and then also couching your recommendations. I have a brief comment and then a question.

The comment is that in the mid-1980s there was a report in one of the pediatric journals -- you didn't mention it here -- of adolescents who successfully committed suicide with medicines, taking medicines primarily with tricyclics and salicylates and a couple of other things. What they pointed out in there was that the majority were young women and that the taking of ipecac in the manner that you described was not uncommon in those successful suicides. The point being that they present in the emergency room and to critical areas very, very significantly impacted by electrolyte abnormalities, all the things that you've commented on. I should have brought the article. I thought it would be here. It's something that we use to teach our students about how important

something like an over-the-counter, when it's used in a manner that you described, can create problem.

My question to Dr. Silber is that is there any data on the geographic distribution of this particular condition. Is it seen in certain areas of the country more frequently or maybe because reporting is better? I'm asking that because maybe that way we can begin to see how syrup of ipecac is being dispensed or given, all the aspects of why this is a particular problem. Is it national or do you think it might be more geographic? We know that in certain areas with OTCs, Texas, Arizona, there seems to be spots where this is more frequent. Do you find that with syrup of ipecac?

DR. SILBER: Again, there are isolated reports. We don't know the extension. Eating disorders programs are usually developed in metropolitan areas. As a matter of fact, many of them, because of insurance issues and other complications, are going broke and there is a decline in the eating disorders programs and to services that they can give. So there's a large underserved area, and of course, the metropolitan areas are the ones that have the most reports on this.

DR. CANTILENA: Dr. Wood?

DR. WOOD: I just wanted to go back to what Frank said. I drew the same conclusion that Frank did that

these numbers were pretty high. Are you disagreeing with him? Because if so, I'd like to hear that run through again. 4 percent seems to me a pretty high number for a disease with as high a frequency as this.

DR. SILBER: No, no. I don't disagree at all. What I'm saying is these are good studies with a biased population which is the sickest of the sickest. So not everybody that is self-inducing vomiting will be in the same situation. However, for all the reasons that I said before, it actually may be more. So the reason I'm actually here to testify is because I think we have a problem. I would love to quantify it, and I think it's a serious problem. What we need to do is take this into account and balance it with the information on how good and effective this is to see if this ought to continue over-the-counter or if what I presented and doubts about efficacy may be sufficient grounds to make this a prescription instead of over-the-counter. And I don't feel capable to make that decision. I just want to contribute to it.

DR. WOOD: So what you're saying is that you think this is of relatively high frequency and that the numbers that were in these papers are underestimating it. Am I understanding that right? And that in your experience with the patients you see, this is --

DR. SILBER: I think that is so. I cannot prove it.

DR. CANTILENA: Yes, Dr. Patten.

DR. PATTEN: Thank you.

I have a question about socioeconomic correlates with eating disorders and use of ipecac in the context of an eating disorder. Has this been looked at? We had Dr. Tong's question about geographic variables. I'd like to ask the same question about socioeconomic.

DR. SILBER: In general, the victims of eating disorders belong to affluent socioeconomic groups. Most of my patients are children of physicians, professionals, nurses, et cetera. But in the last 10 years, there has been a change, and we are seeing what we call working class anorexia, and we're seeing the eating disorders emerging with some strength in minority groups, in African Americans and Hispanics, et cetera. So the old stereotype of eating disorders is getting old, and although it predominates in the affluent population, it certainly is occurring much more extensively among young people in the country now.

DR. CANTILENA: Thank you. Any other questions from the committee of the speaker?

(No response.)

DR. CANTILENA: Very good. Well, Dr. Silber, thank you very much for a very informative presentation.

DR. SILBER: Thank you.

DR. CANTILENA: We have reached almost on schedule, just slightly ahead of schedule, the lunch break. So why don't we adjourn for lunch and return at 1 o'clock to start with the open public hearing.

(Whereupon, at 11:56 a.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:10 p.m.)

DR. CANTILENA: If I could have your attention please, we'd like to resume the meeting.

The next agenda item for this meeting is the open public hearing, and we have a few items and one speaker for the open public hearing.

DR. TEMPLETON-SOMERS: We did receive a few letters on this topic, and they're available in the desk copy at the registration desk if people in the public would like to see them. They have been provided to the members of the committee, except for one which arrived later last night. One letter is the one that Dr. Silber referred to from the woman whose daughter died, anorexia and bulimia I guess. And one is from a physician who recommends having ipecac available. Then we do have a response from industry to this meeting, and the response was prepared by Humco Holding Group, Cumberland Swan Holdings, and Denison Pharmaceuticals. This has been provided to the committee and to the FDA. There are a few copies I think left out there for the public if you're interested.

We also have one person who would like to speak at the open public hearing.

DR. CANTILENA: Our single open public hearing speaker will be Armond Welch, senior consultant with the

AAC Consulting Group, Rockville, Maryland. We have 5 minutes allocated.

MR. WELCH: Thanks for the opportunity. It brings back old memories. I was the panel administrator for the Miscellaneous Internal Panel, and we had many meetings in these rooms across the hall. We had 17 overall panels and, of course, many reports. But there are a few things I observed here that I'd like to point out.

As you were advised earlier, the Laxative Panel dealt with emetics, and they dealt with that not as a poison control kit, and I'll deal with that a little bit later.

Earlier, as you were advised and the notes show that in '65 this was switched to over-the-counter, and that was, as I recall, a period of time when FDA had the poison control center. They were the focal point, and the poison control centers, as they're constituted around the country now -- some were in existence but not as much. But at that time, FDA allowed the switch from Rx to OTC. FDA was always slow to allow any Rx to OTC switch. So they dealt further.

Now, the charge to the panel is -- as a lot of the panelists know and maybe the speakers don't know, the OTC review is a review of the active ingredient and not necessarily of the dosage form. The only time the dosage

form is involved is if it affected the safety and efficacy of the active ingredient.

OTC drugs are also described as GRAS and GRAE; generally recognized as safe, generally recognized as effective. What's not often appended to it, the requirement, and not misbranded. It was a well-recognized thing in my history of FDA -- and I joined in 1946 -- that over-the-counter drugs -- you can't prevent misuse. You can't prevent misuse of Rx drugs either, but that's one of the problems our panelists had to deal with. I was the second person in to the OTC review, and the doctor who was in charge quit after two weeks. So I've had a long history there.

There were seven voting members on those review panels and they were diverse in background. We had two pediatricians that were pretty well recognized in their field. One was Dr. Sandy McCall from Group Health in Seattle. Kind of a bit of humor here. He was also on the vaginal drug product dealing with chlorophyll, and he said, that stinking goat on yonder hill spends all day eating chlorophyll.

When I spoke to Dr. Jay Arena about serving on the panel -- he had been nominated by a group, and he asked a little bit about it. And I said, well, we're dealing with poison control kits. And he said, oh, when I got out

of medical school, I unfortunately made the statement -- and none of you are old enough to recall it. I recall it as a younger person -- that mother, if your kid takes some poison, give them tea and toast. Well, the panel didn't deal with the tea very long. And Dr. Arena said, what I've tried to overcome in the years since, that toast is not activated charcoal. When the speakers talked about charcoal here, I assure you they're talking about activated charcoal.

The panel focused primarily on the fact -- well, in deciding whether something is GRAS and GRAE, they took in the historical knowledge. There are a lot of things where it's hard to do a well-controlled study like you would expect to find under an NDA, but the panel was allowed to apply their own expertise and knowledge. And the knowledge and expertise of the panel at the time that they met, '79 to '80 -- I've forgotten the exact dates -- is not the state of knowledge that you're dealing with now.

Like I said, they took up this. They did not have to follow the Laxative Panel. And they did consider it. They also considered the fact that FDA had put it OTC many years before. But the individual panel could disagree with any previous decision. And I must point out the panel's report outside of the preamble and the legal closing was always the panel's word. FDA employees could

not direct what they said.

The history on these panels are transcripts are made, but they're not the official record. It would take too long to edit them. So we depended on summary minutes. Of course, summary minutes sometimes leaves some of the things out.

I just want to emphasize that the panel's concern was -- I have to tease the gentleman from Seattle. You know, they can't use helicopters there. It's so rainy and overcast all the time, where in San Diego they can use helicopters. They don't have that problem.

They were concerned that people out in the hinterland would have a poison control kit not to be used until they contacted a physician or poison control center. What a way to pass the buck to the poison control center. Somebody would have to make a judgment. But that was the whole basic philosophy, and that's the main point I want to make here is that they thought the availability of this -- and in effect said, when you start having children, have a poison control kit. If something happens, get a hold of the poison control center or your doctor and find out what to do. They were concerned about the time lag between the episode and when you can get something in it. Maybe part of the value is -- what do you want to call it? Compassionate training. You know, it just sounds good.

Hey, you're doing something. Whether it's effective or not I don't know.

I think that takes care of my points. Thank you very much for your time. If I can be of any value in anything historically, I'd be glad to. It's a good forum here.

DR. CANTILENA: Thank you very much for your comments.

Is there anyone else who at this time would like to make a comment in the open public hearing to the committee?

(No response.)

DR. CANTILENA: Okay. Seeing no takers, then why don't we move to the interesting part of the afternoon at least, which is the discussion. I think from my perspective, we always try to do things based on the available information and as much science as possible, and then we talk about things in terms of OTCness criteria that were established some years ago I think by Dr. Weintraub, which looks at the safety in terms of assessing the risk and the efficacy in terms of assessing the benefit and then tries to also look at things such as the ability to self-diagnose, appropriateness of the labeling, et cetera. I think that's sort of the essence of our discussions, and ultimately the questions are what really is the OTCness.

I just had a couple of questions for the FDA at least initially, and then I'd like to open it up and we'll actually go through and discuss categories by the committee.

But, Curt, have you looked at or do you have any information that would suggest what the impact would be of changing this from OTC to prescription and the impact specifically on access for perhaps financially challenged subpopulations in rural areas? Do you have any way of assessing impact in terms of access to the medication?

DR. ROSEBRAUGH: That's not something we've really looked at, but something that you should consider is if you do come to a conclusion that this should not be an OTC drug, that does not automatically make it a prescription drug. So that's something you need to consider during your deliberations.

DR. CANTILENA: Okay. Could you expand on that? Are you talking about like a behind-the-counter category?

DR. ROSEBRAUGH: No. I'm going to try to give you a simple answer to that. It's actually a lot more complicated than what my brain can wrap around. We have some regulatory people who can help.

But if you decide that it's not OTC, it does not immediately go to prescription status. It would

probably require the filing of an NDA, and it would have to be re-reviewed. Now, if the committee is saying this shouldn't be OTC because we think the safety is such that people can't use OTCness, that's one issue. If the committee is saying it shouldn't be OTC because it doesn't work, that's a whole different issue.

DR. CANTILENA: So let's just walk through a couple of scenarios. For example, if we say that we're not convinced there is adequate efficacy and we have concerns for safety, we recommend it not be over-the-counter, then would the process then be -- first of all, it's advice. So then would the process then be that you would have to amend the monograph with the comment period or can you immediately have it removed as an OTC and then await the filing of an NDA? So would there be a period of time where you were unable to get this?

DR. ROSEBRAUGH: Well, like I said, since you're starting to get into some complicated issues, I'm going to turn it over to Tia Frazier who's one of our regulatory experts.

MS. FRAZIER: I don't know about a regulatory expert.

Some of the advice that we have would be ongoing, depending on what the outcome of your deliberations here are. But if ipecac was not covered

under the monograph, it would require a new drug application, and there may be temporary or some period of time -- we don't know how long -- before ipecac would be available Rx. Before the drug was approved, it would not be available in the marketplace.

DR. WOOD: Is it currently available by prescription?

MS. FRAZIER: There are some new drug applications for ipecac syrup, but the indication was thought to be over-the-counter.

DR. WOOD: No, that wasn't my question. Is it available by prescription right now?

MS. FRAZIER: Not that I'm aware of.

DR. WOOD: Do we know that for sure?

MS. FRAZIER: Can I tell you that I'll get back to you?

DR. WOOD: Sure.

DR. CANTILENA: So if I understand, if you look at sort of the history, the motivation for a company to file an NDA, looking at the slides that we were shown in terms of number of doses available, it's highly unlikely that there's a market there. So then it would be, I guess, almost like an orphan drug.

So the answer to the question, if I can be clear, is that there would be a time -- if we raise

concerns of a significant level regarding safety, where you felt compelled to remove it from the market for safety reasons, there would be a period of time, which could be years, before it were available anywhere in the United States by Rx or OTC. And that would really sort of depend on the timing of the filing of an NDA.

DR. ROSEBRAUGH: What I would say is if we were going to take it off OTC status and we didn't consider it an emergency to get it off, it would require rulemaking to do, and that is a rather lengthy process. So there would be plenty of heads-up for a company that they need to file an NDA and get moving if they want it to be prescription drug. So potentially there would not be a period of time when it is not available, but we cannot force manufacturers to file an NDA.

DR. WOOD: The answer to my question was we don't know if it's available on prescription right now.

DR. ROSEBRAUGH: There actually is an NDA that was inactive is my understanding. So as far as we know, there's not an active NDA where it's available by prescription.

DR. BULL: I would add, though, that the NDA can be marketed OTC, that an NDA doesn't mean it's prescription status. I think the question we're addressing is whether or not if there is a recommendation that the

drug is not safe for OTC marketing and that means that it's not going to fall under the OTC framework of GRAS and GRAE, then there would have to be an alternative regulatory path if there's a determination by manufacturers of maintaining a market presence for the drug.

DR. CANTILENA: Does anyone else have any questions of clarification in terms of regulatory process from FDA? I wanted to handle that first just so everyone was clear on what the possible outcomes were from an actual regulatory standpoint.

Okay, then what I'd like to do is -- I'm sorry. Dr. Williams?

DR. WILLIAMS: My concern is are those the only two options that are available if we have some problems with the efficacy or the potential abuse of the product. Are those the only two solutions that we have? Continue OTC or withdraw it?

DR. BULL: Excuse me. I invite Charlie and Curt to chime in, but I think the determination we really need the committee's input on is to address the clinical science and the risk-to-benefit and to help us in terms of assessing and providing your input and advice on its value based on the information that's available and the appropriateness of its current marketing schema.

DR. CANTILENA: Right. But I think really what

I was asking and what also Dr. Williams is asking is what would be the consequences of answering the last question regarding OTC status. In other words, would that result in a lack of access to the product for a period of up to years? Or what I'm hearing is that one possible outcome -- and please correct me if I'm wrong -- is that we would recommend it's not safe for OTC, but then it would go into a rulemaking process which can go on for a year or two or more before an actual action occurs. Did I hear you correctly?

DR. ROSEBRAUGH: Well, you're a little more brave than I am in putting any kind of time limit on a rulemaking, but rulemakings can be a very lengthy process, yes.

DR. CANTILENA: In a case such as this, is there a threshold that must be exceeded before you avoid the process of rulemaking and you just say it's not safe to be over-the-counter and we don't have to go through that process?

DR. ROSEBRAUGH: I think the definition is an imminent public health risk.

DR. CANTILENA: Any further points of clarification from the FDA?

(No response.)

DR. CANTILENA: How about if we start with a

general discussion relating to the first discussion point which is a discussion on the role of gastrointestinal decontamination in the management of poisoning? Here I would actually like to confine the discussion to really the role of ipecac in this setting. I think it's sort of beyond the scope to talk about activated charcoal, beyond the scope to talk about gastric lavage, whole bowel irrigation, and those sorts of entities. I think if I can just open this up for general discussion about the role of syrup of ipecac, if any, in your opinion in terms of decontamination.

Dr. Wood, would you like to go first?

DR. WOOD: Yes. I'm concerned that we don't fall into the trap of addressing surrogate endpoints that are inappropriate. It seems to me the indication for ipecac or anything else as a treatment of poisoning is to improve the morbidity and mortality in patients who've been poisoned. We've been caught innumerable times with what we thought were reasonable surrogates and finding ourselves trapped into treating the surrogates. So we didn't recognize for a long time that it was inappropriate to reduce the frequency of arrhythmias rather than recognize we were trying to prevent sudden death or we were trying to prevent cardiac mortality. So we zealously worked on demonstrating the efficacy of antiarrhythmics by showing

that they reduced the frequency of arrhythmia.

So I think we've got to watch here that we keep our eye on the ball and understand that the purpose of giving the drug is to improve outcome in patients who have been poisoned. I don't see any evidence that we've been presented that the drug does that.

There's not even evidence that it consistently improves the surrogate. When you start to think about it as looking at that as improvement in outcome as your endpoint, as I said earlier, you can't ignore the fact that the drug produces toxicity in that almost everybody who gets it has significant vomiting. That's not the endpoint. That's a side effect. If we had another therapeutic strategy that allowed you to reduce drug exposure with no vomiting, we'd think that was better than this. So that tells you what we're thinking about here.

So I think we need to be careful that we don't get ourselves trapped into evaluating whether the drug reduces arrhythmia frequency rather than looking at the appropriate endpoint.

DR. CANTILENA: I would just comment that the way I view it is if you assume that toxicity is proportional to exposure and exposure relates to absorption, in some of the studies, as was pointed out, the average is closer to a 50 percent reduction if given very

early. Actually really the sort of scenario that I'm focused on, Alastair, is having this available for immediate use in the home within a few minutes of the exposure. I would agree in the emergency department, no role; after 30 or 60 minutes, no role, or no evidence of a role. But there is pretty good data, as was pointed out, that in some studies, the Bond study from '93, in pediatric patients, an average of a 50 percent reduction in the amount absorbed by actually looking at the concentration in plasma.

So that's the surrogate that I'm focused on, and if you say that that is your surrogate for efficacy, we've approved things for OTC switch with much less than a 50 percent effect size.

DR. WOOD: Yes, but the effect size -- we've got a mortality of whatever it is, 25 in this country. If we went back to the days where 150,000 children were getting this, 150,000 children got to vomit for a day and in some cases longer for no proven benefit. It's interesting. I'm not so sure we'd be so comfortable advocating this therapy for adults where they might be more able to make their own decisions as we are for advocating this on behalf of children where it's easier to sort of say to them, swallow this and we'll make you sick.

So I think we don't have evidence that it

improves outcome. We don't have compelling evidence it even reduces plasma exposure in most cases. I think we've got to be very cautious when we go with a drug that we clearly know produces toxicity as part of its mechanism.

DR. CANTILENA: Any other comments from anyone else in terms of the role of ipecac for home use as an agent for gastrointestinal decontamination? Ted?

DR. TONG: Thank you, Lou.

Yes, I can support the committee's recommendation that syrup of ipecac be removed from an OTC status if that's the decision. Then what I would need to do is to think about the so-called unintended consequences of doing that in a community of families and children that our poison center in Arizona serves.

Clearly what was presented this morning suggests that the question answered is what difference does it make. It certainly works if you hear Dr. Robertson and his situation of 90 percent and all the way down to 30 percent in those cases. But does it make a difference? I think outcome.

And the question that Dr. Alastair Wood is pointing out is the outcome is pretty significant in terms of adversity. Having children vomit all day wouldn't be a desirable outcome, and in fact, I think all the speakers here this morning would say it's pretty uncommon to have

intractable vomiting, but we've all seen that. We've seen that in cases, and it's pretty unpredictable as who. And that requires follow-up and particular careful management and oftentimes even admission to an emergency room or to a doctor because intractable vomiting is a very serious problem.

We don't use ipecac in adults. When I say "use," I'm talking about recommending in a poison control sense because in the majority of ingestions, gastric decontamination has extremely limited value and certainly they're usually from overdoses, intentional suicide. Again, managing a suicide at home is totally inappropriate and not in any of the recommendations.

So I would have to think in terms of a poison center practitioner and the people that we care for and the caregivers that are given the information that we provide in terms of the proper use of ipecac. I thought the FDA did an extremely good job 20 years ago focusing on the labeling and saying how important it was to have a learned intermediary between the patient, the family, the caregiver, the child, and the pharmacist, the source of the ipecac.

I'm thinking if syrup of ipecac is not available and used in the way that we normally use as teaching clearly the label's instruction, and people would

be calling the poison center at least without -- the fact that now we have a national 800 toll-free number for poison control centers around the United States, thanks to the American Association of Poison Centers, again, the question about people are going to take it without calling, without getting advice is going to be diminished because every year in March we carry on campaigns about poison safety, although fewer and fewer of our campaigns are focusing on syrup of ipecac. Clearly our trend in the poison center in Arizona mirrors what the national trend is. It's fallen dramatically in terms of the amount of ipecac used. So that's clear.

So I'm concerned about the unintended consequences, which we will address as poison center specialists and as poison control centers.

Again, well, what about in Arizona? We will find ways to make sure that when children accidentally ingest materials, that a home management is appropriate and proper with proper follow-up care, that we'll find other ways. Our message then will be not to do things, not to use salt water, not to use peroxide. Isn't there some chemical that can produce -- how about soap? That's a good idea. I see my child drinking soap and he vomited in 10 minutes. Again, the inclination is get it out of the stomach, and for all the data that's been shown, getting it

out of the stomach 30 minutes to an hour afterwards isn't going to be very effective in terms of the outcome.

So I could support a committee decision about saying that -- the OTCness I don't think has changed. I think the OTCness still remains. I was on this committee in '93 to '97. So I learned a great deal from Dr. Weintraub and from the FDA staff and from Lou. Focus on OTCness. In the discussions this morning, I'm going to try to continue to do that and think about that.

I know you're going to have other questions about misuse and abuse. So I'll just hold off.

I think the question is in my work in the poison center, in my teaching of pharmacology/toxicology, clearly gastric decontamination is limited. And I would use the story of ipecac, the history of ipecac, and whatever is going to happen as an example of how to think in terms of a therapeutic agent. What is the outcome? So it works. It's impressive when it works because I've had ipecac thrown up all over my coat standing in the ER. I've also seen what happened in adults, like the alcoholics who got ipecac and shouldn't have and exsanguinated in the emergency room for a Mallory-Weiss tear. So I know we spent some time on history today, and I just hope that whatever comes out of here, that there's enough of us to convey that history to our students because this will come

back again in 20-30 years if we don't.

DR. CANTILENA: If I can just ask a follow-up, Ted. Is your poison center still using ipecac at home?

DR. TONG: We still recommend ipecac at home, but like I mentioned, our use has declined very, very rapidly. If we use it more than 100 times, 200 times a year, I'd say that's probably where our usage is. So it reflects pretty much what the national data is. So we're part of that declining trend.

But also, our outcomes are also very much improved. And we've also accepted a higher toxic dose ratio. I think Dr. Manoguerra and Dr. Tenenbein pointed out that we're keeping people at home today a little more liberally than we did 20 years ago.

The toxic time bomb is the one that we're concerned about that oftentimes gets misplaced. We were talking about acetaminophen. That's a toxic time bomb. Well, the child took a couple of Tylenol -- or I shouldn't use that word -- acetaminophen and nothing has happened. So no big deal. But I think we all know that's a signal for medical attention if a child has taken a significant amount of Tylenol. But the point being that the person looking says there's no problem with the child so there can't be a toxic ingestion here.

So we continue to use it, but our usage has

been very much minimized. It's the distance. And I agree. Rural maybe does not cover everything, but it's in inaccessible situations where ipecac, if it's at home, we'll recommend it. But we don't send people out to get ipecac, nor do we sent emergency personnel to the home with bottles of ipecac. And we don't use ipecac in our emergency room.

DR. CANTILENA: What would be sort of the characteristics of a case in which you would strongly recommend ipecac? In other words, if it's no longer available by any route, who would we really be impacting in terms of what you see in your practice?

DR. TONG: It will probably be the people who already have ipecac in the home calling us and we're telling them don't take it. And they say, but you gave this to me five years ago, and my first son didn't use it, but my third daughter has ingested the same thing or the same situation. So we'll need to explain why now we're telling them not to use it even though five years ago it produced a good outcome.

In Arizona we have a lot of isolated regions in northern Arizona in the Native American region, and we have good public health physicians and public health caregivers there. And ipecac seems to be a helpful thing for them because then they get access to the patient, and again this

whole instruction, teaching them of how to manage something when an accidental ingestion has occurred. I think the ipecac ends up sort of being the information link. People look at ipecac. They know to call somebody because it's related to a poisoning problem.

DR. UDEN: Excuse me. But I'm still confused, Ted. I mean, ipecac is going to work as well or poorly in a rural area as it does in an urban area. So I'm having a hard time understanding what makes rural any different in terms of access or anything. If the stuff doesn't work or doesn't work well, it doesn't work well in Blackduck, Minnesota or in Minneapolis.

DR. TONG: So the point being that if it's not going to be efficacious in terms of outcome, we shouldn't even be recommending it in those areas. Well, that's where, again, we know a large quantity of home ipecac is stored. So again, it gives us reason to ask them usually, do you have ipecac in the home. If they say no, we go on and continue our description of how to manage the patient. But very often because of our 30 years of effort in getting ipecac into the home, we'll ask, do you have ipecac, and they say yes, by the way, it's right here by the telephone like you told us when the nurse visited us a couple months ago. And then the whole question is, well, don't do anything because it's not effective.

DR. WOOD: Yes, but we move on. I mean, just because we used leeches at one time, we don't say, do you have leeches in the home and use that. If we don't think the drug works, I agree with Don, if it doesn't work in Nashville, it doesn't work outside of Nashville either. There aren't many drugs we have that are indicated for rural Americans and not for urban Americans. That seems to me just counterintuitive. If it doesn't work, it doesn't work.

DR. TONG: The question was what I do in Arizona and the situation in Arizona. That's what we've been faced with. Sure, I appreciate that.

DR. CANTILENA: Right. So you don't see any population or group of patients, pediatric or otherwise, that would really be harmed by not having it available.

DR. TONG: Be disenfranchised or disadvantaged? No.

DR. CANTILENA: But if I heard you correctly, when I asked you when you use it, you're actually just using it as a vehicle to establish the communication. But I was sort of getting at what type of patients would you actually recommend that they give the ipecac for at home and then observe. Is there a specific population if you looked through your exposure use, every time that you used ipecac?

DR. TONG: No, not a specific population.

DR. CANTILENA: Okay.

DR. TONG: If it's one or two aspirin, that type of thing, again that fits within the criteria of what can be managed at home, which is again general agreement with the business, then we'll go ahead and do it. But no, not a specific population.

DR. CANTILENA: Dr. Blewitt?

DR. BLEWITT: Well, I would take issue with the statement that the drug doesn't work. No one knows that the drug doesn't work. The appropriate studies haven't been done to look at outcomes in cases of overdose. The studies that have been done have been done in a clinical setting, as everyone has noted here. So the fact is that it would appear, based on the clinical pharmacology, on what data is available, that time is of the essence, and so the ability to have it in the home where it may have some effect is, I think, particularly useful.

Now, there are practicalities here. There is a practicality, and that is if anyone considered removing this product from OTC use, it requires, as we've heard, a new drug application. My argument would be that perforce this will remove it from the marketplace entirely because I personally -- and I'm speaking for myself -- can't envision any company with a market that is this small and small

companies undertaking all of the work that would be necessary to go through the entire NDA process. They'd simply take it off the market. I think that's the practicality of it. So it's not OTC versus Rx. It's OTC versus does it stay around at all. So I think that's really what people have to address here.

I think, as Ted has said, there are possible situations where it's of value, and it's still used not only by Ted, but other poison control centers. I think that a great deal of consideration has to be given to its availability in the marketplace, just for that particular rationale.

DR. CANTILENA: Thank you.

Dr. Clapp?

DR. CLAPP: There are several things that come to mind in considering the efficaciousness of this drug. First of all, from the history that we've heard and some of the data that we've heard today, right now we're approximately at 25 deaths annually with children secondary to ingestion. Then I hear the 16,000 number of how many calls came in or were received at the poison control center having referenced ipecac. Whether or not they received it on the advice of the poison control versus had administered it and then informed poison control wasn't clear. That's a huge drop with an increase of, I think it was, 1.5 million

calls to the poison control centers.

Dr. Tong references 100 to 200 cases in Arizona that received ipecac, but I'd like him later to clarify the indications for that, what were the clinical indications for the advice as opposed to the fact that it was in the home and the parents were perhaps using it as a vehicle to access medical care. What were the medical considerations given to advising those parents to use ipecac?

What the interesting consideration is, with the advent of so many other safety precautions, from child-proof tops to safer medications, we have very few medications right now I think in pediatrics -- well, no, that's not true. Perhaps children are ingesting less of the highly toxic medicines as they were before because of safety precautions.

So then we come down to what drugs are we really fearful of and what is their lethal dose, what will cause lethality in children. Once considering that, then you have to consider what is the dose and timing of ipecac and does it really reduce the lethal burden that that child has in the ingestion. And we get back to the 25 percent or was it one-quarter full versus three-fourths full cup.

My feeling is I heard something that stood out today. Efficacy does not improve with distance, and I think that's an important statement to consider. If we are

kind of quibbling over the dosages that the children are receiving that are putting them at risk of death and then ipecac is not the first drug of choice to decrease that lethality, then we are talking about giving children a medicine that's very inconvenient. And that's true.

And I liked what Dr. Wood said about if you were an adult, would you take a medicine that made you vomit regardless of the outcome? We do lots of things to children that adults wouldn't tolerate, unfortunately.

Getting back to my point, I don't hear that the efficacy is significant in reducing the outcome of lethality in children. I hear that the medicine does make you vomit, but I don't see, in reading this, convincing evidence that the vomiting is reducing a significant amount of morbidity and certainly no mortality with the administration of ipecac. This is what I get out of the presentations today.

So my biggest question was is there a certain subcategory of people who we must be concerned about that if they are not accessing ipecac will access no medical care.

Then I come back to the 25 number. We could ask the FDA to give us information of where these people were. Are they rural people who have no access to medical care? Or are they urban dwellers who just wouldn't have

responded to medical care had they used ipecac initially or not? 25 is not a convincing number that sort of addresses whether or not is working on a widespread basis. If it were -- no, I shouldn't say that. I can say that the number that poison control is advising to use ipecac doesn't seem to be significant enough that that is responsible for the decreased number of mortalities to 25.

DR. CANTILENA: Thank you. I think you had about four or five questions.

DR. CLAPP: But the one I'd like is the clinical indications, the specific medical indications for which the Arizona poison control advises patients to use ipecac.

DR. CANTILENA: Right, and I would actually like to hear from Dr. Tong. I think I sort of asked him that and he sort of dodged it twice. But I think we're going to make him answer it this time, and then ask actually Dr. Robertson if he can share his experience from Seattle.

DR. TONG: Well, thank you for a tough question. It reminds me of when I had to take the boards for the American Board for Applied Toxicology, and we should be on the hot seat because we're on it 200 to 300 times a day.

I'm just thinking of some examples. Since I'm

not on line making the response all the time, I'll give you an example of like 1 or 2 tablets of Tylenol and it's very certain that that's what we're talking about. One that I recall the last time I was on the line was 20 to 25 children's chewable vitamins with some iron in it.

Again, the protocols for managing children who have ingested potentially toxic materials are actually very rigorously examined and overseen by the American Association for Poison Control Centers. So that's the work of people like Dr. Manoguerra, Dr. Robertson.

But again, they're the kind of situations where exactly what was said here that if you left them alone, they'd be okay. The real value of a poison control center is the continuing follow-up, and the poison center staff will ask questions like if there's no opportunity to follow up, how do we deal with that. We have a medical director. We have physicians in our poison center, and that's a judgment call. I mean, every call involving an ingestion is a judgment call. You know, how is the child doing? How long was it? Is the caretaker able to manage through directions over the telephone that particular situation?

So I'm still kind of dodging it. I don't have a list with me to say here are the 10 things that we would do in case of an ingestion.

But clearly, we all understand that and we

ascribe to what Academy and the Association are all looking at and waiting for their decision. It's taken many years and the deliberation continues.

So the example would be things that are not anywhere near a medium to severe toxic situation. Clearly anything that's not manageable in the home, and that list is quite extensive, suspected abuse, again a care situation that's unstable, a number of other things. So there are a lot of reasons why managing a child who has ingested something at home shouldn't be done.

DR. WOOD: Ted, I believe I want to try and force you here. Is what you're saying that the group of kids that you think should get this are the group of kids who would do fine if they didn't get it? Is that fair?

DR. TONG: Yes, I'd agree. Sure. Those would be situations where if we didn't give it, they didn't have it at home, we wouldn't go rushing out --

DR. WOOD: So if they didn't have it at home, you wouldn't give it to them and you wouldn't bring them into the hospital.

DR. TONG: We'd still manage them at home, sure. We give them calls back.

DR. WOOD: So what we do is we take somebody who we believe who will get better spontaneously and we make them sick. That's what I'm hearing. So we take

somebody who's going to do fine with nothing, and we make them throw up a few times and we all feel better because, you know, we've done something. But that's not medicine. That's black magic.

DR. TONG: Well, I said I could practice the poison control center without the assistance of syrup of ipecac.

DR. WOOD: That's hardly a ringing endorsement for a therapy, it seems to me. So I think if that's the indication part, then that's a worry to me.

Then the second thing is if the other group that's supposed to be treated with this are people who we're not sure we can get back for a follow-up, I see that as equally disturbing. If you've got a child who's taken a potentially lethal overdose of acetaminophen and you have doubts about their ability for follow-up, none of us would believe that ipecac would be sufficient therapy on its own without appropriate --

DR. TONG: No. I didn't mean to suggest that we give people ipecac because we don't have follow-up. In fact, that's a reason not to do that. I'm sorry to mislead you on that one, but you're absolutely right. We don't do that.

DR. TENENBEIN: (Inaudible.)

DR. CANTILENA: If you can hold that thought, I

actually will ask you to comment on that. But I was wondering if I can get Dr. Robertson to comment on the question that we've been asking Dr. Tong in terms of who is really the ideal ipecac patient, and if it were not available at all, Rx or OTC, who would be hurting the most.

DR. ROBERTSON: Let me address that last one because there are other alternatives that haven't been mentioned. In the '60s, there were a lot of studies using various detergents, not the real alkaline or the real acid ones, but others, and the emetic response is remarkably good. So there is an alternative. It's better than soap. We've studied gagging. Gagging isn't worth the time of day. So if ipecac is not there, then one does have the detergents.

I don't care whether it's ipecac or any emetic agent -- and I've even talked about putting apomorphine in capillary tubes and dropping it into the conjunctival sac to induce emesis.

But the product of emesis can reduce the amount that's available for absorption, and if I have a child -- an example would be -- who takes 10 calcium channel blockers, 10 of them, and is 2 years old and I'm concerned about this child, and I'm going to send him to hospital for some appraisal, I would be inclined, if there were two parents there, to introduce the ipecac to reduce the amount

that he's going to absorb by the time he gets to the hospital. And that's going to be more efficient in my book, as I read the data, than doing charcoal 2 hours later.

With ipecac there hasn't been a single acute death in 17 years in prepubertal kids. There have been repeated doses that have done that, but there are a lot of children, when they get to the hospital, even though the amount is borderline, they go for 18 doses of treatment and 3 days of hospitalization and lots of opportunity for mistakes. And if I can reduce the amount that that child shows up with in the emergency department, that's going to save him, quotes, child abuse by over-treatment, I think that's a reasonable cause.

Now, am I saving a life? I doubt it unless he has something really screwed up in the hospital.

The last thing, and I neglected to mention this this morning. This is not science. What I've said so far I think is science. But opinionairres were sent out to poison centers and were sent out to the medical directors of poison centers in the last couple of years, and there was an overwhelming majority that advocated from both of these -- and I can send you the abstracts for them -- that yes, we keep the ipecac available.

But I tend to disagree with what Dr. Tong is

saying. I don't do it for appearance. I'm going to try and get something done. If I can't persuade people over the phone or by mail, life is tough.

DR. CANTILENA: Thank you very much.

Comments from Dr. Tenenbein and Dr. Manoguerra, and then we'll go back to the committee.

DR. MANOGUERRA: Well, I have a lot of respect for Dr. Robertson's experience, but I just have to comment that the last child that I would want to give ipecac to is a child who has taken a calcium channel blocker that is going to have bradycardia, and the vagal response from the ipecac very likely may make him asystolic.

I personally cannot think of a situation where I would recommend ipecac at the present time.

Getting back to the question that was given to Dr. Tong, I can reminisce back to when we stopped using ipecac in our center. The hardest time that we had was convincing the staff not to want to continue using it because they were so comfortable doing it year after year after year, that it was difficult to get them to stop. And I think that's the same problem that Ted would have if he went to his staff and said we're going to stop using ipecac today. There are going to be those staff members who have been giving it for -- I mean, children's chewable vitamins with iron are totally nontoxic. There's never been a

serious poisoning with children's chewable vitamins with iron. But my staff lined up at my door and said, what are we going to do with all the kids who get into chewable vitamins with iron? Are we going to stop giving them ipecac? And we said, yes, we are, because all we're doing is making them sick. I think we're taking kids who are going to be completely asymptomatic, maybe a little upset stomach, and we're making sure that they get an upset stomach by giving them ipecac.

As far as the question about in what situations is ipecac currently being given, I was told that the data that I was e-mailed last night has that information in it, being taken out of the AAPCC database.

In response to, I think it was, your question about the deaths that are occurring, if you look at those deaths, the vast majority of them are not orally ingested medications. The vast majority of them are corrosives, pesticides, petroleum distillates, carbon monoxide exposures, therapeutic misadventures, children given 10-fold overdoses in the hospital. They are those kinds of exposures that are resulting in death. The typical child who's ingesting mom's or dad's medication at home are not ending up as fatal ingestions as they did 30 or 40 years ago.

DR. CANTILENA: Any comments, Dr. Tenenbein?

Those are your comments. Okay, good.

Dr. Tong?

DR. TONG: There is one situation in Tucson -- well, in Arizona we have the monsoons, and if you monitored the use of ipecac, you'll see a blip because there are mushrooms that come up post monsoon. We know from our own studies in our own area in our state, that children who take the bite or two bites of the lawn mushroom -- it's not the liver-damaging mushrooms -- and a good portion -- you say, well, what's a good portion? 50 percent plus will have GI upset, gastrointestinal upset. So I know our staff will recommend syrup of ipecac in those situations, given all the other caveats that we can call back to monitor and they're not in a car, they're not locked out someplace. So I think Dr. Manoguerra is correct.

I think the other thing is that even with prescription medicines, the one or two tablets, it depends on what that prescription medicine is. Clearly calcium channel blockers I would agree in our experience also would not be something that you'd stop at just giving ipecac and monitoring at home. So there are situations case by case.

But since Dr. Wood was asking give me an example. Plants, the small pieces of plants. We're not talking about ingesting the medications. Again, we've successfully managed ingestions of those kinds of

situations with syrup of ipecac, but we can treat them without it too. You're correct.

DR. CANTILENA: If I could ask the committee if you wouldn't mind just taking a quick 5-minute break. We have to confer on a point of procedure. So if we can just take a 5-minute break, we'll be back in exactly 5 minutes. Thank you.

(Recess.)

DR. CANTILENA: If we can take our seats again and resume.

We will actually move to the questions. As we deal with the first question, I guess what I would like to propose is we'll sort of go around the table, and if the committee members can comment just on what the question asks, which is what is their opinion regarding the role of gastric decontamination in poison management. Important, not important, unnecessary? That would be one way of handling it.

And then question 3 is the one that we're actually going to spend some time on and dissect that one out.

Let's start --

DR. WOOD: Lou, are we only talking under gastrointestinal decontamination ipecac? Are we also talking about charcoal there?

DR. CANTILENA: Charcoal, lavage, ipecac, but we are especially interested in syrup of ipecac, but just sort of the general role of gastric decontamination.

Are there any questions or items that people want to discuss before they give their opinion on that question? Dr. Davidoff.

DR. DAVIDOFF: Well, I had a question that really gets to the Bond study which has been quoted a number of times which I think potentially may be a very important bit of information. But it is a rather slender reed. My question has to do with whether the study corrected for the ingested dose of the toxin because if not, then we don't know if this apparent 50 percent lower blood levels in the patients who had gastric decontamination -- whether you can attribute the lower levels to the gastric decontamination. Does anyone know? Do you know, Dr. Robertson, if the ingested doses were comparable of the toxin?

DR. ROBERTSON: I've talked to Dr. Bond about that, but I don't have the article with me, so I got to trust memory.

When you ask the parents how much the kids eat, the accuracy of that number is enormously varied. The assumption that the group made was that all of the kids came from one group and had a normal distribution curve,

and they got different estimates and felt that the estimates for the ones who got the stuff and didn't get the stuff were within the same ball park. That's what their assumption was.

DR. DAVIDOFF: Thank you.

DR. TENENBEIN: This was a multi-center study on historical data. The short answer to your question is no because you don't know how much these children have taken. What they were relying on is that the n, the sample size, was large enough to correct for whatever errors there might be in that both populations were similar. Having said all of that, of course, all of these patients had ingested nontoxic amounts.

DR. CANTILENA: Thank you.

Any other comments or questions? Dr. Johnson?

DR. JOHNSON: I guess I have a question perhaps for the experts, and that relates to the available literature on a do-nothing approach. It seems that there's been a lot of, at least, suggestion that in most cases do nothing is more than okay, and I think at least one of the studies had a do-nothing arm. But I'm wondering if there is more literature available that really discusses the outcomes in patients where nothing is done in terms of gastric decontamination.

DR. CANTILENA: Dr. Tenenbein, do you have a

comment?

DR. TENENBEIN: Well, again, the study that you're quoting about the do-nothing arm is not relevant because that was an emergency department. It wasn't soon after.

The short answer to your question is there are no specific data on that.

There are ways, of course, of analyzing the data that are available to us. It's that poison deaths have decreased. The use of ipecac has decreased, and no other country in the western world has this intervention and they don't have an epidemic of little children dying.

And that's the best that it gets. It just doesn't get any better than that. And the type of data you're asking for will never be produced. So it's a decision of best practice based on those types of data.

DR. JOHNSON: So along with deaths decreasing, are hospitalizations from ingestions also decreasing? Have they decreased over time?

DR. TENENBEIN: Yes.

DR. CANTILENA: Any other comments?

(No response.)

DR. CANTILENA: Okay. Let's start actually with Dr. Blewitt and if you can address the issue of a role of gastrointestinal decontamination in poison management.

Obviously, we care about ipecac, but any other comments that you'd have for the other modalities are welcome.

DR. BLEWITT: I'll confine myself to ipecac. The evidence would support, at least clinical pharmacology evidence would support, that time is of the essence for the drug at all to be effective, and it does demonstrate that there is efficacy in reducing the amount of ingested material.

The database, as I've said before, lacks the studies of effects of home use or even, frankly, of abuse and misuse. But it does appear to work in the acute situation. Outcome data is lacking clearly. Those kinds of studies haven't been done, probably never will be done.

In my own opinion, it simply offers another therapeutic modality option.

DR. CANTILENA: Thank you.

Dr. Clapp?

DR. CLAPP: I think I'd have to read more specifically on activated charcoal and gastric lavage to give an informed opinion.

As far as ipecac is concerned, it seems efficacious in inducing vomiting. Now, it seems that the question as to whether or not it is efficacious in reducing the morbidity and mortality from poisonings doesn't seem to be borne out with the evidence that I've been presented

with.

DR. CANTILENA: Dr. Johnson?

DR. JOHNSON: I too would prefer not to comment on anything besides ipecac. I guess my assessment is that while administration of ipecac very shortly after the ingestion may numerically reduce the exposure, the plasma concentration, it appears that it provides no benefit in outcome. I guess I concur with Dr. Wood's assessment that outcome is really what we're after, and if the outcome was going to be good with nothing, then we're only creating problems by administering the ipecac, even if the ingested concentration does reduce slightly.

DR. CANTILENA: Dr. Tong?

DR. TONG: Well, on the issue of gastric decontamination as a procedure, I clearly believe in it. We're not talking about charcoal. I think you've heard me say enough about syrup of ipecac. I agree that if we're looking at outcomes, that's the question. It works but does it change anything? And clearly what we've heard is that it doesn't.

My feeling is I can practice poison control centers without syrup of ipecac. If we were talking about a home management gastrointestinal decontamination, ipecac certainly is a practical agent if it were available. Thank you.

DR. CANTILENA: Dr. Williams?

DR. WILLIAMS: As a topic of gastrointestinal decontamination in a time-oriented fashion, I still have a belief that syrup of ipecac will be satisfactory in a short period of time from onset of installation to the time of its action, which we're talking about 15 and certainly no longer than 30 minutes. So I would continue the usage of it in that format as a home preparation as an emergency preparation, but certainly not as an emergency room effort.

DR. CANTILENA: Thank you.

Dr. Davidoff.

DR. DAVIDOFF: Well, I came into the meeting pretty much convinced by the intuitive rightness of gastric decontamination with ipecac and perhaps other things. I guess after hearing the information presented today and reading the papers, I'm much less convinced of its value. Or maybe it's better to put it the other way around. I think there almost certainly are a few kids who treated at home with ipecac would probably be better off in terms of either, say, a hospital course or even potentially, very rarely, preventing serious morbidity or mortality. But after hearing the presentations today, I'm impressed that those numbers must be very, very small.

In relation to that, I think even though I understand it's important and convenient to discuss these

questions in isolation, I think discussing gastric decontamination by itself, without putting that up against all the other issues that we'll get to in the other questions, is artificial. So I'm reluctant to rely too much on how I feel about decontamination alone.

DR. CANTILENA: I guess my feelings on this are that as has been said, time is of the essence. I think there is a role for the overall decontamination, but very, very early on. I think lavage has pretty much fallen by the wayside. Part of my practice involves medical toxicology and I'm not sorry to see that go. But I think in my mind there is still a role for this early on, very, very early after the ingestion in the home, and I don't see that role being occupied by activated charcoal. So we'll get into the specifics later on, but that would be where I stand at this point on that question.

Dr. Wood?

DR. WOOD: Like some of the others, I'm going to confine what I say to ipecac. I think there's no good evidence of beneficial therapeutic effect of ipecac. There's clear evidence of toxicity, and I'm reassured about the lack of real effect of ipecac from the San Diego data that when they stopped using ipecac, there's not been an outbreak of disasters in the San Diego area. Nor, interestingly, have there been problems in most other

countries, including the UK, Canada, and most European countries in which ipecac is not available over-the-counter and not available in the home. So it's not like the standard of care worldwide is that we use ipecac. So I'm not persuaded that this has beneficial effects, nor am I persuaded that removal of it would produce problems, and I'm strengthened in that, as I said, by the San Diego and international experience.

DR. CANTILENA: Thank you.

Dr. Uden?

DR. UDEN: When I came to this meeting, I was in the "use it early" camp. I've had a lot of experience back in my early pediatric days managing poisonings. But I've been painfully torn away from that, I think, at this meeting. You can use it early, but if it doesn't make any difference in the outcome, you shouldn't use it at all. So that's where I am at right now.

DR. CANTILENA: Dr. Patten?

DR. PATTEN: I defer to the experts on all of these questions. Remember, I'm a consumer rep and an anthropologist. However, there does seem to be a tremendous amount of information accessible to us that indicates that this is not a particularly effective kind of procedure to use.

I guess I worry less than Dr. Wood does about

the experience of emesis on a child. There are all kinds of medications that children get that have all kinds of adverse side effects. As a mother, I can recall episode after episode of profound diarrhea as a consequence of administration of antibiotics, for example. So that part doesn't worry me.

But I think I do agree with Dr. Wood that we must think of the outcome. The outcome is what should help us determine. And if the outcome is not improved by this procedure, then I would not endorse it.

DR. CANTILENA: Dr. Lam?

DR. LAM: Based on the presentations and the evidence, I think ipecac has some but limited efficacy, and certainly has no impact or no study to show the impact on morbidity and mortality.

I certainly have not heard so far that there is one subpopulation that it would be harmful if we take ipecac out of the management procedure. So I would say that there is not much of a role. I wouldn't say no role, but not much of a role in terms of the management of poisoning.

DR. CANTILENA: Thank you.

Curt, was that an adequate discussion for that point?

DR. ROSEBRAUGH: Yes.

DR. CANTILENA: Okay. Let's move on to the next one, which is, is the availability of emergency medical treatment, rural versus urban, clinically relevant to whether of syrup of ipecac is used for gastric decontamination? I guess the people who say that it has no role, I think I know your answer. But for everyone else, we can just go around. Basically what we're asking here is does it make a difference to you. Does it impact your opinion on the use of ipecac whether you're in the rural environment or urban environment? And we'll have a yes/no vote on this, and we'll start with Dr. Lam.

DR. LAM: I will say no, there's no evidence that there's any difference between whether it's an urban environment versus a rural environment.

DR. PATTEN: I would not completely reject any differential. Although distance doesn't impact efficacy, time may. And there is some information in the literature, as I read it, a very short interval of time, 5 minutes, perhaps not much more. And if you are 90 minutes from an emergency medical center or if you are living in a part of the U.S. that is now being so heavily impacted by cuts in funding, local government aid, et cetera, first responders or rural hospitals are taking a big hit. So whatever the situation is now, it's going to grow worse. So I would say clearly more research is needed, but it's that 5- to 10-

minute window of opportunity for people who are distant from professional care that I'd worry about.

DR. CANTILENA: Dr. Uden?

DR. UDEN: I'd say no, and my comments are in the transcript already about this.

DR. CANTILENA: Yes, but who reads the transcripts? I'm just kidding.

DR. UDEN: I don't know. I don't.

(Laughter.)

DR. CANTILENA: Dr. Wood.

DR. WOOD: I would say no, but I would supplement that by saying that I think we've got to be awfully careful about advocating ineffective therapies for the poor or the disadvantaged or rural dwellers. I come from a rural state, and we certainly try to provide the same standard of care to everybody whether they're city dwellers or rural dwellers. I'd be very concerned about the idea that we would have the children of the disadvantaged being made nauseated when we wouldn't have our own children doing that.

DR. CANTILENA: Dr. Wood, I would agree that we would never suggest doing that, and actually I'm influenced by my years of working with the poison control centers in Kansas and New Hampshire. So I do believe, for the reasons that were articulated by Dr. Patten, that there's a very

limited -- because of the time factor and because of the setting, there may be -- so I'll help Karen by saying that's a yes. But it's quite finite and has limits.

Dr. Davidoff.

DR. DAVIDOFF: Well, I would also reemphasize what a number of people have said, which is that it's perhaps less rural versus urban, that it is difficulties getting to care, which can be all kinds of things besides distance. And those can certainly apply in cities very easily and probably do more often than in rural areas because there are more people living in cities.

That said, I will try to be consistent with what I said earlier, and that is that deep down I do believe there are a very small number of kids who are potentially benefitted by ipecac decontamination. But those probably can be found equally in many parts of the country.

DR. CANTILENA: Dr. Williams?

DR. WILLIAMS: My answer is no, not because of urban or rural. My answer is time-oriented. I think being a practitioner here in Washington, as well as being a practitioner in rural Virginia, I think that time is of the essence in both situations. So it's a no for difference, but yes for the same reasons that we need something as an intervention on an immediate time frame for the patient and

the family.

DR. CANTILENA: Dr. Tong?

DR. TONG: Well, I'd say no here based on the fact that there are no data to show relevance, the connection there. But clearly, it's been said here about the time issue. But I'll stand by saying no because the data is not there.

DR. CANTILENA: Dr. Johnson?

DR. JOHNSON: No, I don't believe that the thought process is affected by rural or urban or time. It's intuitively attractive to sort of think that way, but I think if your assessment is that it doesn't change outcomes, it doesn't matter where the person lives or how far they are from health care.

DR. CANTILENA: Dr. Clapp?

DR. CLAPP: No, and Dr. Johnson articulated the reasons very well. I agree.

DR. CANTILENA: So the yes votes were 3, the no votes were 7 on that question concerning rural versus urban.

Now, we're actually just going to ask a question that's not really been listed for us, and it has to do with several members were talking about outcome data as it relates to adverse effects from ipecac. There were, I guess, in the data that were shown, Dr. Tenenbein, 20,000

patients who received ipecac. Was that in 2001 or 2002?

DR. TENENBEIN: Those were not my data.

DR. CANTILENA: Whose data was that?

DR. MANOGUERRA: It was about 16,000 cases in -- I don't remember if it was 2001 or 2002. 2001, about 16,000.

DR. CANTILENA: I guess what I would like to suggest to the committee and propose as a question, if seconded, would be to ask that the FDA obtain the actual outcome data on those doses, on the 16,000, or perhaps even go back for three years, and see what the outcome was from the ingestion of ipecac to see if we had a significant number of adverse events, to see exactly what -- favorable versus unfavorable, or if it really, truly made no difference. Because I know from that database there's actually quite a bit of follow-up. If you call, then you'll be called back. That's sort of a standard for the poison control centers. So there is the opportunity to obtain follow-up data. As I understand, Curt, you don't have that information. Is it just from 2001 or you don't have that information at all from any year?

DR. ROSEBRAUGH: I don't think we have it at all.

DR. CANTILENA: So my proposal would be that we ask FDA to obtain that and to use that information to track

actual outcome. If you think about OTCs, as has been said, the reporting of adverse events is relatively low for the OTCs. But here, I think you have an advantage in that at least when ipecac is administered at the recommendation of a poison control center, there's always a follow-up call. Obviously, it isn't 100 percent follow-up, but it's pretty darned good. So I think unlike an OTC drug that would be used where it's totally voluntary, at least there's an opportunity here for active follow-up.

So my proposal would be to the committee to offer the question to the committee whether or not we should recommend that they obtain that follow-up and use that information as they assess the adverse effects from ipecac.

DR. WOOD: I don't understand that question.

DR. CANTILENA: Okay, the question is --

DR. WOOD: Let me just develop it. The database is going to be 100 percent of the people who got it. Is that what you're saying? And what are you going to compare that to?

DR. CANTILENA: Part of the criticism was that the adverse effects of ipecac are under-reported because it's an over-the-counter drug. My position is that it's not your usual over-the-counter drug in that you have active follow-up that occurs in a very high percentage of

people who actually are exposed to the drug when it's recommended by the poison center, which is the vast majority.

So you have an opportunity basically to complement the adverse event system that exists, which is under-reported, we know vastly under-reported. Now you have the opportunity to at least look at a more complete, in terms of outcomes -- we're not saying that we just want to know if they had vomiting. That's also reported. But we want to know exactly what happened. Did they have to go to the hospital anyway? What was the outcome? Were there serious adverse events? I think it's information that I would certainly like to see.

I would have liked to have had that information here for this meeting because when you had raised the question sort of characterizing this as a high toxicity drug in terms of an OTC, and I'm saying that we have a situation we should take advantage of so when the FDA takes our advice internally, I would like to recommend or at least ask the question to the committee if they would like to have the FDA consider that as a source of information regarding adverse events and outcome.

DR. TENENBEIN: May I interject a point of information?

DR. CANTILENA: Yes, Dr. Tenenbein.

DR. TENENBEIN: It's my understanding in discussion with Dr. Manoguerra that the adverse effects of ipecac are not systematically collected during those follow-up calls. The data that are specifically collected are the adverse effects of the poisoning. So although some of those data may be collected, it would be under-reporting.

DR. CANTILENA: But you would agree with me that it is active collection of data. It's not like we're just relying on spontaneous reports for over-the-counter drugs like aspirin or ibuprofen.

DR. TENENBEIN: It's prospective collection of data but not the data that you're interested in.

DR. CANTILENA: Well, but there is outcome data. You do ask what happened to the subject.

DR. TENENBEIN: In the sense of did they suffer toxic effects from the presumed poison, yes.

DR. CANTILENA: Right. I think that's valuable personally.

DR. TENENBEIN: We know all of those patients do well. We know that because they're not dying.

DR. CANTILENA: No, no. I'm not saying we're looking for mortality. I'm saying we're looking for additional information regarding outcome.

DR. WOOD: Let me justify what I said. I said

this was one of the most toxic over-the-counter drugs. And I don't think we need any more information to know that. I challenge you to come up with a drug that produces 95 percent nausea and vomiting in patients that's available over the counter. I'm not sure that we need the FDA to spend a lot of time coming up with a bunch more information. I can't conceive of how we're going to get data that helps us with that.

DR. CANTILENA: I guess that's the first time I've heard you ask that we not look for more information.

(Laughter.)

DR. CANTILENA: Especially if it's free or if it just involves Curt's time, which he has plenty of time to do this.

(Laughter.)

DR. CANTILENA: I'm really actually surprised by that because if we were about to approve an over-the-counter analgesic and we had an opportunity to say we're going to say -- we actually have a system in place where we phone everyone who took a dose of this drug to see what happened to them, I think this committee in the past would be quite enthusiastic to at least have that information looked at. So I'm somewhat surprised.

We have one comment from Dr. Silber, and then I believe there's someone here from the American Association

of Poison Control Centers who has a comment as well. Dr. Silber.

DR. SILBER: My comment is that there are two aspects to information gathering. One is the information that can easily be gathered and another one is the information that is necessary to be gathered. The problem here is that those individuals who use ipecac and actually abuse ipecac in a secret or surreptitious way are the ones that we are most interested in learning about the magnitude of the issue. And the problem here is this is going to be very difficult to obtain. Not that it shouldn't be done.

But the issue that I'm wrestling with in my mind is the following. Is it worth it to put out the effort to gather exact information about something that is very dangerous or may it be worthwhile to take protective measures without the complete data? I don't know how long it would take to do the study that I'm advocating.

DR. CANTILENA: I think you may not have understood what I was asking for. This really doesn't address the abuse population. This addresses the adverse event population. The data is already in hand. It exists. It's already on file and we just have to obtain it and analyze it.

DR. SILBER: No, no.

DR. CANTILENA: So it doesn't address your

population.

DR. SILBER: I know. I understood it. What I meant by that is even if we get all that information, in a way it would be incomplete if it's not presented in the context of the total population, what's the numerator, what's the denominator, in other words. This may be a specific segment of people who are exposed to ipecac. It may be useful, but it should be analyzed in the context of the general situation.

DR. CANTILENA: Thank you.

Is there a comment from the American Association of Poison Control Centers?

MS. SOLOWAY: Yes, thank you, Dr. Cantilena.

DR. CANTILENA: Your full name, your association --

MS. SOLOWAY: I'm Rose Ann Soloway, and I'm Associate Director of the American Association of Poison Control Centers.

DR. CANTILENA: Any conflicts?

MS. SOLOWAY: None that I know of.

DR. CANTILENA: Okay.

MS. SOLOWAY: I wanted to make one point of clarification about the data that you referred to, the Toxic Exposure Surveillance System data. It's been referred to several times today and especially in the

context of the 16,000 cases in which ipecac administration was carried out in calendar year 2001. These are cases that were managed by poison centers or about which poison centers were consulted.

But the very specific point of clarification was about the clinical effects and adverse effects that can be learned about on follow-up. When cases are followed up, not only are clinical effects, if any, associated with the poison exposure categorized, there's also an opportunity for the poison center staff to categorize adverse effects due to treatment. So in cases where ipecac was administered, if there were adverse effects as a result of the ipecac, as opposed to a toxic effect of the substance involved, they would be captured separately.

Thank you.

DR. CANTILENA: Thank you very much.

DR. UDEN: Dr. Cantilena?

DR. CANTILENA: I'm sorry?

DR. UDEN: Before she goes, can I ask a follow-up, please?

DR. CANTILENA: Sure.

DR. UDEN: So is that information gathered by somebody in the poison center in asking questions, do you have muscle aches and pains, are you weak, are you tired? How is that information -- is that just volunteered by the

family that you're calling, or do you actually proactively ask certain things?

MS. SOLOWAY: It depends on the situation, quite frankly. There are about 130 clinical effects available to be coded, and so whether the information is entirely volunteered or elicited as a result of questioning really would depend on the circumstances of the exposure.

DR. CANTILENA: Thank you.

We have Drs. Clapp, Ganley, Davidoff, Johnson.

DR. CLAPP: If you are going to pursue finding out more specifics about the 16,000, I think what would be relevant to our consideration is to assess whether or not there was a true clinical indication for use of ipecac with that 16,000. We can find adverse effects, we can find out if they vomited, but if we don't know whether or not it was advised for a spurious reason or a reason that could have been managed without ipecac, then we won't have a true assessment as to even how appropriate it was to use it. So I would like to have an addendum to your interest to add that we find the clinical indication to the use of ipecac in the 16,000, but then not only have that, but determine as to whether or not it was appropriate.

DR. CANTILENA: I know that information is collected in terms of indication. Dr. Tong or perhaps the individual from the American Association, can you tell us

if there's a scoring or an evaluation of the appropriateness of the recommendation? Is that already automated or is that something that would have to be done in addition?

DR. CLAPP: If I can interject, for example, with the example of the mushrooms, if they're advising use of ipecac for mushrooms in Arizona, if they didn't have the ipecac -- was that an appropriate recommendation? I think we need someone to determine whether or not, in fact, the advisement of ipecac was appropriate in the circumstance of the poison control center or have an algorithm that they use.

MS. SOLOWAY: The short answer to that question is that those data are not gathered as a part of this process. Those would be issues addressed in the quality assurance program at a poison control center level.

DR. WOOD: Is that right? I mean, what we heard earlier was that the poison centers were likely to come out with a recommendation that ipecac shouldn't be used. Let's just take that for the moment. Then wouldn't the answer to her question be that there would be no indication?

MS. SOLOWAY: Well, I don't feel comfortable speculating on behalf of the organization --

DR. WOOD: I understand.

MS. SOLOWAY: -- since we don't have a policy at this point. However, if the consensus view was that it was not indicated, then that is information that individual poison centers would need to communicate to their own staffs and incorporate into their protocols.

DR. WOOD: Well, let me turn the question around. If the San Diego poison center has a position that says it shouldn't be used, presumably the national organization has not struck them off. So they can't right now have operating procedures that say when it should be used. Otherwise, they're out of compliance.

MS. SOLOWAY: There are in fact no operating procedures at the national level right now, and part of it is because of the very kind of discussion you're having today. There are people who are evaluating the same information and reaching different conclusions.

DR. WOOD: Sorry. I know I'm pushing you. So, therefore, the answer to the question, will you be able to evaluate if the indication was appropriate, is no. Because if you can have such diverse indications where one group doesn't use it at all and one group uses it widely in Seattle, I don't see how you can have an approved indication within your organization that would allow you to come up with an answer that says it was appropriate or it wasn't appropriate.

MS. SOLOWAY: Well, as I said, those data are not part of the national data collection process, and they are part of the quality assurance process in individual poison centers not at the national level.

DR. CANTILENA: Drs. Ganley, Davidoff, Johnson, Wood, unless you jumped ahead actually, Alastair.

DR. GANLEY: I think Dr. Clapp made the point that I had an interest in because everyone has been struggling, is there a population out there, and actually looking at some of that data may give you a sense that there may be a population out there that it did have effect on. I think it's difficult to make that determination without looking at the data of the people who did receive ipecac and who recommended it, when it was given with regard to the ingestion and things like that because it seems clear that there's an appropriate time to give it. And people question whether it's an outcome-based or a surrogate-based benefit here. So I think that data may be important to look at, and I think Dr. Clapp had covered that in her comments.

DR. CANTILENA: Thank you.

Dr. Davidoff.

DR. DAVIDOFF: Yes. It seems to me that there's quite a bit of agreement that if there is efficacy for ipecac use, it is in a fairly small population now, and

even that's in some doubt. And the toxicity of ipecac itself is also sort of an uncertainty. And it strikes me that the action that the San Diego poison center took was courageous and reasonable in many respects, but in some respects it's disappointing because it seems to me that that group was in a position -- any poison center is in a position now -- to actually conduct a prospective study -- and I don't think it would take all that long, particularly if there was a multicenter study and the recruitment numbers went up rapidly -- once the potential eligibility for reasonable use of ipecac was established on the phone, that the patients were randomly assigned to get ipecac or not. And then prospectively the data were collected on both outcomes of the poisoning and of the potential toxicity of ipecac.

That, it seems to me, would be actually ethically probably more defensible than just plain stopping it without having the data in hand to know what the outcomes were likely to be. It seems to me that that would be certainly acceptable ethically from the point of view of what's known now about the potential efficacy or lack of it and potential toxicity or lack of it because there's equipoise.

It doesn't seem to me the FDA needs to be in a huge hurry to make this decision, and waiting 6 months or

whatever it might take to do that study might be reasonable. I know the FDA can't go ahead and suggest that such a study be done, but I'd like to suggest it because it seems to me if we came together in this room with those data, we'd be in a lot better position to make these decisions.

DR. CANTILENA: Thank you.

Dr. Johnson.

DR. JOHNSON: With regard to the question you're posing, I guess I have sort of two views. One is that adverse effects is really kind of a relative thing and what's acceptable in terms of an adverse effect is related to the efficacy. So toxicity with an antineoplastic that's acceptable would be totally unacceptable in an antihypertensive. In the absence of efficacy, anything that occurs is a toxicity. So from that perspective, I would sort of agree with Dr. Wood that we have a 95 percent toxicity rate for this drug.

But if you want to sort of push that view aside, then it would seem to me that if you're going to request such data in the 16,000 who got ipecac, standing alone, it would be hard to assess that so that you would, if possible, need to try to collect another 16,000 matched control group so that you could have some assessment in terms of ER visits. Again, that sounds like a great thing

to do and I'm not sure, sort of like your suggestion, why members of the poison control community have not done that if it's something that's relatively easy to do.

As it relates to the tagging of information in terms of adverse outcomes relative to the ingested toxin versus adverse outcomes from ipecac, I'm curious how things are put into one of those two boxes. I would presume that the parent would not be able to make that judgment, and so is it the poison control center person -- so this is a question to poison control center people. Is it the poison control center staff member who is making the assessment that the adverse outcome was ipecac-related instead of being related to the ingested toxin?

DR. CANTILENA: Dr. Tong, do you want to answer that in terms of a follow-up database?

DR. TONG: In direct response to Dr. Johnson, it would be our staff. It would be the individual who's talking to the mother. It's often not the individual who initially recommended the syrup of ipecac. As you know, there's a continuous flow of people in the center.

I was thinking about all the suggestions here, and it would be worthwhile if the association and all of us who are in the business wanted to do that, the suggestions I've heard around here.

I'm just reflecting back that we home manage

about 15,000 to 16,000 cases of children, and out of that large group, we'll sort out 100. And that number is declining to study, to evaluate, to come back to this committee in a year or two years. It may be a situation in our center where ipecac will not be used, but it would be worth looking at if we want to pursue the study. But I know that the association and academy has a lot on the table, primarily trying to stay open. Poison centers like in Arizona.

DR. CANTILENA: Yes, a comment, Dr. Manoguerra.

DR. MANOGUERRA: In my presentation this morning, I mentioned that we had looked at our referral patterns during the time that we used ipecac, and we did this a few years ago. We looked at 10 years during the time period we used ipecac and we looked at 10 years after we stopped using ipecac. And there was no difference in the percent of cases that we had to refer to the emergency room before and after. So I think that's kind of what you were getting to. It's not a controlled situation.

One of the things that I have asked for for the consensus panel's deliberations is similar data from the AAPCC looking at referral patterns in children who were given ipecac versus those that weren't to see if there's a difference between the two groups.

DR. CANTILENA: Dr. Wood?

DR. WOOD: Well, I'm always pleased, Lou, when I can astonish you. I want to come back to that in a second.

I want to sort of put the three poison center directors on the spot and make sure that we're understanding this right. As I understand your positions, is there a specific subgroup that you feel there's data-driven indication for ipecac? My understanding from each of you is that your answer to that is no. Am I wrong? Am I misunderstanding that?

DR. MANOGUERRA: That's my answer. I don't know of a group where I would consider using ipecac.

DR. TONG: Dr. Wood, I said no.

DR. WOOD: Okay.

DR. CANTILENA: But in fairness, Dr. Robertson said yes, and he's not here right now.

DR. WOOD: Well, he presented a lot of anecdotes, but he certainly didn't present data to support that position.

So I'm worried that we are sort of sitting around this table divining subgroups that we might be able to imagine would benefit when the three poison center directors are unable to define one. So if there isn't a data-driven group that they can define, I'm unclear how anyone can define such a group. That's the first thing.

And then the second point, Lou, is that you were astonished when I said I didn't think we should send the FDA off to waste Curt's time collecting more data. Although it's easy to waste the government's money, I guess, the reason I'm somewhat hesitant or very hesitant to do that is that I think if we lack evidence of efficacy, as Julie said, then the risk/benefit ratio becomes infinite. So we certainly know the risks of vomiting. That's well described. If we have zero evidence of benefit, then it's not the same as an effective analgesic that we're about to approve. It's quite different. It's a drug for which we appear not to be able to demonstrate benefit for which we know toxicity. So I don't need a lot of additional data to make a decision on that.

DR. CANTILENA: I understand exactly where you're coming from, and in the next question, we're actually going to address that specifically. And if you say no efficacy, then it's the end of the conversation. But we'll talk about that in just a minute.

Dr. Davidoff, did you have a comment?

DR. DAVIDOFF: Yes. Alastair, I think in fairness you're making the statement that there's no evidence of efficacy, but I think the fairer description of the situation for home use of ipecac is that there's an absence of evidence. It's not there's evidence of absence

of effect. So I think that you can't really make the claim quite as strongly as you've made it.

I would agree with you from what I've seen that if there is efficacy, it's probably limited to a very small group that is yet to be defined, if it is there. But we don't have the information because no one has really tried to approach the study of that, and it's going to be really tough to study. I do think the poison control centers could be in the position to try to get close to that information, but I don't think it's entirely fair to say there's no evidence for efficacy.

DR. WOOD: Yes, that may be right, but no evidence for efficacy in a setting, if this was vitamin C, would be different from no evidence of efficacy where we produce harm.

I said it before, but we're a lot more cavalier doing things to children than we are in asking for consent from adults. Just think of how we expect children to be vaccinated compared to the adults stepping up to the plate for vaccinations recently.

So I think you're right. Absence of evidence is not the same as evidence of absence, but here we've got a drug which clearly produces toxicity, clearly has the potential for abuse and absence of evidence in that setting is very disturbing.

DR. CANTILENA: So if I could, let me make the motion that the FDA obtain from the American Association of Poison Control Centers data on the exposures over one, two, or three years, whatever is reasonable, for people who have had syrup of ipecac. Let me modify it and say, if feasible, that they obtain exposures of the same substances in cases where the poison center did not recommend ipecac and see if there's a difference in outcomes in retrospective fashion and that they use that information to help them internally as they look at this issue of over-the-counter status.

So that's a rather lengthy motion. I apologize. Is there a second?

DR. WILLIAMS: Second.

DR. CANTILENA: Any discussion? Dr. Clapp.

DR. CLAPP: Sorry. My perspective is not necessarily getting a control group of the same ingestion that didn't receive ipecac but having a group of specialists or experts review the appropriateness of the advice to receive ipecac because that colors the perspective as to whether or not the 16,000 were -- I'm not hearing an algorithm. I'm not hearing anything.

DR. CANTILENA: The only reason that I omitted that was not to ignore your comment, which I think is excellent. It's just that I feel that we would not be able

to achieve an agreed-upon set of criteria for the appropriateness.

DR. CLAPP: If you have a child who has a certain weight and got two extra strength Tylenol and someone ipecaced them, you can tell whether or not that was appropriate or inappropriate advice.

DR. CANTILENA: Actually I'm hearing that there would be a difference of opinion. The only one that I would say is if the child ingested nothing and was told to take ipecac, everyone would say that was not appropriate.

DR. CLAPP: I see what you mean.

DR. WOOD: But if none of us can agree on the indication, how can we have a drug for over-the-counter use?

DR. CANTILENA: Stay tuned for the last question.

Any further discussion on the motion?

(No response.)

DR. CANTILENA: Then I would like to ask the question then, and this will be a yes or no vote to have the FDA obtain that information and look at it in that fashion to try to add to the information that they have to help them with their ultimate decision on this issue. And we can start with Dr. Lam.

DR. LAM: I guess if you strictly look at the

wording, should ipecac syrup retain OTC status for use by consumers to treat accidental poisoning --

DR. CANTILENA: Dr. Lam, this is not the ultimate question. There's a motion on the floor to have the FDA obtain additional data from the American Association of Poison Control Centers to analyze it. That was the motion. I'm sorry. You jumped ahead.

DR. LAM: So whether they should or not?

DR. CANTILENA: Yes.

DR. GANLEY: Lou, can I just --

DR. CANTILENA: Yes.

DR. GANLEY: It may be better to put it in the context of question number 3 where it asks for the risk/benefit and someone's response may be that we would like to see the information on 16,000 as their answer. But I think there are already some folks who have made their mind up, and there are others who may say, I can't make that decision unless we get that additional information. So I'm not sure that taking a vote on this is going to help us much. I think question 3 is important to answer, and then part of that answer may be I'd like the FDA to try to get some of that information of the 16,000 before I would make a decision or they may say I don't think it's important to get that information and I can make a decision here.

DR. CANTILENA: So you would like to do a yes/no in terms of 3 as written, and then as a qualifier to your answer include whether or not you want additional data?

DR. GANLEY: That may be part of the answer. Right.

DR. CANTILENA: Is that agreeable to the committee, or do you want to do the vote on the floor? As part of the vote? As part of the question? Who is in favor of rolling the qualifier in for the question that was just articulated concerning additional information from the American Association of Poison Control Centers? Who would like that rolled in as part of your qualifier for your answer for number 3? A show of hands.

DR. WOOD: Isn't the issue if the answer to 3, is the evidence available, is no then Charlie's question becomes relevant. If the answer to 3 is yes, meaning that the evidence is available to make that distinction, then you don't need --

DR. CANTILENA: Right, but actually question 3 will be split into several parts, and that's what we were talking about before on the break, to help to separate out those who are interested only in the surrogate versus those who are interested in only the outcome. So I think it makes a difference in terms of whether or not the committee

feels it's relevant or important for the FDA to consider this available data from the American Association.

DR. GANLEY: Lou, I think in terms of Alastair's way is a good way, but to put in the caveat that we talked about earlier, there are clearly some folks that look at benefit in terms of outcomes and others who look at it in terms of some surrogate whether it be decreasing blood levels. And in their answer, they could give the reasoning for that. We don't need to take a vote on each individual thing.

Also, on the safety side, you could look at it as the adverse events related to the intrinsic effect of the drug, whether it be a Mallory-Weiss tear or not, versus the safety of it with regard to abuse and misuse. So they can mix all that in. We don't need an answer for each individual question on that. People, I think, have had enough discussion and they can give the answer and then break it down in how they arrived at their benefit and how they arrived at their safety assessment.

DR. CANTILENA: All right, but I guess my point is I would like to make a case, if you will, for looking at this available data that sits there by the American Association of Poison Control Centers, and I feel that if we do it that way, there's an opportunity for that not even to be mentioned in all but a couple of the responses. So

that was the motivation for setting that aside as a separate question.

So do you strongly object to that approach, I guess is my question to you, Charlie and Curt. Because I would rather have that as a -- and you can say yes/no or only if this is going to go forward.

DR. GANLEY: I think Alastair had it right. If you think there is enough data and you can make a decision, then you don't need that 16,000, but if you don't think there's enough data and you want that, I think it can incorporate it into that question.

DR. CANTILENA: Right. But hypothetically you're going to get an answer to question 3 which is not unanimous and the point of my asking this question --

DR. GANLEY: That's okay if nothing is unanimous.

DR. CANTILENA: Right.

DR. GANLEY: I think the discussion is more important than a vote is the best way for me to say it. The discussion of how people think and arrive at an answer is more important than taking a vote.

DR. CANTILENA: So Charlie is avoiding a vote and Alastair is avoiding data. This is truly an historical meeting.

(Laughter.)

DR. CANTILENA: This is an historical occasion.

DR. GANLEY: You're taking a vote on number 3, but the discussion of how they arrived at that is as important as their actual vote. That's I think the best way to characterize it. It's an important to get an opinion, but I think the discussion and understanding how people arrived at that decision and whether they think it's important to have the additional data is the best way I can characterize it.

DR. CANTILENA: All right. Well, let's phrase it this way. Let's look at question 3 and let's say, is the evidence available adequate to establish the risk/benefit ratio of syrup of ipecac for over-the-counter use?

When you look at the question of benefit, I would like you to answer it such that the efficacy side that you're concerned about, that you're using to base your answer, is either the surrogate marker for decreased absorption or for ultimate outcome. If that's what you're using to establish your assessment of the benefit, I'd like you to state that either way. In terms of risk, I'd like you to talk about the risk that you're concerned of, the adverse events versus the abuse factor.

And then if there isn't adequate evidence, you can then comment on the kind of evidence that you'd like to

see. Dr. Davidoff's point of a prospective study I think is quite good. I don't know who would fund that study and what the impetus would be, but that would obviously be something that we'd like to see.

So as we look at this, we'll go around and we'll talk about the benefit. If the committee states or if you're saying that there is no benefit, then basically you're saying this product should be removed from the market. OTC or Rx, it should not be out there. So that's what the regulatory translation will be of a statement of no efficacy. So that's why it's important for you to specify what marker or what variable you're using to determine efficacy.

So let's first do efficacy, and we'll start on this side with Dr. Lam. If you can say whether or not the evidence available in the literature is of adequate quality and quantity to establish the benefit, that is, efficacy, of syrup of ipecac and state whether or not you're using the ultimate clinical outcome versus the surrogate marker for the efficacy variable.

DR. LAM: In my opinion, there's no efficacy and that is based on the ultimate outcome.

DR. CANTILENA: Dr. Patten?

DR. PATTEN: I do not think that efficacy has been established or unestablished at this point. I look to

the clinical summary that we have where we learned that in animal studies it has been efficacious in removing up to 60 percent of an ingested substance, and in clinical studies the range is between 28 and 83 percent of removal of the ingested substance. We're told clearly that effectiveness dissipates over time. So I put all of those things together and I come back to this initial period and I wonder to myself if it is not, indeed, important in some instances to remove that toxic substance as soon as possible.

I think another important thing to look at here, we are told that most studies exclude the use of ipecac syrup in life-threatening intoxications. So it's difficult to determine the benefit of ipecac syrup in those situations. There's no information there.

DR. CANTILENA: So it's not a yes or no. It's an either.

DR. PATTEN: Yes, I think it is not established. Lack of efficacy has not been established.

DR. CANTILENA: So it's a no. Okay. Sorry. I misunderstood.

Dr. Uden?

DR. UDEN: Mine would be a no and it's based on -- not that ipecac doesn't cause vomiting. It does. But it's based on the ultimate outcomes, and it's also based on

what I've heard from poison centers not using ipecac anymore and Canada and Europe not using ipecac at all anymore. I think the data that we were presented, the seven studies -- there are holes in that data. Clearly there are holes in that data. But if I look at the big picture, given that information, I would have to say no for efficacy.

DR. CANTILENA: Dr. Wood?

DR. WOOD: I would say no. The endpoints I'd use are both the surrogate endpoint actually and the ultimate endpoint. I think the evidence that it makes a significant difference to the surrogate endpoint in terms of exposure is limited and not convincing, and I think there's an absolute absence of any evidence of efficacy in terms of improved outcome.

DR. CANTILENA: Thank you.

I would actually say my view of the surrogate data is that there is efficacy. I basically try to standardize my approach to this question with other applications that we've had where we've approved drugs for over-the-counter status based on a p value and a very small effect size. While the range for the effect size for removal or the absorption includes 0, the central tendency is always positive. I think that's an effect size. So based on the surrogate, I would say it is effective. Based

on the ultimate outcome, I will say we have insufficient data.

Dr. Davidoff.

DR. DAVIDOFF: Well, I may have misunderstood how this question is being framed, but if we are talking about the risk/benefit ratio, is there sufficient evidence to make a judgment about the ratio, I would say there's clearly sufficient evidence to decide that the risk/benefit ratio is severely unfavorable for the use of ipecac. Even though there may be some efficacy in a small subgroup, the potential risks across the board are far -- it seems to me the evidence is quite clear that they far outweigh the potential benefit.

DR. CANTILENA: That's sort of the ultimate question, but here we're trying to help FDA in terms of dissecting out safety versus efficacy issues first and then ultimately --

DR. DAVIDOFF: I'm sorry. So the question is being more narrowly framed now on efficacy.

DR. CANTILENA: Right, because if it's not efficacious, the regulatory options are it's off the market, regardless of OTC or Rx. Then really the fourth question is risk/benefit.

DR. DAVIDOFF: But I thought we had already talked about efficacy a long time ago.

DR. CANTILENA: We have but we haven't actually individually expressed our opinion in terms of the surrogate versus outcome and whether or not you're convinced about either one.

DR. DAVIDOFF: Okay, sorry. Well, I'll restate it. I think there is not adequate evidence to rule out efficacy in probably quite a small subgroup.

DR. WILLIAMS: I do not believe that there's enough evidence to firmly establish efficacy, and I think more study is definitely needed especially in the real-world circumstance of people who are using it on a daily basis, not anecdotal decisions of administrative policy.

DR. CANTILENA: So there is not adequate evidence.

DR. WILLIAMS: No.

DR. CANTILENA: Dr. Tong?

DR. TONG: My answer would be no. In terms of benefit, I see it as a surrogate marker of the indication that there is removal. I can't base benefit on outcome for all the reasons that we've already talked about.

In the risk balance, I don't consider an adverse effect emesis.

DR. CANTILENA: We're just doing efficacy now.

DR. TONG: Okay. The answer is no.

DR. CANTILENA: So the answer would be no,

insufficient efficacy.

Dr. Johnson?

DR. JOHNSON: My overall answer is no. I think there is probably some evidence suggesting that it's efficacious in terms of reducing plasma concentration of the ingested substance, but I view that as being somewhat akin to a finding that's statistically significant but not clinically significant. I don't believe there's any evidence for outcomes being affected, and while it's clear that we don't have perfect data, I also don't believe that there's an absence of data. We have some data, and none of those point to a difference in outcome. They may not be sort of well-designed trials, but the data we have suggest no evidence for outcome. It would seem that the drug has been used long enough and widely enough that if there was clear outcome differences, we would see those.

DR. CANTILENA: Dr. Clapp?

DR. CLAPP: No, and that's based on the clinical outcome.

DR. CANTILENA: Comments by Dr. Blewitt. You're non-voting, but would you like to comment on the question of efficacy?

DR. BLEWITT: I'll repeat my earlier comments that the surrogate data would appear to be supportive, but the database is lacking in outcomes research studies.

DR. CANTILENA: If I'm correct, Dr. Davidoff, you voted that there was evidence of efficacy but only in the case of a surrogate?

DR. DAVIDOFF: No. I voted that the evidence is inadequate to rule out efficacy.

DR. CANTILENA: I don't know if that's a yes or no. It's inadequate to rule out efficacy, so there's efficacy?

DR. DAVIDOFF: No. No, you can't claim there's efficacy. It's like proving the null. It's very difficult.

DR. CANTILENA: So we would count you as a no.

DR. DAVIDOFF: No on the specific question of efficacy or on the adequacy of the evidence?

DR. CANTILENA: Efficacy, by either surrogate or outcome data.

DR. DAVIDOFF: The question is, is there evidence for efficacy? No, there is not evidence for efficacy, but I will add as an addendum there's not evidence to rule it out.

DR. CANTILENA: Okay. So there's data lacking. I'll categorize that as a no, and then you guys can sort that out. So it's 1 yes and 9 no. That was 3a.

Now, let's look at the risk side. Obviously, for those of you who feel there's no efficacy, we know your

answer to the question, question 4. But we would like a discussion in terms of risk. Is there adequate evidence of risk, and if so, which troubles you the most? Is it the adverse event? Is it the abuse? Is it the combination or other factors?

So let's start over on this side. Dr. Clapp, looking at adverse events, looking at sort of the risk side of the risk/benefit component.

DR. CLAPP: Having recollections of ipecac-induced emesis from residency days long ago, that's a different type of emesis than your gastroenteritis emesis. It's very forceful, hard retching. It's quite agonizing for the recipient of ipecac from my anecdotal recollection. But I do consider vomiting is not an innocuous phenomenon for the person who's vomiting. It's an unpleasant phenomenon. I'm also concerned about things like Mallory-Weiss tears, I think the more common things that you see from hard retching.

But in addition, I don't know if you want me to discuss this, but I think the availability of ipecac and the rise that we see in young women who are anorexic poses a greater risk perhaps than the actual risk from the medication being used for the intended purpose of gastric decontamination. And that concerns me, the availability, because I'm not convinced that the efficaciousness makes it

something to keep on the market.

DR. CANTILENA: Thank you.

Dr. Johnson?

DR. JOHNSON: I would concur with Dr. Clapp that the thing that concerns me the most is the abuse of the product and the adverse effects that result from the abuse of the product. That doesn't mean to say that I don't believe that the adverse effects from the intended use or the therapeutic use of the product are not important, but I think in the big picture the abuse issues are of greatest concern from an adverse effect perspective.

DR. CANTILENA: Dr. Tong?

DR. TONG: Well, I've found that the adverse events from the use of syrup of ipecac in the home to be very low. In terms of the misuse problem, I think it's serious, but the magnitude of the abuse/misuse is unclear and uncertain.

DR. CANTILENA: So overall then you think that there is significant evidence available for safety concerns, which is the risk side of the equation.

DR. TONG: To use in the home management of stomach emptying.

DR. CANTILENA: Thank you.

Dr. Williams?

DR. WILLIAMS: My view is the same, that I do

acknowledge that there is a risk for the abuse. However, with the label of the product, I think that we still would have safety. Efficacy, I don't have the information.

DR. CANTILENA: Dr. Davidoff, evidence of safety concerns, elevated risk?

DR. DAVIDOFF: I think there's quite clear evidence of safety concerns. The exact magnitude again remains to be defined, but I think that the potential numbers of abusers among what is often characterized as the epidemic of anorexia/bulimia is very substantial. I certainly can't disagree with Alastair's forceful point and Dr. Clapp's and many other people's comments about the toxicity of the drug when used as part of its sort of therapeutic effect. So it seems to me that it is pretty clear that even though there might be some subgroup in which there is some efficacy, I think that the evidence is quite clear that the risks and toxicities potentially outweigh the benefits.

DR. CANTILENA: My vote would be yes, that there is evidence of significant concern, and I think here is where I would encourage the FDA to look at other sources of information, such as we almost voted on regarding the AAPCC information database regarding outcomes for individuals who were exposed at the recommendation of the poison center.

Dr. Wood?

DR. WOOD: Yes, I think there's evidence. I'm concerned about all three areas of toxicity. I'm concerned about the abuse potential. I'm concerned about the toxicity from its primary pharmacological effect, and I'm concerned about the toxicity that occurs from other causes as well. I'd just echo what Dr. Clapp said. Vomiting from ipecac is a pretty dramatic kind of vomiting. It's not just feeling a bit nauseated. These people really throw up vigorously.

DR. CANTILENA: Dr. Uden?

DR. UDEN: I really don't have much to add. I do believe that there is risk. The magnitude in terms of poison centers' data, 16,000 individuals were recommended to have it, so at least we know a ball park number there and have no clue of what the number for the anorexic/bulimic population is, and I'm very concerned about that.

DR. CANTILENA: Dr. Patten?

DR. PATTEN: I agree that there is evidence of risk and my greatest concern would be the risk associated with abuse.

DR. CANTILENA: Dr. Lam?

DR. LAM: I think the risk associated with appropriate use of ipecac syrup is probably small, even

based on some of the anecdotal case reports. The major concern obviously would be what has been iterated so many times, is the potential abuse by some of our teenagers, especially the female teenagers, because they either are not aware of or chose to ignore the potential problem with chronic usage of the ipecac.

DR. CANTILENA: And comments from Dr. Blewitt on the question?

DR. BLEWITT: No, I don't have any comments.

DR. CANTILENA: So the vote is 10 say that there is risk or safety concerns; 0 say no.

The last question basically is should syrup of ipecac retain over-the-counter status by consumers. If I could just ask the FDA to review for us sort of their options chart. They had an options chart that they were developing earlier. If the efficacy is nonexistent, then the drug would not be available by either prescription or over-the-counter. Would you run through the options in terms of safety concerns, yes/no, just so we are able to have a fully informed vote in terms of OTC status?

DR. ROSEBRAUGH: We were having a side conversation. You wanted to go over this chart? Is that what you're asking me?

DR. CANTILENA: Just the options. The only part of the conversation that I share with the committee is

that if the vote is for no efficacy, or if you're feeling is no efficacy, then there's no role for this in either OTC or Rx. So you're basically going to remove it, or one outcome would be that you could remove it from the marketplace for safety concerns in the face of no efficacy. Then you had other scenarios where you had yes for efficacy and yes or no for safety in terms of what the possible outcomes were, so that we know that if we say no OTC, we would have an idea of what the other options were.

DR. ROSEBRAUGH: The only reason why I'm asking, Lou, is you've already voted for the efficacy/safety issues. This is sort of like bringing the chart in after you've already had the vote.

DR. CANTILENA: Right. You don't have to show the chart, just sort of run through the options that we started to discuss at the beginning. If not OTC, what are the options for the product other than removal from the entire marketplace.

DR. ROSEBRAUGH: I think I can just summarize it, Karen. If we had rulemaking, if internally we decided that this should not be an OTC drug, so we passed rulemaking to remove it as an OTC status drug, the option to the industry would be to file an NDA for prescription use. There are several things that could occur that can get very complicated, so I'm not going to get into all of

them, but it could be a paper NDA filing where we re-review the literature that's been published and try to decide whether we think there's adequate efficacy and safety for it to be a prescription drug. We would again have to review the efficacy and safety, and we may try to find other avenues like the AAPCC to see if they have data that we could re-review.

But once again, the industry would have to file the NDA. We can't make them do that. That's something they'd have to do. So if it's not OTC any longer, the next step would be somebody would have to file an NDA.

Is that what you wanted?

DR. CANTILENA: Yes.

DR. BULL: I think what we are interested in here is getting input from the committee as to the current framework on which drugs are marketed OTC and whether or not for the average consumer who is faced with making a self-medication choice or having a self-medication option available at home as to the risk-to-benefit for what is basically use that may take place without the learned intermediary.

DR. ROSEBRAUGH: And I would just add it seems to me that whether this went prescription or not really should not enter into the thinking. Our decision should be is this an appropriate drug for OTC use, regardless of what

would happen afterwards.

DR. CANTILENA: That's a helpful clarification.

I think we're starting at Dr. Lam this time. Question 4, should ipecac syrup retain OTC status for use by consumers to treat accidental poisoning?

DR. LAM: Given all the evidence that we have, I would say no, except probably for that small proportion of patients of that population that is yet to be defined, and I don't really know how long it will take for us to define it. Given the potential adverse effects and the potential abuse potential of the drug, I would say that it should not be available over the counter.

DR. CANTILENA: Dr. Patten?

DR. PATTEN: May I ask a question first?

DR. CANTILENA: Certainly.

DR. PATTEN: Where is the general population getting recommendations from to purchase ipecac and keep it in the home? Where does that information come from?

DR. CANTILENA: Dr. Tong, do you want to comment on that?

DR. TONG: Well, it comes from a variety of sources. I certainly have seen poison control centers contribute significantly to that providing information, pharmacy organizations, pharmacies actually providing them without charge to the patients. But that activity has

diminished considerably, probably reflecting on what we've heard earlier certainly on our own experience. But I know that we work closely with other caregivers in the community who come to us and ask about advice on syrup of ipecac. Again, we've narrowed and narrowed and narrowed our providing of the information, again limiting it to a fairly narrow group of people who might need it.

I'm not sure if I answered it, but there are a lot of people out there who are doing it, and we just want to make sure that people who are giving it out are giving appropriate information on it. And the critical thing is what's on the label, which the group here and the committee previous spent a lot of time looking at the labeling. Is the labeling clear enough so that individuals understand that they must get information about the appropriateness of this use?

DR. CANTILENA: Dr. Clapp, did you have a comment?

DR. CLAPP: At routine well visits for children, the 12-month visit is where ipecac is addressed. There's a program by the American Academy of Pediatrics, the TIPP program, that gives anticipatory guidance to parents about everything from firearms to poisonings to certain types of avoidance behaviors for health and safety, water in your house, everything. On the TIPP sheet for the

12-month visit is, have syrup of ipecac at home, emboldened. This is going to take a lot of relearning for pediatricians and family medicine providers I'm sure.

The information that I read here was very eye-opening because ipecac had become of biblical proportions, and it's pretty much assumed that this is what happens at a 12-month visit. But I think that pediatrics has not reassessed it in years, and I see it's happening right now, and appropriately so with the evidence we've seen. But they'll be relearning because all the printed material that is available at this point, even if you order it today, from the American Academy of Pediatrics includes ipecac as part of the 12-month visit.

DR. PATTEN: I'm going to vote to retain it OTC and hope that this will be revisited when there is more definitive information about efficacy, about the magnitude of the risk of abuse, and so on.

DR. CANTILENA: Thank you.

Dr. Uden?

DR. UDEN: I've come a long way today and I have to say no to this question. We're looking forward to the public education, professional education that needs to be done in the future.

DR. CANTILENA: Dr. Wood?

DR. WOOD: No, I don't think it should be

available OTC.

DR. CANTILENA: Dr. Davidoff?

DR. DAVIDOFF: I also don't think, on balance, that it should be OTC.

DR. CANTILENA: Dr. Williams?

DR. WILLIAMS: I think it should retain its OTC status. However, the appropriate data should be collected to confirm whether or not this is true.

DR. CANTILENA: Dr. Tong.

DR. TONG: I feel that syrup of ipecac still meets the principles of OTCness and should stay as an over-the-counter available preparation, although I strongly encourage our academies to look at the data and to address what we've done here today because I think it is an important issue to look at the evidence and any new evidence that can be collected. But I will vote yes to keep syrup of ipecac.

DR. CANTILENA: Dr. Johnson?

DR. JOHNSON: I vote no on retaining OTC status and that's because I do not believe it meets OTC criteria because of the abuse potential, particularly in light of the relative or near complete lack of evidence for benefit of the product.

DR. CANTILENA: Dr. Clapp?

DR. CLAPP: No.

DR. CANTILENA: I'm actually going to vote yes for the following reason. It should stay over-the-counter because again, we're applying the OTCness standards I think fairly. I do accept the surrogate of decreased absorption because it does relate back to exposure. Exposure does relate to toxicity.

I am also troubled by the lack of ability to prove outcome despite all the years that it's been on the market, and I would hope that the associations, academies would be able to put together a single prospective study that showed no improvement in outcome in a prospective fashion with home use of ipecac. And that would convince me that it should not be on the market.

The vote tally for question 4 is 6 votes in favor of no, it should not be over-the-counter, and 4 votes that it should retain its OTC status.

Dr. Rosebraugh, any additional comments, any further advice that you would like from us today?

DR. ROSEBRAUGH: I think I have to digest all the advice we've gotten, but on behalf of the division and the FDA, I'd really like to express our appreciation for the thought and effort that the committee has put into these challenging questions today.

DR. CANTILENA: Thank you very much. I want to thank the committee and the FDA staff for really doing a

very nice job on the documents. One volume of high quality is a lot easier to digest than nine volumes of less than high quality, which we've had in the past.

It's also good to see Dr. Tong back after all these years. Thank you very much for all your comments. They were very helpful.

The meeting is now adjourned.

(Whereupon, at 3:45 p.m., the committee was adjourned.)