TESTIMONY
OF SIDNEY WOLFE, M.D.
DIRECTOR, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP
AND PETER LURIE M.D., M.P.H
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
DEPARTMENTS OF FAMILY AND COMMUNITY MEDICINE AND EPIDEMIOLOGY AND BIOSTATISTICS
FDA OVER-THE COUNTER ADVISORY COMMITTEE MEETING
ON ANTIDIARRHEAL DRUGS
APRIL 9, 1993

Before briefly reviewing our petition and then turning to Dr. Lurie for a review of the efficacy of kaolin, pectin and attapulgite, I would like to make two observations. First, as most clinicians would agree, oral rehydration therapy for the treatment of acute diarrhea is, historically, the most important step forward in the treatment of this disease which kills over three million children under the age of four including as many as 500 children in the United States. Similarly, the use of antidiarrheal drugs is clearly the most important step backwards in the treatment of this not infrequently life-threatening disease, both because of their lack of evidence of efficacy and evidence, for some, of harm and, as will be discussed, because they often displace the use of the definitively safe and effective treatment, oral rehydration therapy. The other point is that treating pneumonia with aspirin, to lower the temperature and possibly make the patient more comfortable, while failing to use an antibiotic to actually treat the disease rather than its symptoms is related to the idea of cosmetic treatment of symptoms of acute diarrhea without definitive treatment of the main problem, fluid and electrolyte loss. The failure of any of the labelling for the kaolin/pectin attapulgite products being discussed today to even mention the use of oral rehydration therapy confirms this point.

The World Health Organization (WHO) has recently published a report entitled "The Rational Use of Drugs in the Management of Acute Diarrhea in Children," which is a thorough review of studies of the efficacy and safety of the most commonly used antidiarrheal preparations. The report concludes, with respect to the drugs evaluated, that "Antidiarrheal drugs should never be used. None has any proven value and some are dangerous." These findings were recently echoed by the U.S. Centers for Disease Control and Prevention (CDC) which concluded that "Little evidence exists to support the use of nonspecific drug therapy in children, and much information exists to the contrary." At least ten developing countries namely Indonesia, Korea, Lebanon, Libya, Mexico, Pakistan, Peru, Philippines, Sri Lanka, and Turkey have acted more expeditiously than the U.S. in reacting to the WHO report by banning or relabeling some or all of the drugs addressed in this petition.

Ban Both Adult and Pediatric Formulations of the Following Over-the-counter and Prescription Drugs:

kaolin and pectin (Donnagel-PG and others). The WHO report concludes that "Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."

attapulgite (Diasorb, Donnagel, Kaopectate, Rheaban, and others). The WHO report concludes that "[A]ttapulgite [has] no place in the management of acute diarrhea in children and should not be used."

Charcocaps, Diasorb, Donnagel, Imodium A-D, Kaopectate, Pepto Diarrhea Control and others are available over-the-counter. Many parents may be unaware of the ineffectiveness and/or potential hazards of these drugs or of the appropriate therapy for the management of diarrhea. Parents can thus take immediate action to protect their children by no longer using these ineffective and potentially hazardous medications and using Oral Rehydration Solution (ORS) instead.

These drugs are marketed in the U.S. for the treatment of diarrhea, although there has never been any convincing evidence of their effectiveness in reducing the fluid and electrolyte losses associated with this disease. By contrast, management of diarrhea with ORS is considered one of the most important medical advances of this century. ORS is a simple, low-cost, and easily obtainable method to prevent or correct the dehydration (the loss of body fluids and salts) that often accompanies diarrhea.

There are multiple problems associated with the widespread use of these drugs in diarrhea. The CDC report has summarized these succinctly "[S]ide effects of these drugs are well known, including opiate-induced ileus (cessation of the function of intestines), drowsiness and nausea due to atropine effects, and binding of nutrients and other drugs .... In addition, reliance on antidiarrheal agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy; can interfere with oral therapy; and can unnecessarily add to the economic cost of the illness." Recently at least six infant and child deaths with loperamide were reported from Pakistan, and hundreds of poisonings in children in the U.S. have been attributed to diphenoxylate.

Review of Efficacy and Safety Data

In the following sections, we review in detail the data on the efficacy of each of these drugs, and briefly summarize the WHO's assessment of their safety. Only controlled studies have been considered, as other research designs contribute little to evaluations of drug efficacy in this setting. We believe further that all efficacy studies must be placebo-controlled. The WHO report says,

The ultimate test of antidiarrheal efficacy is the extent to which the drug checks the loss of fluids and electrolytes; thus it is also essential to measure stool weight or stool volume in clinical trials, and not merely to report on a change in stool appearance or consistency.

Drugs that have not been shown to diminish fluid and electrolyte losses under the experimental conditions outlined above cannot be considered effective. Studies that report decreases in stool frequency alone or suggest changes in stool consistency ("cosmetic" effects, according to the WHO) are also not considered acceptable evidence of antidiarrheal efficacy. This is because frequency of stool correlates poorly with fluid loss and is more reflective of whether the diarrhea is an upper or lower bowel disorder [Greenough WB, personal communication, November 23, 1992].

In the U.S., diarrheal illnesses remain among the most common problems seen by pediatricians. An estimated 16.5 million children in the United States younger than 5 years old experience between 21 and 37 million episodes of diarrhea each year. Of these, 2.1 to 3.7 million episodes lead to a physician visit, resulting in 220,000 hospitalizations, representing 10.6% of all hospitalizations in this age group. The annual incidence of hospital admissions for diarrhea in babies under 1 year old is 7.9 cases per 1000, with an average stay of 4.4 days. In day care centers in the U.S., diarrhea rates range up to 3.64 cases per child per year. Approximately 500 children (400 infants) die each year with diarrhea listed as a principal cause of death. These deaths represent approximately 10% of the preventable deaths in infants between 1 month and 1 year of age. Diarrheal deaths occur in about 1/15,000 live births or 1/500 children hospitalized.

Thus diarrheal diseases represent a considerable disease burden and cause economic loss in both developed and developing countries. By contrast, drug companies, including U.S. multinationals, continue to reap profits peddling the ineffective and often dangerous drugs named in this petition. In the U.S., the non-prescription antidiarrheal drug market was $120 million in 1990, $155 million in 1991, and is expected to surge to $170 million in 1992. Of this the best seller is Imodium A-D with approximately 50% ($60-85 million) of the market share, followed by Kaopectate with approximately 33% ($40-55 million) [Kline & Co, Fairfield, NJ, personal communication, November 13, 1992]. The sale of ORS in the U.S. was $40 million in 1990 and $55 million in 1991 [Pritech, Arlington, VA, personal communication].

ORS is effective in 90-95% of cases of acute watery diarrhea. Unfortunately, however, such proper treatment of diarrhea "remains the exception rather than the rule." In particular, studies of current patterns of diarrhea treatment have shown that a large number of pharmaceutical agents of dubious efficacy and potential toxicity are widely used. For example, 59 of 75 pharmacies in three Asian developing countries recommended drugs for the treatment of acute diarrhea.

Studies have clearly demonstrated that ORS is also little used by U.S. parents and pediatricians despite its endorsement by the American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the National Research Council. A recent marketing survey found that less than 20% of infants with diarrhea received ORS from their U.S. parents. By contrast, at least one-third of all families in the developing world now use ORS. Outmoded feeding practices like the slow reintroduction of food are still common even though available evidence indicates that continued human milk feeding during diarrheal illness results in reduced severity of diarrhea and may also decrease the duration of illness. Thus, U.S. children are far behind their developing world counterparts in the proper treatment for acute diarrheal illnesses, with ineffective and/or dangerous antidiarrheal drugs too often supplanting the use of ORS. Similar findings have been reported in Newcastle, England. There is no longer any excuse for ignoring the long-established and proven guidelines for oral rehydration and feeding of infants and children with diarrhea.

Acute Diarrhea In Older Adults

The elderly also have a substantial risk of hospitalization and death from diarrheal diseases. In the U.S., in adults aged 55 years and above, 22,430 deaths due to diarrhea were reported from 1979 to 1987. There are few studies which address diarrheal treatment issues in the elderly, but ORS appears to perform as well in older age groups as it does in children.

Before Dr. Lurie's presentation, I would like to briefly read from some of the letters to FDA and HHS which have supported our petition. The full text of these letters is enclosed after Dr. Lurie's testimony.

Peter Lurie, MD, MPH

University of California, San Francisco
Department of Family and Community Medicine
Department of Epidemiology and Biostatistics

Testimony before FDA Nonprescription Drugs Advisory Committee on the Efficacy of Attapulgite and Kaolin/pectin in the Treatment of Diarrhea

April 9, 1993

Essential Elements of a Clinical Trial of an Antidiarrheal Drug

- Randomized
- Placebo control, single ingredient
- Blinded
- Assessment of fluid balance
  - number and frequency of stools
  - stool weight or volume
  - urine volume

Author: "1974 study"

Design: Randomized, double-blind

Comparison: Attapulgite/pectin v. placebo

Subjects: 50 subjects, aged 22 - 65 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatement
d. total number of bowel movements
e. total number of cramps

FDA: "The study cannot be used to demonstrate the effectiveness of attapulgite alone."
Letter to Pfizer, 10/14/82

Author: "1980 study"

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 50 subjects, aged 12 - 75 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatement
d. total number of bowel movements
e. total number of cramps

Author: DuPont, et al. Am J Med, 1990

Design: Randomized, unblinded

Comparison: Attapulgite v. loperamide

Subjects: 194 adult subjects with acute diarrhea

Findings: Favorable findings for loperamide with respect to:

a. number of unformed stools
b. time to last unformed stool

Author: Madkour, unpublished, 1990

Design: ? randomized, ? blinded

Comparison: Smectite v. placebo

Subjects: 90 hospitalized boys < 3 years, with acute diarrhea

Findings:

a. Decreased duration of diarrhea in smectite group

b. No change in stool output (g/kg body weight)

Author: Charritat, et al. Ann Pediatr (Paris), 1992

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 113 subjects, mean age 28 months, with acute diarrhea

Findings:
1.Favorable findings for attapulgite with respect to:
    a. time to first and second formed stools
    b. time to resumption of normal diet
2. No difference between groups with respect to:
    a. mean number of stools
    b. consistency or character of stools

Summary of Studies on Attapulgite

Study	Randomized ?	Drug v. Placebo ?	Blinded ?	Asses s Fluids ?
1974 Study	Yes	No	Yes	No
1980 Study	Yes	Yes	Yes	No
DuPont	Yes	No	No	No
Madkour	?	Yes (smectite)	?	Yes (Not effective)
Charrita t	Yes	Yes	Yes	No

WHO: "Smectite and attapulgite have no place in the management of acute diarrhea in children and should not be used"
WHO Monograph, 1990

Author: Nalin and Cash, J Pakistani Med Assoc, 1970

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 49 adult cholera subjects

Findings: No difference between kaolin and control with respect to:

a. total stool volume
b. duration of diarrhea
c. time to first negative rectal swab

Author: Portnoy, et al. JAMA, 1976

Design: Randomized, ? blinded

Comparison: Kaolin/pectin v. kaolin v. pectin v. diphenoxylate/atropine v. placebo

Subjects: 80 subjects, aged 3 - 11 years, with acute diarrhea

Findings:
1. Kaolin/pectin group tended to have more formed stools
2. No difference between groups with respect to:
    a. frequency of stools
    b. water content of stools
    c. stool weight

Author: Alestig, Trollfors, Stenqvist, The Practitioner, 1979

Design: Randomized, unblinded

Comparison: Kaolin/pectin v. charcoal v. diphenoxylate v. placebo

Subjects: 204 adult subjects with acute diarrhea

Findings: No difference between groups with respect to:

a. stool frequency
b. stool consistency

Author: Watkinson, J Trop Peds, 1982

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 97 subjects, aged 3 - 18 months, with acute diarrhea

Findings: No difference between groups with respect to:

a. duration of diarrhea
b. stool water content
c. mean number of stools per day
d. maximum number of stools per day
e. change in body weight

Author: Ambroziatis, et al. ("Study 295"), 1982

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. placebo

Subjects: 213 subjects with acute diarrhea

Findings:
1. Favorable findings for kaolin/pectin with respect to:
    a. proportion of subjects with diarrhea on second day
    b. consistency of stools on second day
2. No difference between groups with respect to total frequency of stools

Author: Ambroziatis, et al. ("Study 303"), 1987

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. kaolin v. pectin v. placebo

Subjects: 508 subjects with acute diarrhea

Findings:
1. Better stool consistency for kaolin/pectin and kaolin than for pectin or placebo
2. Shorter duration of diarrhea for kaolin/pectin compared to all other groups

Summary of Studies on Kaolin/pectin or its Ingredients

Study	Randomized ?	Drug v. Placebo ?	Blinded ?	Asses s Fluids ?
Nalin	Yes	Yes (kaolin)	?	Yes (Not effective)
Portnoy	Yes	Yes (kaolin, pectin, kaolin/-pectin)	?	Yes (Not effective)
Alestig	Yes	Yes (kaolin/-pectin)	No	No
Watkin-son	Yes	Yes (kaolin)	?	Yes (Not effective)
Study 295	Yes	Yes (kaolin/-pectin	Yes	No
Study 303	Yes	Yes (kaolin, pectin, kaolin/-pectin)	Yes	No

WHO: "Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."
WHO Monograph, 1990

Summary

A. Attapulgite

- There are three placebo-controlled trials of attapulgite
- Of these only one assessed fluid balance, and in that trial attapulgite was found to be ineffective in preventing fluid loss

B. Kaolin/pectin

- There are six placebo-controlled trials of kaolin/pectin or its ingredients
- Of these only three assessed fluid balance, and in all three kaolin/pectin or its ingredients were found to be ineffective in preventing fluid loss

C. Conclusion

- Due to lack of evidence of efficacy in preventing fluid loss, both attapulgite and kaolin/pectin and its ingredients should be immediately removed from the market

APPENDIX

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER

1725 WEST HARRISON, CHICAGO, ILLINOIS 60612

RUSH MEDICAL COLLEGE

RICHARD H. SANDLER, M. D.
Director
Pediatric Gastroenterology & Nutrition
(312) 942-3034

March 26, 1993

Lee Zwanziger, MD
Executive Secretary
Non-Prescription Drugs Advisory Comittee
Center for Drug Evaluation and Reserach (HFD-9)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: LETTER TO THE FDA IN SUPPORT OF THE CITIZEN'S PETITION[1] OF PUBLIC CITIZEN REQUESTING A BAN AND/OR RELABELING OF FIVE PREPARATIONS OF ANTIDIARRHEAL MEDICATIONS

Dear Dr. Zwanziger:

I am writing today in support of the above petition. I am an academic pediatric gastroenterologist with considerable experience in diarrheal diseases here and abroad, and am director of our section at Rush University. In reference to the petition, there are a few key points that I think need to be made:

1. Diarrheal illness in infants and children in this country is, in general, a self-limited illness. There are, however, several hundred childhood deaths each year in the USA from diarrheal illness. All of these deaths are preventable with "proper therapy."

2. **"Proper therapy" means oral rehydration therapy (ORT)**, begun early and given properly.[2]

3. **Antidiarrheal drug therapy should not be used in the management of acute diarrheal illness in infants and children.** As amply documented in the literature and summarized in a WHO monograph[3] and CDC reports[4], the reasons for the above

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[1] Ahmad SR, Lurie P, Wolfe SM. Citizen's petition for a ban and/or relabeling of antidiarrheal drugs. Public Citizen, Health Research Group, 2000 P St NW, Washington DC 20036. January 7, 1993.

[2] Hirschhorn N, Greenough III WB. Progress in oral rehydration therapy. Scientific American 1991;264:50-56.

[3] World Health Organization. The rational use of drugs in the management of acute diarrhea in children. Geneva, WHO, 1990.

statement include:

(a) Antidiarrheal therapies are marginally effective at best;

(b) There may be dangers inherent in their use (a statement particularly true of diphenoxylate);

c) Use of antidiarrheals serves to divert attention from the preferable and effective therapy, ORT;

d) To the degree that anti-motility agents are effective in controlling stool output, medical practitioners and families can be lulled into thinking that diarrheal illness has been successfully treated. This impression may exist even if large amounts of fluid are "third spacing" into the bowel. This latter condition, especially in infants, might not be recognized until it is too late.

4. There may be a role for selected antidiarrheal therapy for a few pediatric patients with **chronic diarrheal** conditions.[5] Although as a pediatric gastroenterology specialist this includes a fair number of my patients, compared to the incidence of acute diarrheal episodes such situations are rare.

5. For these limited legitimate uses, pediatric gastroenterologists and pediatricians could continue to use agents such as loperamide if the FDA makes the changes urged by the petitioners. Since it is only the pediatric form of loperamide which would be banned (or relabeled), practitioners **could still prescribe the adult formulations** which can be easily crushed and placed in apple sauce, or suspended.[6]

5. I see a **dual purpose** in banning the pediatric preparations of

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[4] Anon. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. MMWR 1992;41:1-20.

[5] These chronic diarrheal conditions include inflammatory bowel disease, chronic non-specific diarrhea of toddlerhood, and short bowel syndrome.

[6] A large percentage of all medications used in pediatrics are in fact the adult formulations which are crushed or suspended in a manner such as mentioned here.

the diarrheal medications in the USA. The first is to help the children in **our own country**, and the second is to serve as an **example for third world** governments and practitioners who often look to us for guidance on what their health policies should be vis-a-vis use of various medications. Although there may be few children in the United States dying from the inappropriate use of these medications, undoubtedly there are tens of thousands of children a year in developing nations succumbing unnecessarily to diarrheal illness because of inappropriate antidiarrheal medication use (instead of ORT).

6. A final point on the efficacy of antidiarrheal drugs. None of the studies proclaiming diarrheal control efficacy of which I am aware are solidly designed. Although a rare study is randomized, double-blind and placebo controlled, the N has usually been small, and the outcome variables qualitative and subjective parameters such as stool consistency.

The number of stools by itself is not an adequate measure of antidiarrheal effectiveness, especially in pediatrics. This is so because infants often have frequent small bowel movements. A medication which decreases the number of bowel movements slightly, but does not decrease the total water loss per day, should not be considered an effective antidiarrheal agent.

Endpoints used for assessing efficacy of antidiarrheal therapy should therefore include measurement of stool weight per day. The populations should be matched by age, and if this is not done, the stool should output be adjusted in some fashion to account for the child's weight.

Because in pediatrics the risk of dehydration is great, it is important that studies of anti-motility agents also examine the risk of third spacing:

a) Such studies should address common signs of hydration status such as heart rate, mucosal membrane moistness, urine output, urine specific gravity, BUN, etc.; and

b) To assess third spacing (besides the hydration parameters), abdominal girth, discomfort, and bowel sounds should be mentioned.

I want to thank the Advisory Committee for taking the time to review this important petition. I would be happy to try and answer any questions you may have.

Sincerely,

Richard H. Sandler, M.D.,
Director, Pediatric Gastroenterology and Nutrition
Assistant Professor of Pediatrics
Rush Medical College

RHS/mmm

cc. M Shalala

unicef

United Nations Children's Fund
Fonds des Nations Unies pour l'enfance
Fondo de las Naciones Unidas para la Infancia

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212 326-7000
Telex: 175989

VIA FAX: 202 690 7203

5 April 1993

Dear Secretary Shalala,

I refer to my letter of 23 March and hope that an opportunity for us to meet will soon be possible.

The survival of young children remains a major problem in the globe, particularly in developing countries. It is estimated that 12.9 million children below 5 years of age die every year - sixty per cent of these deaths could be prevented through low-cost and effective measures. Vaccine preventible diseases, diarrhoea and pneumonia account for three-fourths of these deaths. Over three million young children still die annually from diarrhoeal diseases. Although one million young lives are estimated to be saved by the use of oral rehydration therapy for diarrhoea, more needs to be done in this area. UNICEF, along with other agencies, is involved in most developing countries (as well as globally) in activities related to child survival and the control of diarrhoeal diseases. The widespread use of ineffective and sometimes dangerous antidiarrhoeal drugs in young children is a major issue. The World Health Organization estimates that over one billion dollars are spent annually in harmful or useless anti-diarrhoeals globally. This is often done in places with least resources.

Even in the industrialized world, diarrhoea is one of the most common causes of illness in children below five years of age. The Centers for Disease Control and Prevention in Atlanta estimate that at least 16.5 million children in the United States have diarrhoea at least once a year, and between 300 to 500 die each year. Most of these deaths could be prevented, if immediate action was taken at home and appropriate care made available at health facilities. The disease accounts for 3 million visits to paediatric offices and 220,000 hospitalizations, or about 10% of all hospitalizations of children five years and younger.

The Honourable Donna Shalala
Secretary, Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Public Citizen, an American Consumers Rights group, has submitted a petition to the US Food and Drug Administration that calls for banning and/or relabeling of ineffective and potentially harmful antidiarrhoeal drugs sold in the U.S. These drugs have no place in the management of acute diarrhoea in children.

The World Health Organization (WHO) reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" and submitted their comments to Dr. David Kessler, Commissioner of the Food and Drug Administration. WHO supports Public Citizen's petition.

The decision of the Food and Drug Administration will have far reaching consequences for the developing world, considering that most developing countries often refer to the findings of the FDA before deciding about the efficacy, safety and need of drugs. The decisions made here would therefore affect millions of lives throughout the world.

This consumer movement could spearhead global action. The issues related to antidiarrhoeal drugs could become the first in a series of activities to assure **safe medicine** for young children. The alternative use of scarce financial resources, both personal and public, which is now used for useless and often harmful antidiarrhoeals, is important. At a time when the U.S. is grappling with lowering health care costs, it seems appropriate to review policies and guidelines related to the control of diarrhoeal diseases.

Giving top priority to programmes for reducing child health..... promoting correct case management in medical colleges and at home (including promotion of ORT)..... reviewing and rationalizing medical insurance and reimbursement policies according to standard case management guidelines..... and reviewing drug policies, are some steps that will facilitate the control of diarrhoeal deaths.

The outcome of Public Citizen's petition is of great importance not only for young children in the U.S., but throughout the world. I write today to seek your personal attention to the problem.

With best wishes.

Yours sincerely,

James P. Grant
Executive Director

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30/3/93

Dr Lee Zwanziger,
Executive Secretary,
OTC /Advisory Committee,
Food and Drug Administration,
CDER, HFD-9, 88-45, 5600 Fishers Lane,
Rockville, Maryland 20857, USA.

Dear Dr Zwanziger,

Subject: Public Citizen's Petition for a Ban and/or Relabelling of Antidiarrhoeal Drugs.

This letter reflects the views of a number of UK-based development agencies, all of whom have health programmes in developing countries, and who wish to support the Public Citizen's petition on ineffective and dangerous antidiarrhoeal drugs in young children.

While diarrhoea is a significant cause of preventable deaths of infants in industrialised countries - 10% of the total in the USA itself - the overwhelming burden falls on children in the developing world, where WHO calculates that 3 million deaths occur every year.

In our opinion the widespread sale of unscientific and expensive antidiarrhoeal drugs contributes to this appalling toll. First, it encourages the mistaken view that drugs, and not oral rehydration, are an appropriate treatment for acute diarrhoea. WHO states categorically in its scientific review 'The Rational Use of Drugs in the Management of Acute Diarrhoea in Children':

"Antidiarrhoeal drugs and emetics should never be used. None has any proven practical value and some are dangerous".

Second, the cumulative cost of inappropriate antidiarrhoeal drugs is an unnecessary and highly damaging misuse of scarce resources in countries where national and household budgets for health are grossly inadequate. The production and promotion of oral rehydration solution, with continued feeding, could save lives at a cost of only 50 cents per child.

The 1986 Drug Exports Amendment Act prevented the direct export of drugs to developing countries which were not licensed for use in the USA. The full value of this legislation is felt when drugs are adequately regulated in the domestic market. As we understand the OTC Advisory Committee will confine itself to discussion of kaolin and attapulgite on April 9th we can only reiterate WHO's position on the lack of evidence on efficacy and safety of these preparations. Neither reduces fluid or

electrolyte loss, and kaolin may interfere with efficacy of antibiotics, when these are indicated. Therefore they have no place in the management of acute diarrhoea and should not be used.

In addition, we would like to draw to your attention an entry in the Physicians' Desk Reference (1992) which gives the dangerously misleading impression that the drug Imodium should be used as a primary agent in the treatment of acute diarrhoea in children. This states:

"the use of Imodium does not preclude the administration of appropriate fluid and electrolyte therapy"

Drug Regulatory Authorities in developing countries frequently lack the capacity to evaluate drugs, and to provide high quality information. They often depend on the US-PDI, PDR, and on regulatory decisions in developed countries.

We urge that this extra dimension of responsibility is noted by the committee, and that action is taken in response to the petition.

Yours sincerely,

David Bryer

Director, Oxfam.

Martin Griffiths

Director, Action Aid.

Richard Harrow

Director, Save the Children Fund.

Jeremy Bowden

Deputy Director, Christian Aid.

Richard Reiter

Assistant Director, Cafod.

Mike Whitham

Director, British Red Cross.

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Message No. _____ Page 1 of 2 pages Date: 9 March 1993

From: Director, Division of Diarrhoeal and Acute Respiratory Diseases Control

To: Dr David A. Kessler, Commissioner, Food and Drug Administration, Rockville, MD 20857 USA

Our ref.:

Fax No.: 301 443 3100

Originator: Dr L. Richards	Subject: CITIZEN'S PETITION FOR A BAN AND/OR RELABELING OF ANTIDIARRHEAL DRUGS

TEXT

Dear Dr Kessler,

We recently reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" submitted to your office by Public Citizen. We share the concerns voiced in the petition over the widespread use of ineffective and often dangerous antidiarrhoeal drugs in young children.

We are particularly concerned that some antidiarrhoeal drugs marketed in the United States and developing countries are being promoted by their manufacturers as adjuncts to oral rehydration therapy. In fact, Janssen's entry for IMODIUM in the Physicians' Desk Reference (1992, p. 1139) goes a step further, stating that "the use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy". This statement conveys to us the message that IMODIUM should be the first agent used to treat diarrhoea in children but that oral rehydration therapy might also play some role. While ORS treats dehydration by replacing electrolyte and fluid losses, we do not feel that the use of IMODIUM has a significant effect on fluid and electrolyte loss or on the duration and severity of diarrhoea. IMODIUM is easier than ORS to administer to children, however, and it is reasonable to suppose that a mother giving IMODIUM to her child in the belief that it will "stop" diarrhoea will pay scant attention to feeding and rehydrating the child.

The claim made by Janssen in the Physicians' Desk Reference that IMODIUM "diminishes the loss of fluid and electrolytes" cannot in our view be supported by published studies. It is misleading, therefore, for the manufacturer to imply that IMODIUM is in any way a substitute for oral rehydration therapy, or to advise that it be used in conjunction with oral rehydration therapy.

In a similar fashion McNeil Consumer Products, manufacturer of IMODIUM A-D (an over-the-counter preparation of loperamide) has linked the use of its product with oral rehydration therapy. In a letter dated 31 July 1992 to the Medical Lobby for Appropriate Marketing, which MaLAM has shared with us, Dr Anthony R. Temple of McNeil states that:

Copies to: Director, FNA
Dr J. Yunes, Chief, Special Program, HMP, AMRO

"It has been standard practice by physicians in the U.S. to use rehydration initially and then to use oral antidiarrheal medications as appropriate."

A review of current pediatrics textbooks, however, failed to find any that advocate the use of antidiarrhoeal agents, including antimotility drugs, for the routine management of acute diarrhoea.

While our Programme is particularly targeted at developing countries, where diarrhoeal diseases account for more than 3 million deaths in young children each year, diarrhoea is associated with significant childhood morbidity and mortality in the United States as well, causing some 900 deaths annually, and 10% of preventable postneonatal infant deaths.

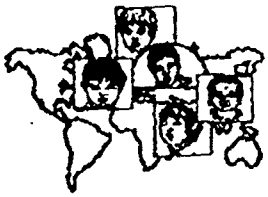
We would also like to point out that in formulating their drug policies, developing countries often consider the findings of the Food and Drug Administration and American and European pharmacopoeias before deciding about the safety and efficacy of a drug. We urge you to bear in mind that the decisions made by your agency affect not only Americans but also policy makers and prescribers from other countries who look to the FDA as a source of objective and accurate information.

We are sending, under seprate cover, a copy of our publication entitled "The rational use of drugs in the management of acute diarrhoea in children". This book reviews published studies of the efficacy and safety of antidiarrhoeal drugs, including loperamide, that are commonly administered to children in developing countries. Also enclosed is a recently published article outlining WHO's case management strategy for diarrhoea in developing and developed countries. We hope that these will serve as a useful reference, and would be pleased to answer any queries you may have or to provide further information.

We will follow with interest the outcome of the Public Citizen petition.

Yours sincerely,

Dr J. Tulloch
Director
Division of Diarrhoeal and Acute
Respiratory Disease Control



International Child Health Foundation

10630 Little Patuxent Parkway • Century Plaza • Suite 325
Columbia, MD 21044
Telephone: (301) 596-4514 or FAX (410) 992-5841

March 29, 1993

Dr. David A. Kessler
Commissioner, Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Kessler: RE: FDA hearing on antidiarrheal drugs

We share the concerns expressed by the World Health Organization in response to the Public Citizen petition to the U.S. Food and Drug Administration (FDA) asking for a relabeling of some antidiarrheal drugs and a banning of others. This petition recognizes that there has been widespread and inappropriate use of drugs for treatment of children with acute diarrhea and that most drug use for diarrhea is expensive, unnecessary, and potentially harmful.

Every year over 3 million children under age 4 die from effects of diarrheal disease. As reported by the Centers for Disease Control (CDC), children in this country are among those afflicted (CDC reports 350-500 deaths and over 200,000 hospitalizations of young children in the U.S. each year are from diarrheal disease). Ten percent of postneonatal infant death and ten percent of non-surgical hospitalizations of children in the U.S. are results of diarrheal disease.

Most of the diarrhea-related hospitalizations and deaths could be prevented with oral rehydration therapy (ORT) alone. ORT includes use of an oral electrolyte solution and appropriate feeding. To be most effective, treatment is started at the onset of diarrhea-related illness. In most cases this early treatment prevents serious consequences of diarrhea and, in most cases, ORT and feeding are all that are needed.

Sadly, education about how to prevent and how to treat diarrheal diseases effectively and correctly is missing both from both public education and appropriate medical education. We are actively working on this with our Partners for Better Health network, which includes physicians at a growing number of U.S. schools of medicine and hospitals such as Cincinnati Children's Hospital, Grady Hospital, Johns Hopkins, Harvard, Massachusetts General Hospital, University of Maryland Hospital, Texas Children's Hospital, Tulane, and others.

We at International Child Health Foundation (ICHF) first began our promotion of oral rehydration therapy in 1987 with a symposium at the National Academy of Sciences. Since then, we are glad that awareness of the potential to save lives and health care

costs through appropriate management of diarrheal disease is spreading. We began our efforts to increase use of ORT in the United States because U.S. health practices are followed closely by Third World leaders and institutions. What we do here in the United States has a major impact on practices and beliefs abroad.

Implementing the long-recommended preferred treatment of diarrhea with ORT and feeding would reduce our own problems and costs and, at the same time, help worldwide efforts to stem millions of preventable deaths. While drugs that are used in appropriate ways can save lives, widespread and inappropriate use of drugs can kill. The potential costs of inappropriate drug use are deaths and millions of wasted dollars.

Sincerely,

FOR THE INTERNATIONAL CHILD HEALTH FOUNDATION

Charlene B. Dale

Charlene B. Dale
Executive Vice President

W. B. Greenough, III, M.D.
Johns Hopkins University
and President, ICHF

Ronald L. Kleinman, M.D.
Chairman, Pediatric Gastroenterology
and Nutrition Department,
Massachusetts General Hospital, and
Committee on Nutrition,
American Academy of Pediatrics
and
ICHF Board of Trustees

David A. Sack, M.D.
Department of International
Health
Johns Hopkins University
and
Chairman
ICHF Task Force on
Cereal-based ORT

Enclosures:
Training Manual for Treatment and Prevention of Childhood Diarrhea with Oral Rehydration Therapy, Proper Nutrition, and Hygiene, a publication of the International Child Health Foundation, Columbia, Maryland, 1992.

Summary: Description of the ICHF Partners for Better Health Program
ICHF Newsletter

"The Management of Acute Diarrhea in Children: Oral Rehydration, Maintenance and Nutritional Therapy," Report of U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention (CDC), October 16, 1992, Volume 14, No. RR16. *Note: Most of the consultants and reviewers are ICHF technical advisors and trustees.*

Peter Lurie, MD, MPH

University of California, San Francisco
Department of Family and Community Medicine
Department of Epidemiology and Biostatistics

Testimony before FDA Nonprescription Drugs Advisory Committee on the Efficacy of Attapulgite and Kaolin/pectin in the Treatment of Diarrhea

April 9, 1993

Essential Elements of a Clinical Trial of an Antidiarrheal Drug

- Randomized
- Placebo control, single ingredient
- Blinded
- Assessment of fluid balance
  - number and frequency of stools
  - stool weight or volume
  - urine volume

Author: "1974 study"

Design: Randomized, double-blind

Comparison: Attapulgite/pectin v. placebo

Subjects: 50 subjects, aged 22 - 65 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatement
d. total number of bowel movements
e. total number of cramps

FDA: "The study cannot be used to demonstrate the effectiveness of attapulgite alone."
Letter to Pfizer, 10/14/82

Author: "1980 study"

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 50 subjects, aged 12 - 75 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatement
d. total number of bowel movements
e. total number of cramps

Author: DuPont, et al. Am J Med, 1990

Design: Randomized, unblinded

Comparison: Attapulgite v. loperamide

Subjects: 194 adult subjects with acute diarrhea

Findings: Favorable findings for loperamide with respect to:

a. number of unformed stools
b. time to last unformed stool

Author: Madkour, unpublished, 1990

Design: ? randomized, ? blinded

Comparison: Smectite v. placebo

Subjects: 90 hospitalized boys < 3 years, with acute diarrhea

Findings:

a. Decreased duration of diarrhea in smectite group

b. No change in stool output (g/kg body weight)

Author: Charritat, et al. Ann Pediatr (Paris), 1992

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 113 subjects, mean age 28 months, with acute diarrhea

Findings:
1.Favorable findings for attapulgite with respect to:
    a. time to first and second formed stools
    b. time to resumption of normal diet
2. No difference between groups with respect to:
    a. mean number of stools
    b. consistency or character of stools

Summary of Studies on Attapulgite

Study	Randomized ?	Drug v. Placebo ?	Blinded ?	Asses s Fluids ?
1974 Study	Yes	No	Yes	No
1980 Study	Yes	Yes	Yes	No
DuPont	Yes	No	No	No
Madkour	?	Yes (smectite)	?	Yes (Not effective)
Charrita t	Yes	Yes	Yes	No

WHO: "Smectite and attapulgite have no place in the management of acute diarrhea in children and should not be used"
WHO Monograph, 1990

Author: Nalin and Cash, J Pakistani Med Assoc, 1970

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 49 adult cholera subjects

Findings: No difference between kaolin and control with respect to:

a. total stool volume
b. duration of diarrhea
c. time to first negative rectal swab

Author: Portnoy, et al. JAMA, 1976

Design: Randomized, ? blinded

Comparison: Kaolin/pectin v. kaolin v. pectin v. diphenoxylate/atropine v. placebo

Subjects: 80 subjects, aged 3 - 11 years, with acute diarrhea

Findings:
1. Kaolin/pectin group tended to have more formed stools
2. No difference between groups with respect to:
    a. frequency of stools
    b. water content of stools
    c. stool weight

Author: Alestig, Trollfors, Stenqvist, The Practitioner, 1979

Design: Randomized, unblinded

Comparison: Kaolin/pectin v. charcoal v. diphenoxylate v. placebo

Subjects: 204 adult subjects with acute diarrhea

Findings: No difference between groups with respect to:

a. stool frequency
b. stool consistency

Author: Watkinson, J Trop Peds, 1982

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 97 subjects, aged 3 - 18 months, with acute diarrhea

Findings: No difference between groups with respect to:

a. duration of diarrhea
b. stool water content
c. mean number of stools per day
d. maximum number of stools per day
e. change in body weight

Author: Ambroziatis, et al. ("Study 295"), 1982

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. placebo

Subjects: 213 subjects with acute diarrhea

Findings:
1. Favorable findings for kaolin/pectin with respect to:
    a. proportion of subjects with diarrhea on second day
    b. consistency of stools on second day
2. No difference between groups with respect to total frequency of stools

Author: Ambroziatis, et al. ("Study 303"), 1987

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. kaolin v. pectin v. placebo

Subjects: 508 subjects with acute diarrhea

Findings:
1. Better stool consistency for kaolin/pectin and kaolin than for pectin or placebo
2. Shorter duration of diarrhea for kaolin/pectin compared to all other groups

Summary of Studies on Kaolin/pectin or its Ingredients

Study	Randomized ?	Drug v. Placebo ?	Blinded ?	Asses s Fluids ?
Nalin	Yes	Yes (kaolin)	?	Yes (Not effective)
Portnoy	Yes	Yes (kaolin, pectin, kaolin/-pectin)	?	Yes (Not effective)
Alestig	Yes	Yes (kaolin/-pectin)	No	No
Watkin-son	Yes	Yes (kaolin)	?	Yes (Not effective)
Study 295	Yes	Yes (kaolin/-pectin	Yes	No
Study 303	Yes	Yes (kaolin, pectin, kaolin/-pectin)	Yes	No

WHO: "Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."
WHO Monograph, 1990

Summary

A. Attapulgite

- There are three placebo-controlled trials of attapulgite
- Of these only one assessed fluid balance, and in that trial attapulgite was found to be ineffective in preventing fluid loss

B. Kaolin/pectin

- There are six placebo-controlled trials of kaolin/pectin or its ingredients
- Of these only three assessed fluid balance, and in all three kaolin/pectin or its ingredients were found to be ineffective in preventing fluid loss

C. Conclusion

- Due to lack of evidence of efficacy in preventing fluid loss, both attapulgite and kaolin/pectin and its ingredients should be immediately removed from the market

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER

1725 WEST HARRISON, CHICAGO, ILLINOIS 60612

RUSH MEDICAL COLLEGE

RICHARD H. SANDLER, M. D.
Director
Pediatric Gastroenterology & Nutrition
(312) 942-3034

March 26, 1993

Lee Zwanziger, MD
Executive Secretary
Non-Prescription Drugs Advisory Comittee
Center for Drug Evaluation and Reserach (HFD-9)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: LETTER TO THE FDA IN SUPPORT OF THE CITIZEN'S PETITION[1] OF PUBLIC CITIZEN REQUESTING A BAN AND/OR RELABELING OF FIVE PREPARATIONS OF ANTIDIARRHEAL MEDICATIONS

Dear Dr. Zwanziger:

I am writing today in support of the above petition. I am an academic pediatric gastroenterologist with considerable experience in diarrheal diseases here and abroad, and am director of our section at Rush University. In reference to the petition, there are a few key points that I think need to be made:

1. Diarrheal illness in infants and children in this country is, in general, a self-limited illness. There are, however, several hundred childhood deaths each year in the USA from diarrheal illness. All of these deaths are preventable with "proper therapy."

2. **"Proper therapy" means oral rehydration therapy (ORT)**, begun early and given properly.[2]

3. **Antidiarrheal drug therapy should not be used in the management of acute diarrheal illness in infants and children.** As amply documented in the literature and summarized in a WHO monograph[3] and CDC reports[4], the reasons for the above

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[1] Ahmad SR, Lurie P, Wolfe SM. Citizen's petition for a ban and/or relabeling of antidiarrheal drugs. Public Citizen, Health Research Group, 2000 P St NW, Washington DC 20036. January 7, 1993.

[2] Hirschhorn N, Greenough III WB. Progress in oral rehydration therapy. Scientific American 1991;264:50-56.

[3] World Health Organization. The rational use of drugs in the management of acute diarrhea in children. Geneva, WHO, 1990.

statement include:

(a) Antidiarrheal therapies are marginally effective at best;

(b) There may be dangers inherent in their use (a statement particularly true of diphenoxylate);

c) Use of antidiarrheals serves to divert attention from the preferable and effective therapy, ORT;

d) To the degree that anti-motility agents are effective in controlling stool output, medical practitioners and families can be lulled into thinking that diarrheal illness has been successfully treated. This impression may exist even if large amounts of fluid are "third spacing" into the bowel. This latter condition, especially in infants, might not be recognized until it is too late.

4. There may be a role for selected antidiarrheal therapy for a few pediatric patients with **chronic diarrheal** conditions.[5] Although as a pediatric gastroenterology specialist this includes a fair number of my patients, compared to the incidence of acute diarrheal episodes such situations are rare.

5. For these limited legitimate uses, pediatric gastroenterologists and pediatricians could continue to use agents such as loperamide if the FDA makes the changes urged by the petitioners. Since it is only the pediatric form of loperamide which would be banned (or relabeled), practitioners **could still prescribe the adult formulations** which can be easily crushed and placed in apple sauce, or suspended.[6]

5. I see a **dual purpose** in banning the pediatric preparations of

---

[4] Anon. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. MMWR 1992;41:1-20.

[5] These chronic diarrheal conditions include inflammatory bowel disease, chronic non-specific diarrhea of toddlerhood, and short bowel syndrome.

[6] A large percentage of all medications used in pediatrics are in fact the adult formulations which are crushed or suspended in a manner such as mentioned here.

the diarrheal medications in the USA. The first is to help the children in **our own country**, and the second is to serve as an **example for third world** governments and practitioners who often look to us for guidance on what their health policies should be vis-a-vis use of various medications. Although there may be few children in the United States dying from the inappropriate use of these medications, undoubtedly there are tens of thousands of children a year in developing nations succumbing unnecessarily to diarrheal illness because of inappropriate antidiarrheal medication use (instead of ORT).

6. A final point on the efficacy of antidiarrheal drugs. None of the studies proclaiming diarrheal control efficacy of which I am aware are solidly designed. Although a rare study is randomized, double-blind and placebo controlled, the N has usually been small, and the outcome variables qualitative and subjective parameters such as stool consistency.

The number of stools by itself is not an adequate measure of antidiarrheal effectiveness, especially in pediatrics. This is so because infants often have frequent small bowel movements. A medication which decreases the number of bowel movements slightly, but does not decrease the total water loss per day, should not be considered an effective antidiarrheal agent.

Endpoints used for assessing efficacy of antidiarrheal therapy should therefore include measurement of stool weight per day. The populations should be matched by age, and if this is not done, the stool should output be adjusted in some fashion to account for the child's weight.

Because in pediatrics the risk of dehydration is great, it is important that studies of anti-motility agents also examine the risk of third spacing:

a) Such studies should address common signs of hydration status such as heart rate, mucosal membrane moistness, urine output, urine specific gravity, BUN, etc.; and

b) To assess third spacing (besides the hydration parameters), abdominal girth, discomfort, and bowel sounds should be mentioned.

I want to thank the Advisory Committee for taking the time to review this important petition. I would be happy to try and answer any questions you may have.

Sincerely,

Richard H. Sandler, M.D.,
Director, Pediatric Gastroenterology and Nutrition
Assistant Professor of Pediatrics
Rush Medical College

RHS/mmm

cc. M Shalala

unicef

United Nations Children's Fund
Fonds des Nations Unies pour l'enfance
Fondo de las Naciones Unidas para la Infancia

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VIA FAX: 202 690 7203

5 April 1993

Dear Secretary Shalala,

I refer to my letter of 23 March and hope that an opportunity for us to meet will soon be possible.

The survival of young children remains a major problem in the globe, particularly in developing countries. It is estimated that 12.9 million children below 5 years of age die every year - sixty per cent of these deaths could be prevented through low-cost and effective measures. Vaccine preventible diseases, diarrhoea and pneumonia account for three-fourths of these deaths. Over three million young children still die annually from diarrhoeal diseases. Although one million young lives are estimated to be saved by the use of oral rehydration therapy for diarrhoea, more needs to be done in this area. UNICEF, along with other agencies, is involved in most developing countries (as well as globally) in activities related to child survival and the control of diarrhoeal diseases. The widespread use of ineffective and sometimes dangerous antidiarrhoeal drugs in young children is a major issue. The World Health Organization estimates that over one billion dollars are spent annually in harmful or useless anti-diarrhoeals globally. This is often done in places with least resources.

Even in the industrialized world, diarrhoea is one of the most common causes of illness in children below five years of age. The Centers for Disease Control and Prevention in Atlanta estimate that at least 16.5 million children in the United States have diarrhoea at least once a year, and between 300 to 500 die each year. Most of these deaths could be prevented, if immediate action was taken at home and appropriate care made available at health facilities. The disease accounts for 3 million visits to paediatric offices and 220,000 hospitalizations, or about 10% of all hospitalizations of children five years and younger.

The Honourable Donna Shalala
Secretary, Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Public Citizen, an American Consumers Rights group, has submitted a petition to the US Food and Drug Administration that calls for banning and/or relabeling of ineffective and potentially harmful antidiarrhoeal drugs sold in the U.S. These drugs have no place in the management of acute diarrhoea in children.

The World Health Organization (WHO) reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" and submitted their comments to Dr. David Kessler, Commissioner of the Food and Drug Administration. WHO supports Public Citizen's petition.

The decision of the Food and Drug Administration will have far reaching consequences for the developing world, considering that most developing countries often refer to the findings of the FDA before deciding about the efficacy, safety and need of drugs. The decisions made here would therefore affect millions of lives throughout the world.

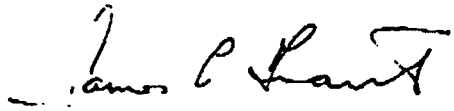
This consumer movement could spearhead global action. The issues related to antidiarrhoeal drugs could become the first in a series of activities to assure safe medicine for young children. The alternative use of scarce financial resources, both personal and public, which is now used for useless and often harmful antidiarrhoeals, is important. At a time when the U.S. is grappling with lowering health care costs, it seems appropriate to review policies and guidelines related to the control of diarrhoeal diseases.

Giving top priority to programmes for reducing child health..... promoting correct case management in medical colleges and at home (including promotion of ORT)..... reviewing and rationalizing medical insurance and reimbursement policies according to standard case management guidelines..... and reviewing drug policies, are some steps that will facilitate the control of diarrhoeal deaths.

The outcome of Public Citizen's petition is of great importance not only for young children in the U.S., but throughout the world. I write today to seek your personal attention to the problem.

With best wishes.

Yours sincerely,



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Executive Director

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30/3/93

Dr Lee Zwanziger,
Executive Secretary,
OTC /Advisory Committee,
Food and Drug Administration,
CDER, HFD-9, 88-45, 5600 Fishers Lane,
Rockville, Maryland 20857, USA.

Dear Dr Zwanziger,

Subject: Public Citizen's Petition for a Ban and/or Relabelling of Antidiarrhoeal Drugs.

This letter reflects the views of a number of UK-based development agencies, all of whom have health programmes in developing countries, and who wish to support the Public Citizen's petition on ineffective and dangerous antidiarrhoeal drugs in young children.

While diarrhoea is a significant cause of preventable deaths of infants in industrialised countries - 10% of the total in the USA itself - the overwhelming burden falls on children in the developing world, where WHO calculates that 3 million deaths occur every year.

In our opinion the widespread sale of unscientific and expensive antidiarrhoeal drugs contributes to this appalling toll. First, it encourages the mistaken view that drugs, and not oral rehydration, are an appropriate treatment for acute diarrhoea. WHO states categorically in its scientific review 'The Rational Use of Drugs in the Management of Acute Diarrhoea in Children':

"Antidiarrhoeal drugs and emetics should never be used. None has any proven practical value and some are dangerous".

Second, the cumulative cost of inappropriate antidiarrhoeal drugs is an unnecessary and highly damaging misuse of scarce resources in countries where national and household budgets for health are grossly inadequate. The production and promotion of oral rehydration solution, with continued feeding, could save lives at a cost of only 50 cents per child.

The 1986 Drug Exports Amendment Act prevented the direct export of drugs to developing countries which were not licensed for use in the USA. The full value of this legislation is felt when drugs are adequately regulated in the domestic market. As we understand the OTC Advisory Committee will confine itself to discussion of kaolin and attapulgite on April 9th we can only reiterate WHO's position on the lack of evidence on efficacy and safety of these preparations. Neither reduces fluid or

electrolyte loss, and kaolin may interfere with efficacy of antibiotics, when these are indicated. Therefore they have no place in the management of acute diarrhoea and should not be used.

In addition, we would like to draw to your attention an entry in the Physicians' Desk Reference (1992) which gives the dangerously misleading impression that the drug Imodium should be used as a primary agent in the treatment of acute diarrhoea in children. This states:

"the use of Imodium does not preclude the administration of appropriate fluid and electrolyte therapy"

Drug Regulatory Authorities in developing countries frequently lack the capacity to evaluate drugs, and to provide high quality information. They often depend on the US-PDI, PDR, and on regulatory decisions in developed countries.

We urge that this extra dimension of responsibility is noted by the committee, and that action is taken in response to the petition.

Yours sincerely,

David Bryer

Director, Oxfam.

Martin Griffiths

Director, Action Aid.

Richard Hatton

Director, Save the Children Fund.

Jenny Borden

Deputy Director, Christian Aid.

Richard Riley

Assistant Director, Cafod.

Mike Whitham

Director, British Red Cross.

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Message No. _____ Page 1 of 2 pages Date: 9 March 1993

From: Director, Division of Diarrhoeal and Acute Respiratory Disease Control

To: Dr David A. Kessler, Commissioner, Food and Drug Administration, Rockville, MD 20857 USA

Our ref.:

Fax No.: 301 443 3100

Originator: Dr L. Richards

Subject: CITIZEN'S PETITION FOR A BAN AND/OR RELABELING OF ANTIDIARRHEAL DRUGS

TEXT

Dear Dr Kessler,

We recently reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" submitted to your office by Public Citizen. We share the concerns voiced in the petition over the widespread use of ineffective and often dangerous antidiarrhoeal drugs in young children.

We are particularly concerned that some antidiarrhoeal drugs marketed in the United States and developing countries are being promoted by their manufacturers as adjuncts to oral rehydration therapy. In fact, Janssen's entry for IMODIUM in the Physicians' Desk Reference (1992, p. 1139) goes a step further, stating that "the use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy". This statement conveys to us the message that IMODIUM should be the first agent used to treat diarrhoea in children but that oral rehydration therapy might also play some role. While ORS treats dehydration by replacing electrolyte and fluid losses, we do not feel that the use of IMODIUM has a significant effect on fluid and electrolyte loss or on the duration and severity of diarrhoea. IMODIUM is easier than ORS to administer to children, however, and it is reasonable to suppose that a mother giving IMODIUM to her child in the belief that it will "stop" diarrhoea will pay scant attention to feeding and rehydrating the child.

The claim made by Janssen in the Physicians' Desk Reference that IMODIUM "diminishes the loss of fluid and electrolytes" cannot in our view be supported by published studies. It is misleading, therefore, for the manufacturer to imply that IMODIUM is in any way a substitute for oral rehydration therapy, or to advise that it be used in conjunction with oral rehydration therapy.

In a similar fashion McNeil Consumer Products, manufacturer of IMODIUM A-D (an over-the-counter preparation of loperamide) has linked the use of its product with oral rehydration therapy. In a letter dated 31 July 1992 to the Medical Lobby for Appropriate Marketing, which MaLAM has shared with us, Dr Anthony R. Temple of McNeil states that:

Copies to: Director, PHA
Dr J. Yunes, Chief, Special Program, HMP, AMRO

"It has been standard practice by physicians in the U.S. to use rehydration initially and then to use oral antidiarrheal medications as appropriate."

A review of current pediatrics textbooks, however, failed to find any that advocate the use of antidiarrhoeal agents, including antimotility drugs, for the routine management of acute diarrhoea.

While our Programme is particularly targeted at developing countries, where diarrhoeal diseases account for more than 3 million deaths in young children each year, diarrhoea is associated with significant childhood morbidity and mortality in the United States as well, causing some 500 deaths annually, and 10% of preventable postneonatal infant deaths.

We would also like to point out that in formulating their drug policies, developing countries often consider the findings of the Food and Drug Administration and American and European pharmacopoeias before deciding about the safety and efficacy of a drug. We urge you to bear in mind that the decisions made by your agency affect not only Americans but also policy makers and prescribers from other countries who look to the FDA as a source of objective and accurate information.

We are sending, under separate cover, a copy of our publication entitled "The rational use of drugs in the management of acute diarrhoea in children". This book reviews published studies of the efficacy and safety of antidiarrhoeal drugs, including loperamide, that are commonly administered to children in developing countries. Also enclosed is a recently published article outlining WHO's case management strategy for diarrhoea in developing and developed countries. We hope that these will serve as a useful reference, and would be pleased to answer any queries you may have or to provide further information.

We will follow with interest the outcome of the Public Citizen petition.

Yours sincerely,

Dr J. Tulloch
Director
Division of Diarrhoeal and Acute
Respiratory Disease Control

International Child Health Foundation

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Telephone: (301) 596-4514 or FAX (410) 992-5641

March 29, 1993

Dr. David A. Kessler
Commissioner, Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Kessler: RE: FDA hearing on antidiarrheal drugs

We share the concerns expressed by the World Health Organization in response to the Public Citizen petition to the U.S. Food and Drug Administration (FDA) asking for a relabeling of some antidiarrheal drugs and a banning of others. This petition recognizes that there has been widespread and inappropriate use of drugs for treatment of children with acute diarrhea and that most drug use for diarrhea is expensive, unnecessary, and potentially harmful.

Every year over 3 million children under age 4 die from effects of diarrheal disease. As reported by the Centers for Disease Control (CDC), children in this country are among those afflicted (CDC reports 350-500 deaths and over 200,000 hospitalizations of young children in the U.S. each year are from diarrheal disease). Ten percent of postneonatal infant death and ten percent of non-surgical hospitalizations of children in the U.S. are results of diarrheal disease.

Most of the diarrhea-related hospitalizations and deaths could be prevented with oral rehydration therapy (ORT) alone. ORT includes use of an oral electrolyte solution and appropriate feeding. To be most effective, treatment is started at the onset of diarrhea-related illness. In most cases this early treatment prevents serious consequences of diarrhea and, in most cases, ORT and feeding are all that are needed.

Sadly, education about how to prevent and how to treat diarrheal diseases effectively and correctly is missing both from both public education and appropriate medical education. We are actively working on this with our Partners for Better Health network, which includes physicians at a growing number of U.S. schools of medicine and hospitals such as Cincinnati Children's Hospital, Grady Hospital, Johns Hopkins, Harvard, Massachusetts General Hospital, University of Maryland Hospital, Texas Children's Hospital, Tulane, and others.

We at International Child Health Foundation (ICHF) first began our promotion of oral rehydration therapy in 1987 with a symposium at the National Academy of Sciences. Since then, we are glad that awareness of the potential to save lives and health care

costs through appropriate management of diarrheal disease is spreading. We began our efforts to increase use of ORT in the United States because U.S. health practices are followed closely by Third World leaders and institutions. What we do here in the United States has a major impact on practices and beliefs abroad.

Implementing the long-recommended preferred treatment of diarrhea with ORT and feeding would reduce our own problems and costs and, at the same time, help worldwide efforts to stem millions of preventable deaths. While drugs that are used in appropriate ways can save lives, widespread and inappropriate use of drugs can kill. The potential costs of inappropriate drug use are deaths and millions of wasted dollars.

Sincerely,

FOR THE INTERNATIONAL CHILD HEALTH FOUNDATION

Charlene B. Dale
Executive Vice President

W. B. Greenough, III, M.D.
Johns Hopkins University
and President, ICHF

Ronald L. Kleinman, M.D.
Chairman, Pediatric Gastroenterology
and Nutrition Department,
Massachusetts General Hospital, and
Committee on Nutrition,
American Academy of Pediatrics
and
ICHF Board of Trustees

David A. Sack, M.D.
Department of International
Health
Johns Hopkins University
and
Chairman
ICHF Task Force on
Cereal-based ORT

Enclosures:
Training Manual for Treatment and Prevention of Childhood Diarrhea with Oral Rehydration Therapy, Proper Nutrition, and Hygiene, a publication of the International Child Health Foundation, Columbia, Maryland, 1992.

Summary: Description of the ICHF Partners for Better Health Program
ICHF Newsletter

"The Management of Acute Diarrhea in Children: Oral Rehydration, Maintenance and Nutritional Therapy," Report of U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention (CDC), October 16, 1992, Volume 14, No. RR16. *Note: Most of the consultants and reviewers are ICHF technical advisors and trustees.*

Peter Lurie, MD, MPH

University of California, San Francisco
Department of Family and Community Medicine
Department of Epidemiology and Biostatistics

Testimony before FDA Nonprescription Drugs Advisory Committee on the Efficacy of Attapulgite and Kaolin/pectin in the Treatment of Diarrhea

April 9, 1993

Essential Elements of a Clinical Trial of an Antidiarrheal Drug

- Randomized
- Placebo control, single ingredient
- Blinded
- Assessment of fluid balance
  - number and frequency of stools
  - stool weight or volume
  - urine volume

Author: "1974 study"

Design: Randomized, double-blind

Comparison: Attapulgite/pectin v. placebo

Subjects: 50 subjects, aged 22 - 65 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatment
d. total number of bowel movements
e. total number of cramps

FDA: "The study cannot be used to demonstrate the effectiveness of attapulgite alone."
Letter to Pfizer, 10/14/82

Author: "1980 study"

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 50 subjects, aged 12 - 75 years, with acute diarrhea

Findings: Favorable findings for drug treatment with respect to:

a. physicians' global evaluations
b. subjects' evaluation of effectiveness
c. use of replacement treatment
d. total number of bowel movements
e. total number of cramps

Author: DuPont, et al. Am J Med, 1990

Design: Randomized, unblinded

Comparison: Attapulgite v. loperamide

Subjects: 194 adult subjects with acute diarrhea

Findings: Favorable findings for loperamide with respect to:

a. number of unformed stools
b. time to last unformed stool

Author: Madkour, unpublished, 1990

Design: ? randomized, ? blinded

Comparison: Smectite v. placebo

Subjects: 90 hospitalized boys < 3 years, with acute diarrhea

Findings:

a. Decreased duration of diarrhea in smectite group

b. No change in stool output (g/kg body weight)

Author: Charritat, et al. Ann Pediatr (Paris), 1992

Design: Randomized, double-blind

Comparison: Attapulgite v. placebo

Subjects: 113 subjects, mean age 28 months, with acute diarrhea

Findings:
1. Favorable findings for attapulgite with respect to:
    a. time to first and second formed stools
    b. time to resumption of normal diet
2. No difference between groups with respect to:
    a. mean number of stools
    b. consistency or character of stools

Summary of Studies on Attapulgite

Study	Randomized?	Drug v. Placebo?	Blinded?	Assess Fluids?
1974 Study	Yes	No	Yes	No
1980 Study	Yes	Yes	Yes	No
DuPont	Yes	No	No	No
Madkour	?	Yes (smectite)	?	Yes (Not effective)
Charritat	Yes	Yes	Yes	No

WHO: "Smectite and attapulgite have no place in the management of acute diarrhea in children and should not be used"
WHO Monograph, 1990

Author: Nalin and Cash, J Pakistani Med Assoc, 1970

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 49 adult cholera subjects

Findings: No difference between kaolin and control with respect to:

a. total stool volume
b. duration of diarrhea
c. time to first negative rectal swab

Author: Portnoy, et al. JAMA, 1976

Design: Randomized, ? blinded

Comparison: Kaolin/pectin v. kaolin v. pectin v. diphenoxylate/atropine v. placebo

Subjects: 80 subjects, aged 3 - 11 years, with acute diarrhea

Findings:
1. Kaolin/pectin group tended to have more formed stools
2. No difference between groups with respect to:
    a. frequency of stools
    b. water content of stools
    c. stool weight

Author: Alestig, Trollfors, Stenqvist, The Practitioner, 1979

Design: Randomized, unblinded

Comparison: Kaolin/pectin v. charcoal v. diphenoxylate v. placebo

Subjects: 204 adult subjects with acute diarrhea

Findings: No difference between groups with respect to:

a. stool frequency
b. stool consistency

Author: Watkinson, J Trop Peds, 1982

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 97 subjects, aged 3 - 18 months, with acute diarrhea

Findings: No difference between groups with respect to:

a. duration of diarrhea
b. stool water content
c. mean number of stools per day
d. maximum number of stools per day
e. change in body weight

Author: Ambroziatis, et al. ("Study 295"), 1982

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. placebo

Subjects: 213 subjects with acute diarrhea

Findings:
1. Favorable findings for kaolin/pectin with respect to:
    a. proportion of subjects with diarrhea on second day
    b. consistency of stools on second day
2. No difference between groups with respect to total frequency of stools

Author: Ambroziatis, et al. ("Study 303"), 1987

Design: Randomized, double-blind

Comparison: Kaolin/pectin v. kaolin v. pectin v. placebo

Subjects: 508 subjects with acute diarrhea

Findings:
1. Better stool consistency for kaolin/pectin and kaolin than for pectin or placebo
2. Shorter duration of diarrhea for kaolin/pectin compared to all other groups

Summary

A. Attapulgite

- There are three placebo-controlled trials of attapulgite
- Of these only one assessed fluid balance, and in that trial attapulgite was found to be ineffective in preventing fluid loss

B. Kaolin/pectin

- There are six placebo-controlled trials of kaolin/pectin or its ingredients
- Of these only three assessed fluid balance, and in all three kaolin/pectin or its ingredients were found to be ineffective in preventing fluid loss

C. Conclusion

- Due to lack of evidence of efficacy in preventing fluid loss, both attapulgite and kaolin/pectin and its ingredients should be immediately removed from the market

Summary of Studies on Kaolin/pectin or its Ingredients

Study	Randomized?	Drug v. Placebo?	Blinded?	Assess Fluids?
Nalin	Yes	Yes (kaolin)	?	Yes (Not effective)
Portnoy	Yes	Yes (kaolin, pectin, kaolin/-pectin)	?	Yes (Not effective)
Alestig	Yes	Yes (kaolin/-pectin)	No	No
Watkin-son	Yes	Yes (kaolin)	?	Yes (Not effective)
Study 295	Yes	Yes (kaolin/-pectin	Yes	No
Study 303	Yes	Yes (kaolin, pectin, kaolin/-pectin)	Yes	No

WHO: "Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."
WHO Monograph, 1990

APPENDIX

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER

1725 WEST HARRISON, CHICAGO, ILLINOIS 60612

RUSH MEDICAL COLLEGE

RICHARD H. SANDLER, M. D.
Director
Pediatric Gastroenterology & Nutrition
(312) 942-3034

March 26, 1993

Lee Zwanziger, MD
Executive Secretary
Non-Prescription Drugs Advisory Comittee
Center for Drug Evaluation and Reserach (HFD-9)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: LETTER TO THE FDA IN SUPPORT OF THE CITIZEN'S PETITION[1] OF PUBLIC CITIZEN REQUESTING A BAN AND/OR RELABELING OF FIVE PREPARATIONS OF ANTIDIARRHEAL MEDICATIONS

Dear Dr. Zwanziger:

I am writing today in support of the above petition. I am an academic pediatric gastroenterologist with considerable experience in diarrheal diseases here and abroad, and am director of our section at Rush University. In reference to the petition, there are a few key points that I think need to be made:

1. Diarrheal illness in infants and children in this country is, in general, a self-limited illness. There are, however, several hundred childhood deaths each year in the USA from diarrheal illness. All of these deaths are preventable with "proper therapy."

2. **"Proper therapy" means oral rehydration therapy (ORT)**, begun early and given properly.[2]

3. **Antidiarrheal drug therapy should not be used in the management of acute diarrheal illness in infants and children.** As amply documented in the literature and summarized in a WHO monograph[3] and CDC reports[4], the reasons for the above

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[1] Ahmad SR, Lurie P, Wolfe SM. Citizen's petition for a ban and/or relabeling of antidiarrheal drugs. Public Citizen, Health Research Group, 2000 P St NW, Washington DC 20036. January 7, 1993.

[2] Hirschhorn N, Greenough III WB. Progress in oral rehydration therapy. Scientific American 1991;264:50-56.

[3] World Health Organization. The rational use of drugs in the management of acute diarrhea in children. Geneva, WHO, 1990.

statement include:

(a) Antidiarrheal therapies are marginally effective at best;

(b) There may be dangers inherent in their use (a statement particularly true of diphenoxylate);

c) Use of antidiarrheals serves to divert attention from the preferable and effective therapy, ORT;

d) To the degree that anti-motility agents are effective in controlling stool output, medical practitioners and families can be lulled into thinking that diarrheal illness has been successfully treated. This impression may exist even if large amounts of fluid are "third spacing" into the bowel. This latter condition, especially in infants, might not be recognized until it is too late.

4. There may be a role for selected antidiarrheal therapy for a few pediatric patients with **chronic diarrheal** conditions.[5] Although as a pediatric gastroenterology specialist this includes a fair number of my patients, compared to the incidence of acute diarrheal episodes such situations are rare.

5. For these limited legitimate uses, pediatric gastroenterologists and pediatricians could continue to use agents such as loperamide if the FDA makes the changes urged by the petitioners. Since it is only the pediatric form of loperamide which would be banned (or relabeled), practitioners **could still prescribe the adult formulations** which can be easily crushed and placed in apple sauce, or suspended.[6]

5. I see a **dual purpose** in banning the pediatric preparations of

---

[4] Anon. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. MMWR 1992;41:1-20.

[5] These chronic diarrheal conditions include inflammatory bowel disease, chronic non-specific diarrhea of toddlerhood, and short bowel syndrome.

[6] A large percentage of all medications used in pediatrics are in fact the adult formulations which are crushed or suspended in a manner such as mentioned here.

the diarrheal medications in the USA. The first is to help the children in our own country, and the second is to serve as an example for third world governments and practitioners who often look to us for guidance on what their health policies should be vis-a-vis use of various medications. Although there may be few children in the United States dying from the inappropriate use of these medications, undoubtedly there are tens of thousands of children a year in developing nations succumbing unnecessarily to diarrheal illness because of inappropriate antidiarrheal medication use (instead of ORT).

6. A final point on the efficacy of antidiarrheal drugs. None of the studies proclaiming diarrheal control efficacy of which I am aware are solidly designed. Although a rare study is randomized, double-blind and placebo controlled, the N has usually been small, and the outcome variables qualitative and subjective parameters such as stool consistency.

The number of stools by itself is not an adequate measure of antidiarrheal effectiveness, especially in pediatrics. This is so because infants often have frequent small bowel movements. A medication which decreases the number of bowel movements slightly, but does not decrease the total water loss per day, should not be considered an effective antidiarrheal agent.

Endpoints used for assessing efficacy of antidiarrheal therapy should therefore include measurement of stool weight per day. The populations should be matched by age, and if this is not done, the stool should output be adjusted in some fashion to account for the child's weight.

Because in pediatrics the risk of dehydration is great, it is important that studies of anti-motility agents also examine the risk of third spacing:

a) Such studies should address common signs of hydration status such as heart rate, mucosal membrane moistness, urine output, urine specific gravity, BUN, etc.; and

b) To assess third spacing (besides the hydration parameters), abdominal girth, discomfort, and bowel sounds should be mentioned.

I want to thank the Advisory Committee for taking the time to review this important petition. I would be happy to try and answer any questions you may have.

Sincerely,

Richard H. Sandler, M.D.,
Director, Pediatric Gastroenterology and Nutrition
Assistant Professor of Pediatrics
Rush Medical College

RHS/mmm

cc. M Shalala

unicef

United Nations Children's Fund
Fonds des Nations Unies pour l'enfance
Fondo de las Naciones Unidas para la Infancia

3 United Nations Plaza
New York, New York 10017
212 326-7000
Telex: 175989

VIA FAX: 202 690 7203

5 April 1993

Dear Secretary Shalala,

I refer to my letter of 23 March and hope that an opportunity for us to meet will soon be possible.

The survival of young children remains a major problem in the globe, particularly in developing countries. It is estimated that 12.9 million children below 5 years of age die every year - sixty per cent of these deaths could be prevented through low-cost and effective measures. Vaccine preventible diseases, diarrhoea and pneumonia account for three-fourths of these deaths. Over three million young children still die annually from diarrhoeal diseases. Although one million young lives are estimated to be saved by the use of oral rehydration therapy for diarrhoea, more needs to be done in this area. UNICEF, along with other agencies, is involved in most developing countries (as well as globally) in activities related to child survival and the control of diarrhoeal diseases. The widespread use of ineffective and sometimes dangerous antidiarrhoeal drugs in young children is a major issue. The World Health Organization estimates that over one billion dollars are spent annually in harmful or useless anti-diarrhoeals globally. This is often done in places with least resources.

Even in the industrialized world, diarrhoea is one of the most common causes of illness in children below five years of age. The Centers for Disease Control and Prevention in Atlanta estimate that at least 16.5 million children in the United States have diarrhoea at least once a year, and between 300 to 500 die each year. Most of these deaths could be prevented, if immediate action was taken at home and appropriate care made available at health facilities. The disease accounts for 3 million visits to paediatric offices and 220,000 hospitalizations, or about 10% of all hospitalizations of children five years and younger.

The Honourable Donna Shalala
Secretary, Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Public Citizen, an American Consumers Rights group, has submitted a petition to the US Food and Drug Administration that calls for banning and/or relabeling of ineffective and potentially harmful antidiarrhoeal drugs sold in the U.S. These drugs have no place in the management of acute diarrhoea in children.

The World Health Organization (WHO) reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" and submitted their comments to Dr. David Kessler, Commissioner of the Food and Drug Administration. WHO supports Public Citizen's petition.

The decision of the Food and Drug Administration will have far reaching consequences for the developing world, considering that most developing countries often refer to the findings of the FDA before deciding about the efficacy, safety and need of drugs. The decisions made here would therefore affect millions of lives throughout the world.

This consumer movement could spearhead global action. The issues related to antidiarrhoeal drugs could become the first in a series of activities to assure safe medicine for young children. The alternative use of scarce financial resources, both personal and public, which is now used for useless and often harmful antidiarrhoeals, is important. At a time when the U.S. is grappling with lowering health care costs, it seems appropriate to review policies and guidelines related to the control of diarrhoeal diseases.

Giving top priority to programmes for reducing child health..... promoting correct case management in medical colleges and at home (including promotion of ORT)..... reviewing and rationalizing medical insurance and reimbursement policies according to standard case management guidelines..... and reviewing drug policies, are some steps that will facilitate the control of diarrhoeal deaths.

The outcome of Public Citizen's petition is of great importance not only for young children in the U.S., but throughout the world. I write today to seek your personal attention to the problem.

With best wishes.

Yours sincerely,

James P. Grant
Executive Director

OXFAM
United Kingdom & Ireland

274 Banbury Road
Oxford OX2 7DZ
Tel: (0865) 311311

Telex: 83610 OXFAM G
Fax: (0865) 312600

30/3/93

Dr Lee Zwanziger,
Executive Secretary,
OTC /Advisory Committee,
Food and Drug Administration,
CDER, HFD-9, 88-45, 5600 Fishers Lane,
Rockville, Maryland 20857, USA.

Dear Dr Zwanziger,

Subject: Public Citizen's Petition for a Ban and/or Relabelling of Antidiarrhoeal Drugs.

This letter reflects the views of a number of UK-based development agencies, all of whom have health programmes in developing countries, and who wish to support the Public Citizen's petition on ineffective and dangerous antidiarrhoeal drugs in young children.

While diarrhoea is a significant cause of preventable deaths of infants in industrialised countries - 10% of the total in the USA itself - the overwhelming burden falls on children in the developing world, where WHO calculates that 3 million deaths occur every year.

In our opinion the widespread sale of unscientific and expensive antidiarrhoeal drugs contributes to this appalling toll. First, it encourages the mistaken view that drugs, and not oral rehydration, are an appropriate treatment for acute diarrhoea. WHO states categorically in its scientific review 'The Rational Use of Drugs in the Management of Acute Diarrhoea in Children':

"Antidiarrhoeal drugs and emetics should never be used. None has any proven practical value and some are dangerous".

Second, the cumulative cost of inappropriate antidiarrhoeal drugs is an unnecessary and highly damaging misuse of scarce resources in countries where national and household budgets for health are grossly inadequate. The production and promotion of oral rehydration solution, with continued feeding, could save lives at a cost of only 50 cents per child.

The 1986 Drug Exports Amendment Act prevented the direct export of drugs to developing countries which were not licensed for use in the USA. The full value of this legislation is felt when drugs are adequately regulated in the domestic market. As we understand the OTC Advisory Committee will confine itself to discussion of kaolin and attapulgite on April 9th we can only reiterate WHO's position on the lack of evidence on efficacy and safety of these preparations. Neither reduces fluid or

electrolyte loss, and kaolin may interfere with efficacy of antibiotics, when these are indicated. Therefore they have no place in the management of acute diarrhoea and should not be used.

In addition, we would like to draw to your attention an entry in the Physicians' Desk Reference (1992) which gives the dangerously misleading impression that the drug Imodium should be used as a primary agent in the treatment of acute diarrhoea in children. This states:

"the use of Imodium does not preclude the administration of appropriate fluid and electrolyte therapy"

Drug Regulatory Authorities in developing countries frequently lack the capacity to evaluate drugs, and to provide high quality information. They often depend on the US-PDI, PDR, and on regulatory decisions in developed countries.

We urge that this extra dimension of responsibility is noted by the committee, and that action is taken in response to the petition.

Yours sincerely,

David Bryer

Director, Oxfam.

Martin Griffiths

Director, Action Aid.

Richard Hatton

Director, Save the Children Fund.

Jenny Borden

Deputy Director, Christian Aid.

Richard Riley

Assistant Director, Cafod.

Mike Whitham

Director, British Red Cross.

WORLD HEALTH ORGANIZATION
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Message No. ____ Page 1 of 2 pages Date: 9 March 1993

From: Director, Division of Diarrhoeal and Acute Respiratory Disease Control

To: Dr David A. Kessler, Commissioner, Food and Drug Administration, Rockville, MD 20857 USA

Our ref:

Fax No: 301 443 3100

Originator: Dr L. Richards

Subject: CITIZEN'S PETITION FOR A BAN AND/OR RELABELING OF ANTIDIARRHEAL DRUGS

TEXT

Dear Dr Kessler,

We recently reviewed a copy of the "Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs" submitted to your office by Public Citizen. We share the concerns voiced in the petition over the widespread use of ineffective and often dangerous antidiarrhoeal drugs in young children.

We are particularly concerned that some antidiarrhoeal drugs marketed in the United States and developing countries are being promoted by their manufacturers as adjuncts to oral rehydration therapy. In fact, Janssen's entry for IMODIUM in the Physicians' Desk Reference (1992, p. 1139) goes a step further, stating that "the use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy". This statement conveys to us the message that IMODIUM should be the first agent used to treat diarrhoea in children but that oral rehydration therapy might also play some role. While ORS treats dehydration by replacing electrolyte and fluid losses, we do not feel that the use of IMODIUM has a significant effect on fluid and electrolyte loss or on the duration and severity of diarrhoea. IMODIUM is easier than ORS to administer to children, however, and it is reasonable to suppose that a mother giving IMODIUM to her child in the belief that it will "stop" diarrhoea will pay scant attention to feeding and rehydrating the child.

The claim made by Janssen in the Physicians' Desk Reference that IMODIUM "diminishes the loss of fluid and electrolytes" cannot in our view be supported by published studies. It is misleading, therefore, for the manufacturer to imply that IMODIUM is in any way a substitute for oral rehydration therapy, or to advise that it be used in conjunction with oral rehydration therapy.

In a similar fashion McNeil Consumer Products, manufacturer of IMODIUM A-D (an over-the-counter preparation of loperamide) has linked the use of its product with oral rehydration therapy. In a letter dated 31 July 1992 to the Medical Lobby for Appropriate Marketing, which MaLAM has shared with us, Dr Anthony R. Temple of McNeil states that:

Copies to: Director, PHA
Dr J. Yunes, Chief, Special Program, HMF, AMRO

"It has been standard practice by physicians in the U.S. to use rehydration initially and then to use oral antidiarrheal medications as appropriate."

A review of current pediatrics textbooks, however, failed to find any that advocate the use of antidiarrhoeal agents, including antimotility drugs, for the routine management of acute diarrhoea.

While our Programme is particularly targeted at developing countries, where diarrhoeal diseases account for more than 3 million deaths in young children each year, diarrhoea is associated with significant childhood morbidity and mortality in the United States as well, causing some 500 deaths annually, and 10% of preventable postneonatal infant deaths.

We would also like to point out that in formulating their drug policies, developing countries often consider the findings of the Food and Drug Administration and American and European pharmacopoeias before deciding about the safety and efficacy of a drug. We urge you to bear in mind that the decisions made by your agency affect not only Americans but also policy makers and prescribers from other countries who look to the FDA as a source of objective and accurate information.

We are sending, under seprate cover, a copy of our publication entitled "The rational use of drugs in the management of acute diarrhoea in children". This book reviews published studies of the efficacy and safety of antidiarrhoeal drugs, including loperamide, that are commonly administered to children in developing countries. Also enclosed is a recently published article outlining WHO's case management strategy for diarrhoea in developing and developed countries. We hope that these will serve as a useful reference, and would be pleased to answer any queries you may have or to provide further information.

We will follow with interest the outcome of the Public Citizen petition.

Yours sincerely,

Dr J. Tulloch
Director
Division of Diarrhoeal and Acute
Respiratory Disease Control

International Child Health Foundation

10630 Little Patuxent Parkway • Century Plaza • Suite 325
Columbia, MD 21044
Telephone: (301) 596-4514 or FAX (410) 992-5841

March 29, 1993

Dr. David A. Kessler
Commissioner, Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Kessler: RE: FDA hearing on antidiarrheal drugs

We share the concerns expressed by the World Health Organization in response to the Public Citizen petition to the U.S. Food and Drug Administration (FDA) asking for a relabelling of some antidiarrheal drugs and a banning of others. This petition recognizes that there has been widespread and inappropriate use of drugs for treatment of children with acute diarrhea and that most drug use for diarrhea is expensive, unnecessary, and potentially harmful.

Every year over 3 million children under age 4 die from effects of diarrheal disease. As reported by the Centers for Disease Control (CDC), children in this country are among those afflicted (CDC reports 350-500 deaths and over 200,000 hospitalizations of young children in the U.S. each year are from diarrheal disease). Ten percent of postneonatal infant death and ten percent of non-surgical hospitalizations of children in the U.S. are results of diarrheal disease.

Most of the diarrhea-related hospitalizations and deaths could be prevented with oral rehydration therapy (ORT) alone. ORT includes use of an oral electrolyte solution and appropriate feeding. To be most effective, treatment is started at the onset of diarrhea-related illness. In most cases this early treatment prevents serious consequences of diarrhea and, in most cases, ORT and feeding are all that are needed.

Sadly, education about how to prevent and how to treat diarrheal diseases effectively and correctly is missing both from both public education and appropriate medical education. We are actively working on this with our Partners for Better Health network, which includes physicians at a growing number of U.S. schools of medicine and hospitals such as Cincinnati Children's Hospital, Grady Hospital, Johns Hopkins, Harvard, Massachusetts General Hospital, University of Maryland Hospital, Texas Children's Hospital, Tulane, and others.

We at International Child Health Foundation (ICHF) first began our promotion of oral rehydration therapy in 1987 with a symposium at the National Academy of Sciences. Since then, we are glad that awareness of the potential to save lives and health care

costs through appropriate management of diarrheal disease is spreading. We began our efforts to increase use of ORT in the United States because U.S. health practices are followed closely by Third World leaders and institutions. What we do here in the United States has a major impact on practices and beliefs abroad.

Implementing the long-recommended preferred treatment of diarrhea with ORT and feeding would reduce our own problems and costs and, at the same time, help worldwide efforts to stem millions of preventable deaths. While drugs that are used in appropriate ways can save lives, widespread and inappropriate use of drugs can kill. The potential costs of inappropriate drug use are deaths and millions of wasted dollars.

Sincerely,

FOR THE INTERNATIONAL CHILD HEALTH FOUNDATION

Charlene B. Dale
Executive Vice President

W. B. Greenough, III, M.D.
Johns Hopkins University
and President, ICHF

Ronald L. Kleinman, M.D.
Chairman, Pediatric Gastroenterology
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Massachusetts General Hospital, and
Committee on Nutrition,
American Academy of Pediatrics
and
ICHF Board of Trustees

David A. Sack, M.D.
Department of International
Health
Johns Hopkins University
and
Chairman
ICHF Task Force on
Cereal-based ORT

Enclosures:
Training Manual for Treatment and Prevention of Childhood Diarrhea with Oral Rehydration Therapy, Proper Nutrition, and Hygiene, a publication of the International Child Health Foundation, Columbia, Maryland, 1992.

Summary: Description of the ICHF Partners for Better Health Program
ICHF Newsletter

"The Management of Acute Diarrhea in Children: Oral Rehydration, Maintenance and Nutritional Therapy," Report of U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention (CDC), October 16, 1992, Volume 14, No. RR16. *Note: Most of the consultants and reviewers are ICHF technical advisors and trustees.*

Public Citizen

Buyers Up • Congress Watch • Critical Mass • Health Research Group • Litigation Group

Ralph Nader, Founder

Public Citizen Health Research Group

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Analysis of 1993 Commerce Department Health Expenditure Data

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ANALYSIS OF 1993 COMMERCE DEPARTMENT HEALTH EXPENDITURE DATA

PUBLIC CITIZEN HEALTH RESEARCH GROUP
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U.S. Commerce Department: $939.9 Billion Health Costs for 1993; $1.066 Trillion by 1994: $2.009 Trillion by 1999

In a Commerce Department report, U.S. Industrial Outlook 1993, embargoed not to appear in print until Jan. 5, 1993, the government estimates that **national health expenditures will increase to $939.9 billion in 1993**, a 12.1% jump from 1992 for yet another year of double digit increases in this, the largest industry in the United States.

This astounding figure provides incontrovertible evidence of a national health care crisis, and demands political leadership to cure this festering wound in our country.

A RECORD INCREASE IN HEALTH EXPENDITURES

The estimate of $939.9 billion for 1993 health expenditures is, to our knowledge, the largest estimate yet made by any governmental agency for 1993 health expenditures and is accompanied by revised 1992 figures--$838.5 billion--which are higher than the $817 billion the Commerce department had estimated would be spent in last year's report. The report also estimates that outlays for hospital care will increase 12.4% to 363.4 billion in 1993. Expenditures for physicians services will amount to an estimated $175 billion, an 11.5% increase over 1992, while spending for nursing homes and home care will approach $92.5 billion, a 15.6% increase.

In addition, because of the still weakened U.S. economy and the very small projected increase in the Gross Domestic Product (GDP) from 1991 to 1992, **the percent of the GNP which went for health expenditures was an all-time record in 1992 and "surpassed 14 percent of the GDP"**. In other words, one out of every seven dollars in our economy was spent for health, despite the fact that, according to data we made public several weeks ago, 35.4 million Americans were without health insurance in mid-1991 and the number is, by now, probably 37 million or more. As more and more people are unemployed, the ranks of the uninsured will grow even more rapidly.

Other extremely troubling aspects of the Commerce Department

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report are the projections for increasingly uncontrolled health expenditures for the next five years. It states that **"Expenditures are expected to rise by about 12-15 percent per annum during the next five years unless significant changes in the healthcare delivery system occur."** This estimate, with a mid-point of 13.5% healthcare inflation a year, is clearly larger than the five-year projection in last year's report which stated that **"expenditures on health care are expected...to increase at an average annual rate of 12 to 13 percent during the next five years."** (mid-point of 12.5%)

Assuming increases of 13.5% each year, the mid-point of the Commerce Department projections for the next five years, we have calculated that this would result in 1994 national health expenditures of $1.066.8 trillion with projected expenditures of $2.009 trillion by 1999. **This would mean that in just six years, 1993-1999, there will be almost a doubling of expenditures with an increase of more than $1.06 trillion, an increase which exceeds the projected total U.S. health expenditures in 1993 of $939.9 billion.**

AN EPIDEMIC OF ADMINISTRATIVE WASTE

Somewhat buried in last year's U.S. Industrial Outlook Report was the statement that "Employment has grown fastest in offices of physicians and surgeons--by 200,000 between 1988 and 1990." Given that the number of physicians in the U.S. only increased from 538,000 in 1988 to 570,000 in 1990, it is likely that most of this increase is in administrative personnel, needed to push the megatons of paperwork generated by having more than 1000 different private health insurers in this country. Similarly, there were 409,000 new hospital employees added between 1988 and 1990, many of whom are also engaged in administrative activities.

In this year's report, the Commerce Department reveals that "employment in the healthcare industry rose from 7 million in 1988 to approximately 10 million in 1992." In other words, this average 9.3 percent annual growth rate, or overall 42.8% in the last four years accompanies the increase in the number of people without health insurance. Most of these jobs are not for people who are actually delivering medical care but are largely administrative jobs, producing or delivering paperwork (the numbers do not include people employed in the insurance industry itself). The Commerce Department goes on to say that "During the past decade, the industry's employment growth surpassed that of the rest of the private economy--a trend which should continue for the remainder of this decade."

THE CASE FOR A SINGLE PAYER SYSTEM

As we have stated previously, there would be enormous annual administrative savings from going to an improved American version

of Canada's single payer system--which eliminates the wasteful role of the private insurance industry and all of the paperwork it foists on hospitals, doctors, nursing homes and the rest of the health care system. Estimates of these savings range from $93 billion a year (GAO estimate) to $140 billion a year (estimate of Physicians for a National Health Program).

A 'MEDICALLY INDIGENT' MIDDLE CLASS

Whereas in the past, it was mainly the poor who did without health care, a dominant concept of this decade is becoming that of **medical indigence**. Millions of middle class people, not poor by traditional standards of poverty, are rapidly becoming medically indigent as health costs vastly outstrip wage increases. In 1991, the latest year for which data are available, there were over one million more middle class people (incomes of $25,000 to $50,000) uninsured than in the previous year with actually fewer poor (incomes under $25,000) and better-off (incomes over $50,000) uninsured than in 1990. It is a national disgrace about which a rich country such as ours should be profoundly embarrassed.

THE PRESIDENT-ELECT'S RESPONSIBILITY

President-elect Clinton has given no indication that he will offer a health plan with any chance of curing this crisis. In fact, he and his advisers have suggested "managed competition" platitudes as their answer to the crisis, even though these grim Commerce Department predictions are based on the supposition that "Rapid growth is seen for...managed care organizations in the years ahead."

Until and unless we abandon the private insurance industry's involvement and place caps on what doctors and hospitals charge or spend and thus halt other out-of-control cost increases, the dire predictions of the Commerce Department will come true, driving millions more Americans into the ranks of the uninsured.

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Health and Medical Services

Expenditures on healthcare (SIC 80) in the United States are expected to rise 12.1 percent to $939.9 billion in 1993. Rapid growth is seen for home health care, nursing home care and for managed care organizations in the years ahead. Expenditures are projected to rise by about 12-15 percent per annum during the next 5 years unless significant changes in the healthcare delivery system occur.

Before reading this chapter, please see "How to Get the Most Out of this Book," on page 1. That section will answer questions you may have concerning data collection procedures, forecasting methodology, and sources and references. For other topics related to the healthcare industry, see chapter 43 (Drugs and Biotechnology), chapter 44 (Medical and Dental Instruments and Supplies), and chapter 52 (Insurance).

The healthcare industry consists of public, private and non-profit institutions. These institutions are hospitals; offices and clinics of medical doctors; nursing homes; other specialized healthcare facilities; managed care consisting of pre-paid plans such as health maintenance organizations (HMOs), preferred provider organizations (PPOs), and independent practice associations (IPAs).

The nation's healthcare services industry currently includes thousands of independent medical practices and partnerships, as well as public and non-profit institutions, and many private corporations. The industry is labor intensive, employing approximately 10 million people of whom more than 600,000 are physicians. America's complex healthcare system relies on some of the most sophisticated and expensive technology in use by any domestic industry.

Health Care Expenditures

Total healthcare expenditures rose 11.5 percent from 1991 to 1992, to reach an estimated $838.5 billion. On a per capita basis, these expenditures exceed $3,160. By 1992, the nation's health and medical care sector outlays surpassed 14 percent of the Gross Domestic Product (GDP). This amount is substantially higher than what is found in other leading industrialized countries. The rate of growth for U.S. healthcare expenditures continues to surpass GDP growth rates.

The rising costs of health care are attributable to many factors, including:

- The use of sophisticated and high-priced equipment;
- Increases in variety and frequency of treatments;

Trends and Forecasts: Health and Medical Services (SIC 80)

(in billions of dollars)

Item	1987	1988	1989	1990	1991[1]	1992[2]	1993[3]	Percent Change 1987-88	1988-89	1989-90	1990-91	1991-92	1992-93
National Health Expenditures	494.2	546.1	604.3	675.0	751.8	838.5	939.9	10.5	10.7	11.7	11.4	11.5	12.1
Health Services and Supplies	476.9	526.2	583.6	652.4	726.6	813.9	914.0	10.3	10.9	11.8	11.7	11.7	12.3
Personal Health Care	439.3	482.8	530.9	591.5	660.2	739.0	830.2	9.9	10.0	11.4	11.6	11.9	12.3
Hospital	194.2	212.0	232.4	256.1	286.6	323.2	363.4	9.2	9.6	11.1	11.8	12.0	12.4
Physicians' Services	93.0	105.1	116.1	128.8	142.0	157.1	175.2	13.0	10.5	10.9	10.2	10.6	11.5
Dentists' Services	27.1	29.4	31.6	34.1	37.1	40.4	44.2	8.5	7.5	7.9	8.8	9.0	9.5
Other Professional Services	21.1	23.8	27.1	30.7	35.8	41.7	47.4	12.8	13.9	13.3	16.6	16.6	13.7
Home Health	4.1	4.5	5.6	7.6	9.8	12.7	16.5	9.8	24.4	35.7	28.9	29.5	30.0
Non-Durable Medical Products	43.2	46.3	50.5	55.6	60.7	66.4	72.6	7.2	9.1	10.1	9.2	9.4	9.4
Durable Medical Equipment	9.1	10.1	10.4	11.7	12.4	13.2	14.2	11.0	3.0	12.5	6.0	6.3	7.5
Nursing Home Care	39.7	42.8	47.7	53.3	59.8	67.3	76.0	7.8	11.4	11.7	12.2	12.5	13.0
Other Personal Health Care	7.8	8.7	9.8	11.5	14.0	17.0	20.7	11.5	12.6	17.3	21.4	21.7	21.8
Administration	23.0	26.9	33.8	38.9	43.9	48.6	54.3	17.0	25.6	15.1	12.9	10.7	11.7
Government Public Health Activity	14.6	16.6	18.9	22.0	24.5	26.3	29.4	13.7	13.9	16.4	11.4	7.3	11.8
Research and Construction	17.3	19.8	20.7	22.7	23.2	24.6	25.9	14.5	4.5	9.7	1.8	6.0	5.3
Research[4]	9.0	10.3	11.0	11.9	12.6	13.3	14.1	14.4	6.8	8.2	5.8	5.5	6.0
Construction[5]	8.2	9.5	9.7	10.8	10.6	11.3	11.8	15.9	2.1	11.3	-1.8	6.6	4.5

[1]Preliminary.
[2]Estimate
[3]Forecast
[4]Research and development expenditures of drug companies and other manufacturers and providers of medical equipment and supplies are excluded from "research expenditures," but they are included in the expenditure class in which the product falls.
[5]Benchmark data by HCFA.

NOTE: Numbers may not add to totals because of rounding.

SOURCE: U.S. Department of Health and Human Services, Health Care Financing Administration (HCFA), Office of the Actuary, U.S. Department of Commerce, International Trade Administration (ITA). Estimates and forecasts by ITA.

- Innovative, but costly treatment of some illnesses such as heart ailments, end stage renal disease, AIDS, and cancer;
- Increased longevity of the population;
- Labor-intensiveness in the health care industry and the high earnings of professional, administrative, and technical workers.

In June 1992, the prospective Payment Assessment Commission in a report submitted to Congress indicated that rom 1985 to 1990, population growth, economywide nflation, medical price inflation, utilization, and intensity f services were factors that contributed to the sharp rises n health care costs (Table 1).

Table 1: Factors Accounting for Growth in Healthcare Spending, 1985–1990

(percent distribution)

Services	Population	Economy-wide price inflation	Medical price inflation	Utilization[1]	Intensity[2]	Total
Inpatient	12.7	44.6	24.5	−23.2	41.4	100
Outpatient	6.0	21.2	11.6	30.6	30.6	100
Physicians	8.3	29.2	21.4	3.7	37.4	100
Nursing homes	10.9	38.4	15.4	2.6	32.7	100

[1]Days or visits per patient.
[2]Services per visit.
SOURCE U.S. Department of Health and Human Services, Health Care Financing Administration, Office of the Actuary.

Cost Factors

From 1980-90, the share of household personal income llocated to healthcare rose from 4 percent to 5 percent. his figure does not include indirect expenditures such as ayroll, income taxes, and other taxes that finance public ealth care programs. In 1991 the estimated healthcare bill or the average U.S. family was $4,296. Of this amount, eneral taxes accounted for 39 percent of the total, out-of-ocket (consumer) costs were 32 percent, insurance premiums 17 percent, Medicare payroll taxes 9 percent, with ledicare premiums accounting for the balance, 3 percent.

Industry sources estimate that, in 1990, the average nployer's share of medical and medically-related costs per nployee surpassed $3,100. Sharp increases in this amount re cited as a main reason for the rise in uninsured people, om 33.6 million in 1988 to approximately 37 million by 992.

During the past two decades many strategies have been nplemented by the Federal Government, states, and businesses, to control escalating costs. Yet healthcare expenditures have risen from $74.4 billion in 1970 to $838.5 billion 1992, at an average annual rate of 11.5 percent.

Among measures taken thus far to address this situation e the following:

- strategies to reduce the use of out-of-pocket share of payment;
- programs to restrict choice of provider;
- programs limiting providers' selection of services;
- direct controls over prices of services;
- policies encouraging increased competition in health insurance markets;
- regulatory policies.

rofit Margins

There is no uniform way of reporting the industry's ofitability. Fragmentary information indicates that fewer an 13 percent of all hospitals, the dominant group of ealthcare providers, are profit-making corporations.

Any analysis of provider services should take into consideration that most hospitals operating for profit or on a on-profit basis *do* make a profit. This enables them to nerate sufficient revenues to buy the latest technology, y competitive salaries, and cover other costs. According the Prospective Payment Assessment Commission, ofit margins have fluctuated since the mid-1970's, when they were 2 percent. They reached 6 percent in 1984, and declined to under 4 percent in 1990.

Profit information on other health care providers (physicians, dentists, nursing homes, management care organizations, and health insurance companies) is sparse. Attempts to secure better data are impeded by a wave of industrywide mergers and buyouts. However, HMOs, which are part of managed care organizations, realized after-tax net income of more than $1 billion in 1990 and again in 1991.

Medicare

Medicare is a Federal program that pays hospitals and other medical providers who care for patients aged 65 years and older, for certain disabled people, and most persons with end-stage kidney disease. There are approximately 34 million Medicare enrollees, including more than 3 million afflicted with disabilities. Total Medicare outlays are projected to rise from $131 billion in 1992 to $145.5 billion in 1993 representing an 11 percent increase.

Medicare consists of two parts, Hospital Insurance (HI) and Supplementary Medical Insurance (SMI). HI is funded primarily by Social Security payroll taxes. HI pays for care provided by hospitals, skilled nursing facilities, home health agencies, and hospices. HI outlays are likely to reach $84.8 billion in 1993, an increase of $7.4 billion over the previous year.

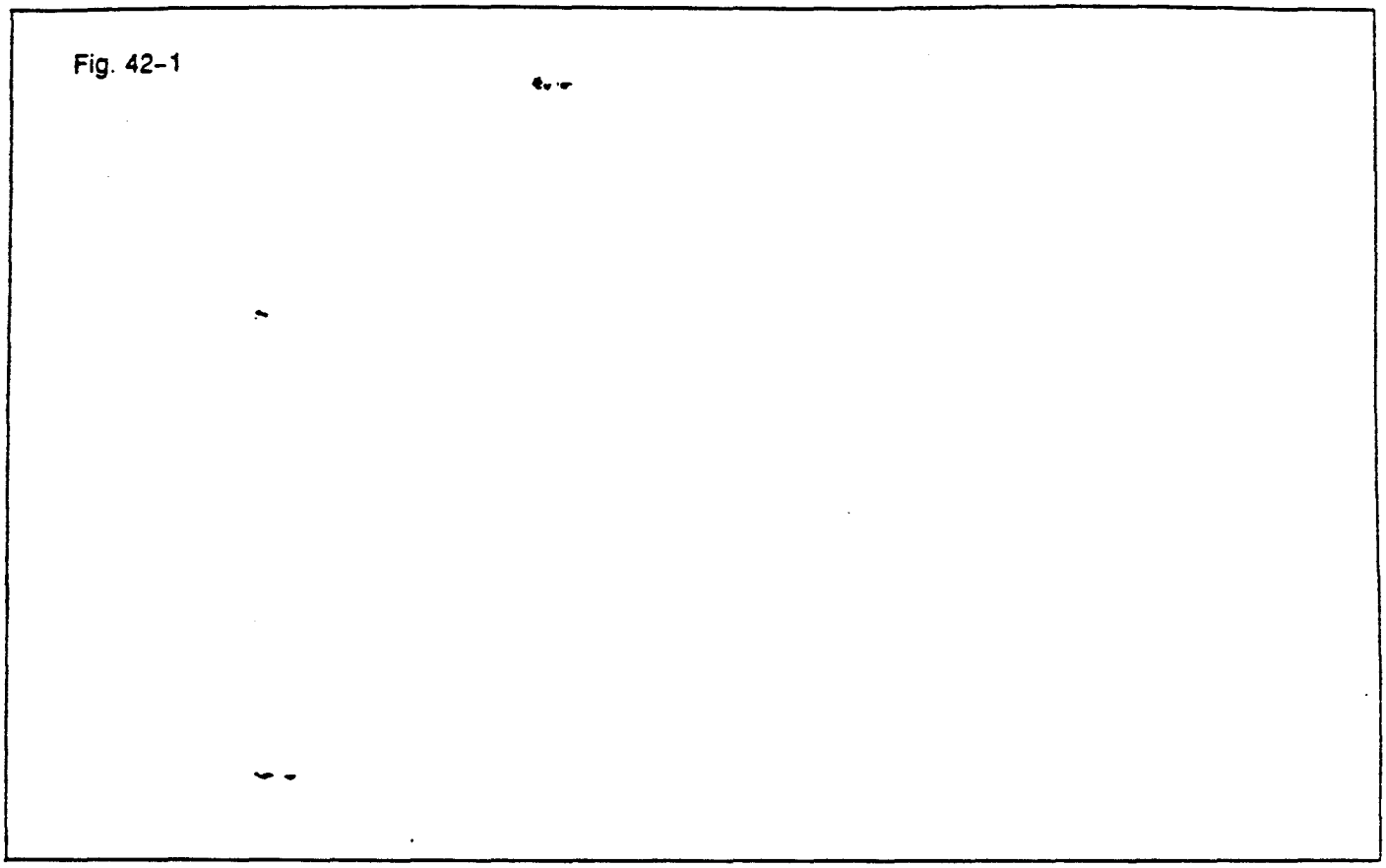
SMI pays for physician services, laboratory services, hospital inpatient costs, treatment for end-stage kidney disease, and for durable medical equipment. SMI outlays are expected to grow from $53.6 billion in 1992 to $60.7 billion in 1993, a 13.2 percent rise. Enrollees pay about 35 percent of costs through premiums, but a subsidy from general revenues finances the bulk of the entire program.

Medicaid

Medicaid is a Federally-supported and state-administered assistance program providing medical care for certain low-income individuals and families. Medicaid covered about 28 million people at a cost of $100 billion in 1991.

Medicaid as well as Medicare programs are subject to periodic changes in laws and regulations. All such changes may materially increase or decrease payments to hospitals, physicians, and other medical providers. As Medicaid and Medicare programs have become costlier in recent years, the tendency by Congress and state legislatures has been to reduce Medicaid and Medicare financing.

Fig. 42-1



While Medicaid programs cover a small fraction of the U.S. population, many compare it to a national healthcare program. Medicaid serves many groups. For poor people with Medicare, Medicaid actually serves as a medigap policy, paying coinsurance, deductibles, and services not covered by Medicare. For all income groups, Medicaid is the ultimate payer for long stays in nursing homes or intermediate care facilities for the mentally retarded. Long-term care for these recipients accounts for 44 percent of all Medicaid spending. Medicaid provides catastrophic coverage for people who have episodes of a variety of problems and have no cash assistance. It automatically pays after both family cash reserves and private insurance are exhausted.

Nursing Home Care and Related Care Homes

Nursing homes are an integral feature of the American healthcare system. They provide medical, social, and residential services to chronically disabled people over an extended period of time. Because chronic disability increases with age, the elderly are the primary recipients of nursing home care.

There are 31 million persons aged 65 and over in the United States. An estimated 7 million require continuous assistance for routine daily functions. In cases where family members are absent, an institutional setting becomes essential. In addition, many of the chronically disabled require intensive medical assistance, and often are served by nursing care on an around-the-clock basis.

Long-term care facilities are of three basic types: (1) nursing homes certified by Medicare and Medicaid as skilled nursing care facilities (SNFs); (2) nursing homes certified for chronically disabled patients or the mentally retarded; and (3) all other facilities that furnish some degree of long-term nursing care.

In 1986, the latest year in which data are available, there were 16,388 nursing homes, and 9,258 residential facilities. Also there were 734 hospital-based facilities providing nursing care services in addition to other forms of treatment. In total, there were 1.8 million beds and 1.6 million residents. The occupancy rate for skilled nursing facilities was 94 percent, and for hospital-based facilities it stood at 92 percent.

Medicare payments to SNFs fluctuated from $3.4 billion in 1989 to $2.4 billion in 1990 and $2.5 billion in 1991. The fluctuation was due to the Medicare Catastrophic Coverage Act of 1988. Following its repeal, those payments and services were decreased. State Medicaid programs provide 45 percent of payments and cover more than 60 percent of all nursing home patients. Medicare covers less than 5 percent of nursing home payments. Future Medicaid policies will greatly influence access to nursing home services for prospective beneficiaries.

Home Health Care Services

Home healthcare is a method of providing healthcare services to disabled people within their homes. There are more than 5 million people in the United States who require such services. These include physicians' care, part-time or intermittent skilled nursing care, physical therapy, and speech therapy. Medical supplies and durable medical equipment used in providing these services are also elements of this system.

In 1990, there were about 11,000 home health service providers in the United States. More than half, 5,700, were Medicare-certified and about 1,780 were provided by hospitals. Home healthcare expenditures rose from $7.6 billion in 1990 to $9.8 billion in 1991, a 28.9 percent increase. Since 1980, they grew at average annual rates of approximately 26 percent. Government financed three-fourths of the total, while out-of-pocket payments accounted for about 12 percent and most of the balance was paid by private health insurance.

The number of home visits by industry professionals to the afflicted and/or disabled increased from 16.3 million in 1980 to more than 17.8 million in 1991. During the same period, numbers of patients served more than doubled (from 726,000 to an estimated 1.7 million).

Private Health Insurance

Health insurance premiums have increased sharply during the past years. Insurers have raised their rates by 8 to 60 percent, citing escalating healthcare prices, ineffectiveness of cost-cutting efforts, and possible discriminating pricing practices by health providers.

In 1990, private health insurance plans disbursed $216.8 billion, an amount which was more than $20 billion above disbursements for 1989. Private health insurance covers three-fourths of the total non-institutionalized population. There are approximately 71 million workers with 69 million dependents, all of whom obtain coverage as an employment benefit. The remaining 44 million people purchase their own coverage.

More than 1,000 private insurance companies in the United States write individual or group health insurance plans. The private health insurance industry has been growing rapidly because (1) consumers seek to reduce risks of high-out-of-pocket expenses, and (2) business health insurance premiums receive preferential tax treatment, estimated at $60 billion annually.

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Equipment Leasing Association

Increasing reliance on sophisticated technology has been a contributing factor to sharp increases in medical costs.

Private coverage is available through insurance companies, hospitals, through medical service plans, and through group medical plans operating on a prepayment basis. The prepayment plans, such as those that managed care organizations provide, have grown rapidly and are creating competition among healthcare insurers.

Private health insurance companies sometimes deny coverage to individuals because they suffer from AIDS, alcoholism, diabetes, coronary artery disease, or cancer. In addition, coverage may be denied to people in high-risk categories, such as drug abusers, older people, and those in certain occupations. The principal reasons for lack of private insurance coverage are that the offer price is more than the uninsured can pay and/or the coverage is not available at any price.

Hospital Waste Disposal

The contamination of New Jersey beaches in 1988 highlighted potential threats to public health arising from improper medical waste disposal procedures. This issue is having a profound impact on healthcare. Since then, Federal and state governments are monitoring the situation far more vigorously, focusing on hospital-generated medical waste and disposal practices. The Environmental Protection Agency, has introduced regulations (and mandated penalties) for hospitals which dispose of substances into the environment. Those substances and materials include red bag waste, incinerator emissions, radioactive waste, laboratory waste, and storage tanks.

The Medical Waste Tracking Act of 1988 forces States to enact or modify regulations dealing with disposal of medical and infectious waste. The Clean Air Act imposes tough restrictions on medical waste incinerators that burn over two tons of waste material daily.

One of the few new technologies available to dispose of medical wastes appears to be cost-effective. It compacts potentially dangerous substances, shredding, granulating, and chemically treating the waste material.

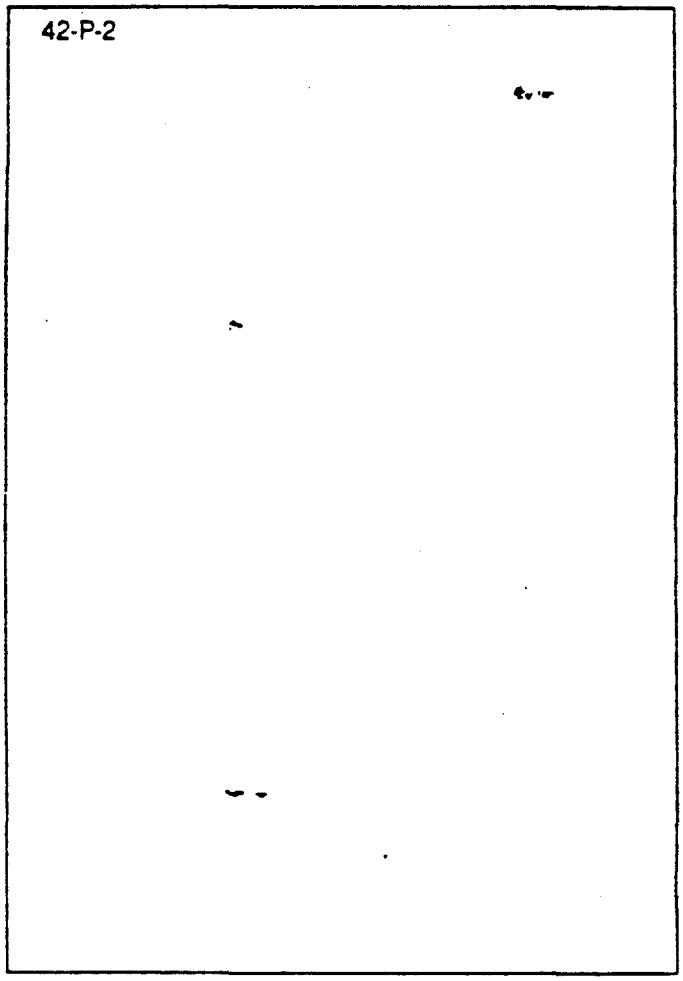
Employment

Employment in the healthcare industry rose from 7 million in 1988 to approximately 10 million by 1992. This represents average annual growth rates of 9.3 percent. During the past decade, this industry's employment growth surpassed that of the rest of the private economy—a trend which should continue for the remainder of this decade.

Healthcare workforce totals are exclusive of employment in the health insurance, medical equipment and supplies, and pharmaceuticals industries. There has been positive employment growth in all these sectors, especially in offices and clinics of medical doctors, as well as in nursing and personal care facilities. Hospitals and nursing homes account for about 62 percent of the total number employed in healthcare.

Allied Health Personnel

Allied health personnel are workers who assist physicians and other specialists. This job category is among the fastest growing occupational sectors of the entire healthcare industry. The Bureau of Health Professionals estimates there were 1.8 million allied health personnel in the United States



National Association of Public Hospitals

Healthcare industry professionals must be attuned to an array of complex issues surrounding public health and medical treatment.

in 1990, a 44 percent increase from 1980. These professionals play an integral role in the delivery of the nation's health services, with 300,000 employed in clinical laboratory positions. More than one-half of the latter are employed by hospitals.

Health Care Reform—A Priority for the Nation

Debate over healthcare reform is accelerating. Attention to this issue rose dramatically during the past decade, and major national healthcare associations—representing business, labor, and other constituencies—advocate modifications in existing policy.

Federal and state lawmakers have introduced proposals. One proposal would direct all employers either to provide medical coverage for their workers, or contribute directly to a government insurance fund ("play or pay"). The U.S. Bipartisan Commission on Comprehensive Health Care for All Americans (the Pepper Commission) recommended such a plan. The Commission also suggested overhauling the nation's private insurance system, and suggested ways of restructuring Medicaid.

Other proposed remedies abound. Some emphasize market competition, tax credits, deductions for the uninsured, capping malpractice awards, and encouraging electronic processing of medical claims. Among those who have made proposals are the American Medical Association, American Hospital Association, U.S. Chamber of Commerce, National Governors Association, Heritage Foundation, and academicians such as professors Uwe Reinhardt and Alain C. Enthoven.

Both business and government agree that the United States should seek to accomplish the following objectives:

- provide cost-effective healthcare services in an era when different factors contribute to high costs;
- design a comprehensive healthcare system that will include 37 million uninsured Americans;
- explore the effects of ever-greater reliance on modern medical technologies;
- review the impact of managed care on overall healthcare expenditures;
- examine access of various socio-economic groups to healthcare services;
- determine levels of healthcare in rural America;
- reduce costs of malpractice liability;
- determine what characteristics best assess quality of service;
- restructure Medicare and Medicaid programs;
- improve medical education as necessary;
- assess healthcare planning;
- explore primary care;
- enhance use of preventive care;
- evaluate issues of bioethics.

Factors contributing to escalating costs are waste, fraud, malpractice and limited effective competition. Waste and fraud alone account for billions of dollars. For example, the Federal Bureau of Investigation uncovered evidence in 1992 that some drug companies were defrauding the Medicare/Medicaid system. Awareness of other abuses has spread, and the call for correction of these abuses will doubtless influence prospects of sectors within the nation's healthcare industry.

The International Health Care Market

The business climate in many foreign countries appears favorable for U.S. healthcare companies to expand into overseas markets. The prospects in Western Europe, Mexico, and in Japan are viewed as particularly promising.

Many foreign governments have designated healthcare as a cornerstone of their social policy, and they plan to provide steady yearly budget increases over the medium term in order to achieve stated objectives. A number of foreign countries strive to modernize both the public and private health sectors, while offering increased market opportunities for services and medical equipment. Others are contemplating privatization, or exploring options to decentralize existing systems for delivery of services. Despite the problems faced by consumers and institutions bearing the burden of escalating healthcare costs within the United States itself, American companies are recognized globally as industry leaders.

In both Western Europe and Japan, demographics (ageing populations as well as increased longevity) and high income levels create growing demand for healthcare services. According to industry specialists, the best prospects in these two regions exist for primary care, home care, and nursing home care services. Also, opportunities in hospital management, and in ancillary services, appear promising.

The newly independent states of the former Soviet Union and countries of Eastern Europe may present some opportunities for U.S. companies. Success in such ventures, however, will demand that U.S. firms tailor their services to the specific needs of each country, while continued efforts by foreign governments to open domestic economies must occur to assure profitability. Although there has been considerable speculation concerning actual healthcare markets across the countries of Eastern Europe and throughout the former Soviet Union, highly volatile commercial and economic conditions prevail in both regions.

In Eastern Europe, U.S. healthcare service providers are frequently in a better position to enter country markets through small, "bite-sized" operations. These undertakings include diagnostic imaging, maternity centers, ambulatory care and surgery, and the sale of computer systems. Several U.S. firms are providing emergency health care services, consulting, and insurance coverage in Hungary. In addition, according to some observers, health maintenance organization (HMO) services may offer a prototype for reform of the still largely state-run health sector in these countries. U.S. government agencies are working to facilitate service providers with market entry through organized trade missions and encouraging liberal trade and investment environments in talks with Eastern European counterparts.

Outlook for 1993

Without modification in healthcare laws and practices, expenditures in 1993 will rise by 12.1 percent, reaching $939.9 billion. Outlays for hospital care are expected to increase 12.4 percent to $363.4 billion. Expenditures for physicians' services will reach an estimated $175.2 billion in 1993, a 11.5 percent increase over 1992, while those for nursing home care will total $76 billion, 13 percent higher than the 1992 total of $67.3 billion. Home care will continue to show strong growth. Its expenditures will rise 30 percent to reach $16.5 billion. Healthcare reforms will be seriously discussed and reviewed by policymakers. One possible outcome within the near term is that through tax incentives and government subsidization, most of the uninsured will gain access to healthcare.

Long-Term Prospects

Consumers, providers, and policymakers will most likely attempt to devise a healthcare system that could increase competition in the United States. The chief goal of any legislative package to emerge will, of course, be cost containment, access and efficiency. However, healthcare spending will continue to absorb a disproportionately high share of GDP. The elderly population already consumes a large share of total healthcare services.

Providing services to all, including the 37 million uninsured, will ultimately increase both the rate of spending and the volume of healthcare services. Health insurance companies may have to make adjustments in their health coverage to comply with any major national healthcare reform that might arise, while health care expenditures will continue to rise but at a slower rate.

Private healthcare institutions may initially realize a lower profit and will have to modify their modus operandi to cope with newly instituted government regulations. Managed care and home healthcare occupy important places in the market, and will undoubtedly continue to do so. Alternatives to institutional care—home healthcare, personal care services, hospice care, and adult care—will increase. Nursing home care will provide a major market for durable medical equipment, supplies and pharmaceuticals.

Efforts to reduce healthcare costs will generate better collaboration between physicians and hospitals in providing services.—*Simon Francis, Office of Service Industries, (202) 482-2697, August 1992.*

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