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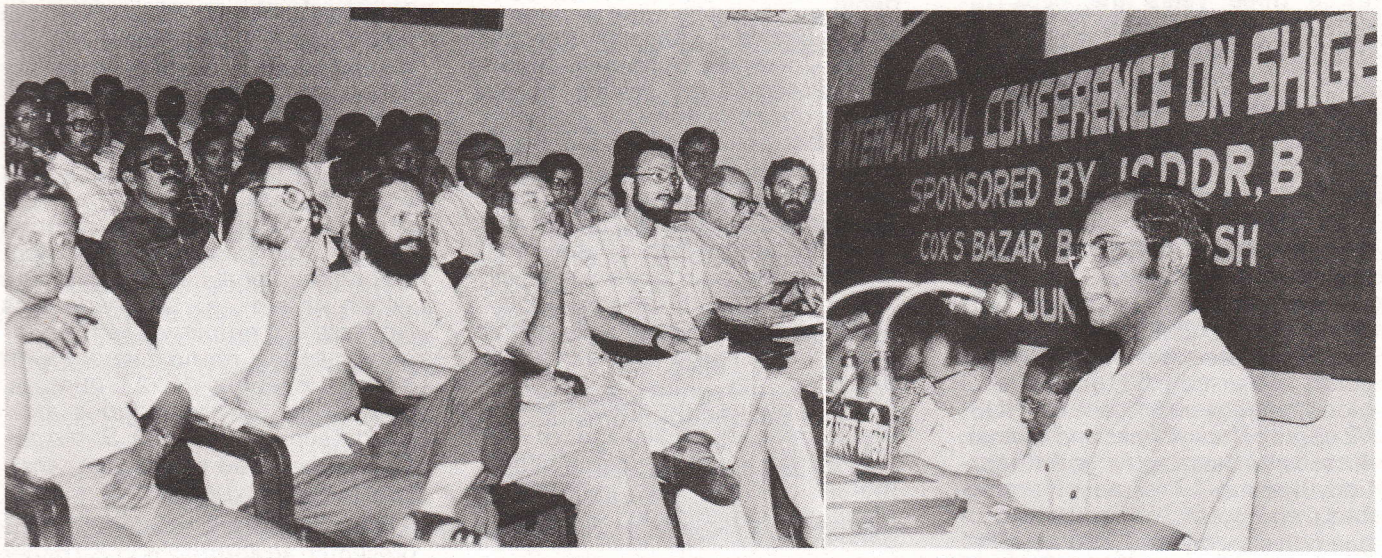

A session of the International Conference on Shigellosis held in Cox's Bazar from 15-19 June 1981

INTERNATIONAL CONFERENCE ON SHIGELLOSIS

A five-day International Conference on Shigellosis sponsored by the International Centre for Diarrhoeal Disease Research, Bangladesh was held from 15-19 June 1981 in Cox's Bazar, Bangladesh. Scientists from Central America, Poland, U.S.A., WHO Switzerland, Mexico, China, Japan and Bangladesh participated in the Conference and presented papers on different aspects of shigellosis.

The following were the objectives of the Conference :

(1) To bring together workers in the various fields of shigellosis to enable them to discuss the latest developments in the subject.
(2) To identify the gaps in our knowledge and to understand the bacteriology, epidemiology, pathology and clinical aspects of shigellosis.
(3) To draw up a list of priority research topics in the field of shigellosis, particularly on the control measures.

The participants of the Conference visited the Teknaf Dysentery Project of ICDDR,B which has been collecting longitudinal information on shigellosis for the last 5 years.

SUMMERIZED VERSION OF ABSTRACTS :

Dr. Rahaman recounted the history of shigellosis in the Cholera Research Laboratory (now ICDDR,B). From 1969, about 35 cases reported to the hospital every year. In the middle of 1972, there was a big epidemic of shigella in Teknaf and Dacca and its surrounding areas. It might have been true for the whole country; but patients reported to the CRL only from and around Dacca City because of its location. These were mostly Shiga (*S. dysenteriae* 1) infections; *S. flexneri* was not a big problem to start with, but increased later with the decrease of Shiga

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cases. These two were almost parallel till 1974, when a big epidemic broke out (this coincided with the famine in Bangladesh) when *S. flexneri* accounted for the major share of dysenteric patients. The trend changed in 1975, when both *S. flexneri* and Shiga cases ran parallel; in 1976 *S. flexneri* became the dominant isolate and this trend continued till 1978. The *S. flexneri* infections staged a comeback in 1979 which is still continuing.

Dr. K M S Aziz of ICDDR,B presented the seasonality pattern of shigellosis in Teknaf, a rural area of Bangladesh for 1977-79. During these three years the peak incidences were in June or July. In July 1978 out of 165 cases, 160 were *S. flexneri.* No *S. dysenteriae* type 1 was detected. Average for all age group incidence rate for these three years was 28.7 with highest rate of 63.9 in children aged <1.

Dr. M R Islam of ICDDR,B retrospectively studied leukemoid reaction in shigellosis and its relation to haemolytic uremic syndrome (HUS). Out of 310 cases attending the hospital who had WBC count more than 50,000/cmm of blood, there were 91 cases of HUS; 62 cases of haemolysis and uremia; 4 cases of haemolysis and thrombocytopenia; 17 cases of uremia and thrombocytopenia; 6 cases of haemolysis only and 120 cases of uremia only were identified. 10 cases had none of these problems. Hyponatraemia was seen in all these patients. Case mortality rate due to HUS was nearly 50%. Success rate however increased after repeated blood transfusion.

Dr. Hanna Stypulkowska-Misiurewicz from Poland also described problems in bacteriological diagnosis of shigellosis. *Shigellae* have the ability to penetrate the epithelial cells to reach submucosa and multiply there. They are less numerous in the stool. Recently modifications have been proposed and some steps are being taken in rechecking bacteriological procedures. Proper collection of sample is the keystone of identification.

Mr. K M B Hussain of ICDDR,B related his experience from five years surveillance of shigellae among patients with diarrhoeal diseases attending a rural hospital. Shigellae ranked third (5.8%) among commonly isolated enteric pathogens. *S. flexneri* was the dominant strain isolated, and accounted for 59% of all shigellosis cases. Children and elderly people were the worst affected.

Dr. M M Levine from the University of Maryland School of Medicine described experiences from induced shigella infections and vaccines in volunteers and controlled field studies. Volunteer studies have demonstrated that the inoculum required to induce shigellosis in healthy adults is quite low (10^1–10^2 organisms). Oral immunization with attenuated *S. flexneri* 2a streptomycin-dependent (SMD) and mutant hybrid (MH) in field studies were found to be sufficiently safe, practical and immunogenic.

Dr. Gerald T Keusch from the Tufts University School of Medicine presented the results of his study on shigellosis, a complex infection involving both small and large bowel. In this disease colonic epithelial cell invasion by the organism is a necessary event and luminal colonization of the small bowel may be critical as well. These events are poorly understood at present, especially in the human and much remains to be done.

The genus produces toxins which reproduce aspects of the disease in a variety of experimental models. While this permits a plausible explanation of pathogenesis, many aspects of the toxin action remain unknown. The hypothesis is testable, however, further work can be planned and pursued now. When these data become available, it should be possible to develop and apply rational therapeutic and prophylactic interventions for this significant human disease.

Dr. L J Mata of INISA documented epidemiology of shigellosis in Central America. All species of shigellae are prevalent in Central America. The commonest species are *S. flexneri* and *S. sonnei.* Though in 1969-71 an extensive shiga bacillus epidemic occurred at present this bacillus is rarely detected. Ampicillin resistance have been found among certain strains. The changes in the diarrhoea mortality pattern in the area in the last fifteen years reflect a change in the socio-economic pattern.

Dr. H Stypulkowska-Misiurewicz from Poland described epidemiology of shigellosis in Poland during the years 1965-1980. Transition from dominating *S. flexneri* infection into *S. Sonnei* infection was observed for the last 20 years. Changing frequency of *S. flexneri* serotypes was established. Rare *Shigellae* taxon infections though imported from abroad were limited to primary cases only.

Dr. M U Khan of ICDDR,B presented epidemiologic pattern of shigellosis in affected families of Dacca City area during 1980. He detected the presence of shigellae cases throughout the year. *S. flexneri* had higher incidence in October-January and accounted for 67.4% of the total number of cases. Highest attack rate was among the 1–4 year age group. Among the family contacts of the index cases, the secondary infection rate was 31.8% and secondary case rate 12.4% with predominancy of *S. flexneri* index cases.

Dr. M I Huq of ICDDR,B reported on the studies of isolation and characterization of a new shigellae phage. During routine search for bacteriophage from stool or bacterial cultures, a phage which lysed *S. flexneri* was isolated. Its properties were described as big round plaque, with burst time about 18-22 minutes, neutralised by homologous antiphage serum. Only the *S. dysenteriae* type I and all the *S. flexneri* type 2, part of type 3 and 4 are lysed.

Mr. K M A Aziz of ICDDR,B presented an anthropological paper on the transfer of human faeces in the rural coastal areas of Bangladesh. Normal regular movements of hands of the mother after defaecation or after cleaning the bottom of her child are likely to play an important role in transmitting faeces among human beings.

Dr. M Yunus of ICDDR,B presented findings of clinical trial in shigellosis. The patients in two comparable treatment groups responded well with Ampicillin and trimethoprim - sulfamethoxazole. There were no significant differences in the mean number of days till stool culture became negative (1.4 days), and disappearance of faecal WBCs (3.0 days). While both the drugs are effective and free from complications trimethoprim-sulfamethoxazole was considered to be superior in terms of abdominal pain, tenesmus and bloody mucoid stool.

(MORE NEXT MONTH)
LIST OF PARTICIPANTS ON PAGE 3

COUNTRY REPORT

BURMA

The Inter-Regional Training Course on Diarrhoeal Diseases—Clinical Aspects was held in Dacca from 8-19 December 1980. Country reports presented by the participants are edited and summarized for our readers; this is the report presented by Dr Daw Myat Thi from Burma

Burma is in the tropics. A sample survey of 10% of patients coming to the 399 hospitals showed that diarrhoea was the second leading cause (7.5%) of all hospitalization. The highest number of deaths was due to malaria. Diarrhoea is the single leading cause of death among children under 12. Cholera has been reported every year from all over the country; since 1970 it has shown an upward trend. The annual incidence rate of diarrhoea in Burma varies between forty to sixty thousand.

At the central level the Deputy Director(Epidemiology) is in charge of all communicable diseases including diarrhoea. He is responsible to the Director (Disease Control). In each state and division there is an Epidemic Mobile Team (EMT). In case of an outbreak the EMT assists (i) the basic health services to co-ordinate measures to control the spread (ii) in investigation with laboratory support. Cholera vaccine is used only during epidemics. It is compulsory to report any suspected case of cholera; control and preventive measures are taken immediately even before laboratory confirmation.

Community Health Workers (CHWs) under Primary Health Care administer oral rehydration (Oralite). To cover 15 townships 700 CHWs have been trained; by 1982, 5,240 CHWs would be trained to cover 147 townships (half of Burma). CHWs are supplied with packets, but if needed they are also trained to prepare ORS (1/2 teaspoon salt; 8 teaspoons sugar mixed with 5 cups boiled and cooled water). A 5-year Public Health Plan was started from 1977/1978 with aid from WHO/UNICEF. The emphasis is on environmental sanitation, food hygiene, water chlorination, fly control and personal hygiene. Among other things the programme includes re-conditioning of existing wells, extensive chlorination, digging of tube-wells and improved excreta disposal.

Surveillance of all diarrhoeal diseases, with particular emphasis on cholera, under national surveillance is implemented on a country-wide basis by the Central Epidemiology Unit aided by the Epidemic Mobile Team and Rural Health Services and by laboratory services. Special surveys or studies are done whenever necessary.

Laboratory confirmation by culture for cholera can be carried out in the state/divisional laboratories with the National Health Laboratory (NHL) as a reference laboratory. Investigations for Salmonella and Shigella are done by NHL and at certain laboratories at the state and divisional levels. An enterovirus laboratory has not yet been established at NHL.

As a paediatrician in a divisional hospital, I take part in the management of the admitted cases referred from all the township health services. I am also involved in the training of the basic health workers, i.e. the Community Health Workers and Auxilliary Midwives.

As I have mentioned above, rehydration units are available up to the township hospital level. In those units patients are referred by the basic health workers. For every case, we grade the extent of the dehydration, and administer rehydration therapy accordingly. We use the intravenous route for the severe grade II and grade III level dehydration. For the milder grade we use oral solution.

As for antibiotic, chloromphenicol and tetracycline were used for very ill patients, but for mild cases we found that oral rehydration therapy prevents children from reaching severe dehydration levels.

LIST OF INTERNATIONAL PARTICIPANTS OF THE SHIGELLOSIS CONFERENCE

Dr. J Kostrzewski
Polska Akademia Nauk
Poland

Dr. Roger A Feldman
Chief, Enteric Diseases Branch
Bureau of Epidemiology
Center for Disease Control (CDC)
U.S.A.

Dr. Samuel B Formal
Chief, Department of
Bacterial Diseases
Walter Reed Army Medical Centre
U.S.A.

Dr. Gerald T Keusch
Professor of Medicine and
Chief, Division of Geographic
Medicine
Tufts University of Medicine
U.S.A.

Dr. H Stypulkowska-Misiurewicz
National Institute of Hygiene
Warsaw, Poland

Dr. Myron M Levine
Director, Center for Vaccine
Development
University of Maryland
School of Medicine
U.S.A.

Dr. Leonardo Mata
Director
Institute De Investigaciones
En Salud (INISA)
University De Costa Rica
Central America

Dr. William P Reed
Professor of Medicine
University of New Mexico
VA Medical Centre
Albuquerque, Mexico

Dr. Duan Shu-Cheng
Associate Professor, Pediatrics
Deputy Director of Children's
Hospital
Shanghai
China

Dr. R Sutton
Scientist
World Health Organization
Geneva
Switzerland

Dr. Yoshifumi Takeda
Associate Professor of
Bacteriology and Serology
Osaka University
Japan

USELESS DRUGS

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standards are too low, considering the needs of doctors and patients alike.

As their leaflet explains, *Lomotil* is a potentially dangerous drug when used in infants and young children and for this reason it is required by law in the U.S., Canada and Australia that it is contraindicated for use in children aged under two.

However, in some developing countries, *Lomotil* is promoted for use in infants aged three or six months only. Used in these age groups, the results may well be disastrous. As the leaflet explains, severe and life threatening reactions to *Lomotil* are *not* rare in this age group.

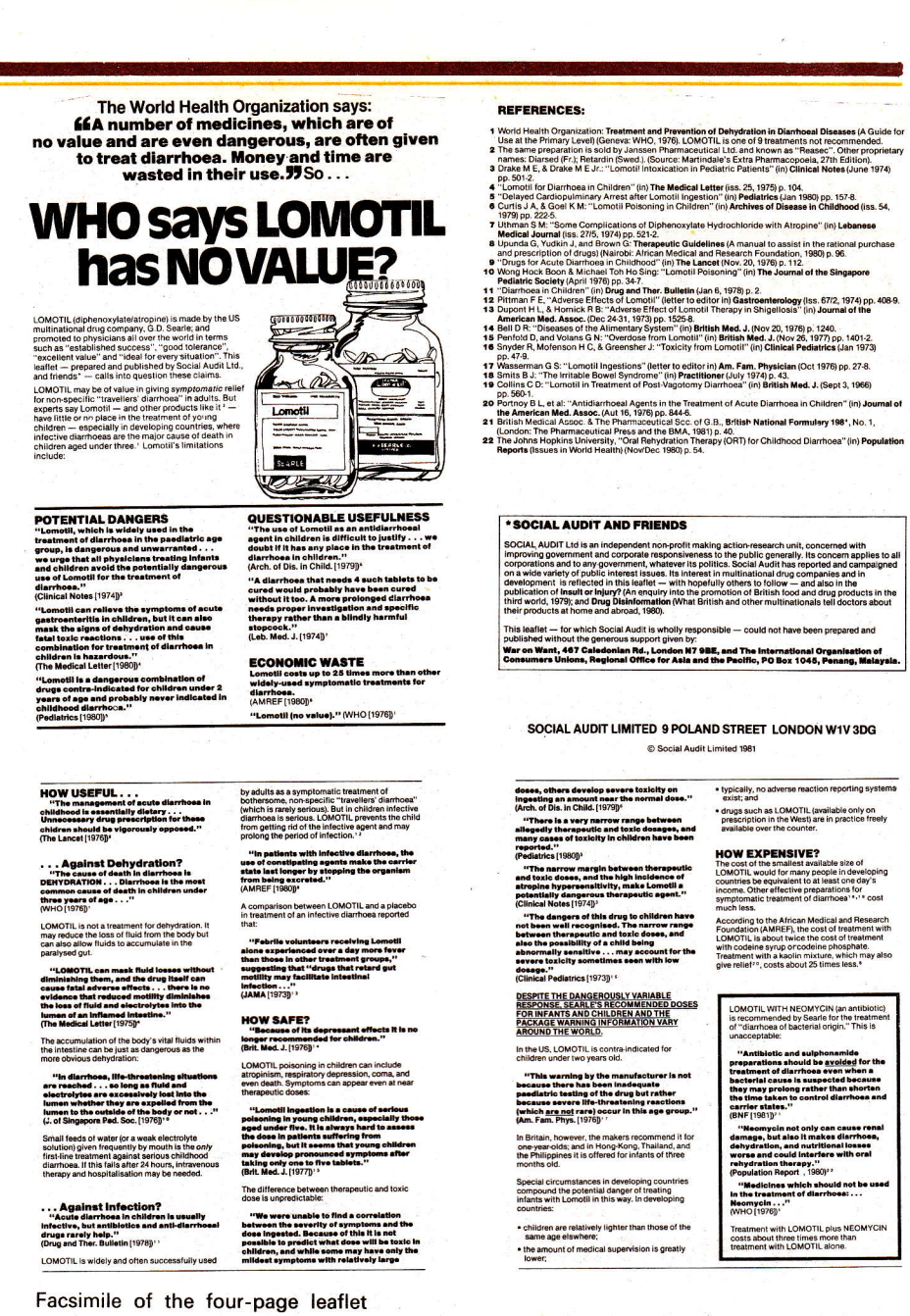
CAMPAIGN AGAINST USELESS DRUGS

At a glance, it looks like an advertisement-like one of the millions of promotional leaflets that multinational drug companies send each year to doctors all over the world. But this four-page leaflet intended as the first of a series is different. It was produced by the British action research group, *Social Audit*. It warns doctors and their patients about the limitations and potential dangers of diphenoxylate/atropine (brand name LOMOTIL).

The leaflet is not only about *one drug,* it aims to draw attention to standards of advertising and promotion of drugs which in developing countries in particular-Social Audit says are "usually indifferent and often downright bad."

Many products sold by multinational companies in developing countries are not "essential"-within the meaning used by the World Health Organization (WHO) while those that are, tend to be relatively expensive. *Lomotil* is not only not essential, it has actually been identified by WHO as one of several products of "no value" in the treatment of diarrhoea. The vigorous promotion of such products inevitably means that national health priorities in developing countries can become distorted.

Some products which may be termed as "good" products in some settings, may be dangerous in others. Take the example of infant formula milk powders-due to the hygienic and other conditions in some settings e.g. the rural areas in developing countries, it is neither safe nor useful, nor cheap enough to do anything but harm, given the circumstances in which they are used.



The World Health Organization says:
"A number of medicines, which are of no value and are even dangerous, are often given to treat diarrhoea. Money and time are wasted in their use." So . . .

WHO says LOMOTIL has NO VALUE?

LOMOTIL (diphenoxylate/atropine) is made by the US multinational drug company, G.D. Searle, and promoted to physicians all over the world in terms such as "established success", "good tolerance", "excellent value" and "ideal for every situation". This leaflet — prepared and published by Social Audit Ltd., and friends" — calls into question these claims.

LOMOTIL may be of value in giving *symptomatic* relief for non-specific "travellers' diarrhoea" in adults. But experts say Lomotil — and other products like it [1] — have little or no place in the treatment of young children — especially in developing countries, where infective diarrhoeas are the major cause of death in children aged under three.[2] Lomotil's limitations include:

POTENTIAL DANGERS

"Lomotil, which is widely used in the treatment of diarrhoea in the paediatric age group, is dangerous and unwarranted . . . we urge that all physicians treating infants and children avoid the potentially dangerous use of Lomotil for the treatment of diarrhoea."
(Clinical Notes [1974])[3]

"Lomotil can relieve the symptoms of acute gastroenteritis in children, but it can also mask the signs of dehydration and cause fatal toxic reactions . . . use of this combination for treatment of diarrhoea in children is hazardous."
(The Medical Letter [1980])[4]

"Lomotil is a dangerous combination of drugs contra-indicated for children under 2 years of age and probably never indicated in childhood diarrhoea."
(Pediatrics [1980])[5]

QUESTIONABLE USEFULNESS

"The use of Lomotil as an antidiarrhoeal agent in children is difficult to justify . . . we doubt if it has any place in the treatment of diarrhoea in children."
(Arch. of Dis. in Child. [1979])[6]

"A diarrhoea that needs 4 such tablets to be cured would probably have been cured without it too. A more prolonged diarrhoea needs proper investigation and specific therapy rather than a blindly harmful stopcock."
(Leb. Med. J. [1974])[7]

ECONOMIC WASTE

Lomotil costs up to 25 times more than other widely-used symptomatic treatments for diarrhoea.
(AMREF [1980])[8]

"Lomotil (no value)."[9] (WHO [1976])[1]

HOW USEFUL . . .

"The management of acute diarrhoea in childhood is essentially dietary . . . Unnecessary drug prescription for these children should be vigorously opposed."
(The Lancet [1976])[9]

. . . Against Dehydration?

"The cause of death in diarrhoea is DEHYDRATION . . . Diarrhoea is the most common cause of death in children under three years of age . . ."
(WHO [1976])[1]

LOMOTIL is not a treatment for dehydration. It may reduce the loss of fluid from the body but can also allow fluids to accumulate in the paralysed gut:

"LOMOTIL can mask fluid losses without diminishing them, and the drug itself can cause fatal adverse effects . . . there is no evidence that reduced motility diminishes the loss of fluid and electrolytes into the lumen of an inflamed intestine."
(The Medical Letter [1975])[9]

The accumulation of the body's vital fluids within the intestine can be just as dangerous as the more obvious dehydration:

"In diarrhoea, life-threatening situations are reached . . . so long as fluid and electrolytes are excessively lost into the lumen whether they are expelled from the lumen to the outside of the body or not . . ."
(J. of Singapore Paed. Soc. [1976])[10]

Small feeds of water (or a weak electrolyte solution) given frequently by mouth is the *only* first-line treatment against serious childhood diarrhoea. If this fails after 24 hours, intravenous therapy and hospitalisation may be needed.

. . . Against Infection?

"Acute diarrhoea in children is usually infective, but antibiotics and anti-diarrhoeal drugs rarely help."
(Drug and Ther. Bulletin [1978])[11]

LOMOTIL is widely and often successfully used by adults as a symptomatic treatment of bothersome, non-specific "travellers' diarrhoea" (which is rarely serious). But in children infective diarrhoea is serious. LOMOTIL prevents the child from getting rid of the infective agent and may prolong the period of infection.[12]

"In patients with infective diarrhoea, the use of constipating agents make the carrier state last longer by stopping the organism from being excreted."
(AMREF [1980])[8]

A comparison between LOMOTIL and a placebo in treatment of an infective diarrhoea reported that:

"Febrile volunteers receiving Lomotil alone experienced over a day more fever than those in other treatment groups," suggesting that "drugs that retard gut motility may facilitate intestinal infection . . ."
(JAMA [1973])[13]

HOW SAFE?

"Because of its depressant effects it is no longer recommended for children."
(Brit. Med. J. [1976])[14]

LOMOTIL poisoning in children can include atropinism, respiratory depression, coma, and even death. Symptoms can appear even at near therapeutic doses:

"Lomotil ingestion is a cause of serious poisoning in young children, especially those aged under five. It is always hard to assess the dose in patients suffering from poisoning, but it seems that young children may develop pronounced symptoms after taking only one to five tablets."
(Brit. Med. J. [1977])[15]

The difference between therapeutic and toxic dose is unpredictable:

"We were unable to find a correlation between the severity of symptoms and the dose ingested. Because of this it is not possible to predict what dose will be toxic in children, and while some may have only the mildest symptoms with relatively large doses, others develop severe toxicity on ingesting an amount near the normal dose."
(Arch. of Dis. in Child. [1979])[6]

"There is a very narrow range between allegedly therapeutic and toxic dosages, and many cases of toxicity in children have been reported."
(Pediatrics [1980])[5]

"The narrow margin between therapeutic and toxic doses, and the high incidence of atropine hypersensitivity, make Lomotil a potentially dangerous therapeutic agent."
(Clinical Notes [1974])[3]

"The dangers of this drug to children have not been well recognised. The narrow range between therapeutic and toxic doses, and also the possibility of a child being abnormally sensitive . . . may account for the severe toxicity sometimes seen with low dosage."
(Clinical Pediatrics [1973])[16]

DESPITE THE DANGEROUSLY VARIABLE RESPONSE, SEARLE'S RECOMMENDED DOSES FOR INFANTS AND CHILDREN AND THE PACKAGE WARNING INFORMATION VARY AROUND THE WORLD.

In the US, LOMOTIL is contra-indicated for children under two years old.

"This warning by the manufacturer is not because there has been inadequate paediatric testing of the drug but rather because severe life-threatening reactions (which are not rare) occur in this age group."
(Am. Fam. Phys. [1976])[17]

In Britain, however, the makers recommend it for one-year-olds; and in Hong-Kong, Thailand, and the Philippines it is offered for infants of three months old.

Special circumstances in developing countries compound the potential danger of treating infants with Lomotil in this way. In developing countries:

- children are relatively lighter than those of the same age elsewhere;
- the amount of medical supervision is greatly lower;
- typically, no adverse reaction reporting systems exist; and
- drugs such as LOMOTIL (available only on prescription in the West) are in practice freely available over the counter.

HOW EXPENSIVE?

The cost of the smallest available size of LOMOTIL would for many people in developing countries be equivalent to at least one day's income. Other effective preparations for symptomatic treatment of diarrhoea [18,19] cost much less.

According to the African Medical and Research Foundation (AMREF), the cost of treatment with LOMOTIL is about twice the cost of treatment with codeine syrup or codeine phosphate. Treatment with a kaolin mixture, which may also give relief [20], costs about 25 times less.[8]

LOMOTIL WITH NEOMYCIN (an antibiotic) is recommended by Searle for the treatment of "diarrhoea of bacterial origin." This is unacceptable:

"Antibiotic and sulphonamide preparations should be avoided for the treatment of diarrhoea even when a bacterial cause is suspected because they may prolong rather than shorten the time taken to control diarrhoea and carrier states."
(BNF [1981])[21]

"Neomycin not only can cause renal damage, but also it makes diarrhoea, dehydration, and nutritional losses worse and could interfere with oral rehydration therapy."
(Population Report . 1980)[22]

"Medicines which should not be used in the treatment of diarrhoea: . . . Neomycin . . ."
(WHO [1976])[1]

Treatment with LOMOTIL plus NEOMYCIN costs about three times more than treatment with LOMOTIL alone.

*** SOCIAL AUDIT AND FRIENDS**

SOCIAL AUDIT Ltd is an independent non-profit making action-research unit, concerned with improving government and corporate responsiveness to the public generally. Its concern applies to all corporations and to any government, whatever its politics. Social Audit has reported and campaigned on a wide variety of public interest issues. Its interest in multinational drug companies and in development is reflected in this leaflet — with hopefully others to follow — and also in the publication of **Insult or Injury?** (An enquiry into the promotion of British food and drug products in the third world, 1979); and **Drug Disinformation** (What British and other multinationals tell doctors about their products at home and abroad, 1980).

This leaflet — for which Social Audit is wholly responsible — could not have been prepared and published without the generous support given by:
War on Want, 467 Caledonian Rd., London N7 9BE, and The International Organisation of Consumers Unions, Regional Office for Asia and the Pacific, PO Box 1045, Penang, Malaysia.

SOCIAL AUDIT LIMITED 9 POLAND STREET LONDON W1V 3DG

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Facsimile of the four-page leaflet

This drug clearly shows some of the gulf between the needs of the North and South, rich and poor. *Lomotil* doesn't "treat" diarrhoea-that is, it doesn't prevent or cure the condition-it just stops the stuff coming out. So in the developed countries of the North, *Lomotil* may have its uses, because there, diarrhoea is essentially a social disease, an inconvenience. In developing countries, by contrast, diarrhoea is frequently a life-threatening illness : it is the major cause of death in children aged under three.

Multinational drug companies typically observe lower standards in developing countries-e.g. in the provision of warning and other useful information-than they would or could elsewhere. The companies usually try to justify this by saying they obey the law in different countries in which they operate, but they do this even when they know perfectly well that those

(Contd on page: 3)

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