The potential for antidiarrheal and nutrient-sparing effects of oral antibiotic use in children: a position paper[1, 2]

Irwin H. Rosenberg, M.D. and Noel W. Solomons, M.D.

In view of the interactions of diarrhea, malabsorption, and malnutrition, particularly in infants living under poor sanitary conditions, one approach for control that has been proposed and debated is the prophylactic administration of antibiotics to children (1, 2). Any decision to recommend such use of antibiotics must be based on a weighing of the seriousness of the public health problem and the likelihood of success of the intervention against the possible alternative approaches, and deleterious and adverse side effects. The present paper examines the relevant previous experience with the chronic administration of antibiotics in animals and man.

Background

In the developing world, there appears to be a synergistic relationship among enteritis, malabsorption, and malnutrition (1, 2). It has been estimated that 25 to 50% of the children born in the developing countries die before the age of 5 years, and that many of these deaths are associated with diarrheal disease (3). Almost all the victims have suffered from malnutrition ranging from mild to full-blown protein-calorie malnutrition. The many interactions of infection and malnutrition have been amply discussed (3). Crowding, poor sanitation, poorly accessible supplies of clean water, and the resultant widespread fecal contamination remain the norm in many parts of the less developed world (4, 5). Regrettably, programs of improved sanitation, diet supplementation, hygiene, and immunization have thus far been too limited in application to have had a major impact on this massive problem.

Current efforts, national or international, have not been sufficient in size or scope to alleviate worldwide malnutrition even if widespread starvation has been averted. Recent efforts have emphasized once again the impact of infectious disease on nutritional status and have called particular attention to the potential importance of enteric disease and malabsorption in the development of malnutrition in developing nations (6, 7). Taken together, infectious disease and enteric disease may be the most important environmental factors that affect the requirement for, and the utilization of, nutrients in countries where malnutrition is common. If true, it follows that interaction in the cycle of enteritis, malabsorption, and malnutrition may be important and that public health efforts to break that cycle should be applied. Evidence that improved nutrition would result from efforts toward the prevention of enteric infection and enteric disease may be summarized as follows:

1) The profound effects of infection on nutritional status induced by excessive metabolic losses and decreased food intake are well documented (6).

2) An additional effect of infection on nutrition must now be considered in view of evidence that when infection, whether systemic or enteric, produces diarrhea, malabsorption of nutrients occurs (7). This malabsorption in association with acute infection is best documented and most devastating in small children (8).

3) To these effects of clinically apparent infectious disease on the hosts' nutrition must now be added the potential effects of chronic, subclinical, enteric disease (9, 10). A morpho-

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois and Division of Human Nutrition and Biology, INCAP, Guatemala City, Guatemala, C.A.

[2] Address reprint requests to: Irwin H. Rosenberg, M.D., Section of Gastroenterology, University of Chicago, Chicago, Illinois.

logical abnormality of the intestine may be observed by biopsy in more than 80% of asymptomatic adults in countries where malnutrition is highly prevalent (11, 12). Defective intestinal absorption of xylose has been reported by clinical tests in 30 to 50% of these individuals. Recent studies in Bangladesh indicate that subclinical malabsorption, as judged by this criterion, is apparent by the end of the first year of life (13). Although the quantitative impact of this malabsorption on nutritional status is not yet known, preliminary studies indicate a relationship among diarrheal disease, subclinical intestinal malabsorption, and delayed growth in children in Bangladesh (13).

4) Several lines of evidence point to chronic or recurrent intestinal infection or altered microbial ecology as contributing factor in the etiology of this widespread intestinal abnormality.

A) Abnormal bacterial colonization of the small intestine has been demonstrated in patients with this nonspecific intestinal abnormality in tropical countries (14).

B) Similar bacterial overgrowth of the gut occurs in children with severe protein-energy malnutrition (15, 16). The bacterial count is greatly diminished after appropriate dietary therapy (15).

C) Bacterial overgrowth in the small intestine is commonly associated with malabsorption in the clinical setting (17).

D) There is clear evidence that the morphological abnormality in the intestine is acquired and not genetic. The abnormality is not present in newborns and, as noted above, may appear early in life (18, 19). Preliminary data from Bangladesh suggest an association between the frequency of diarrheal disease early in life, and the development of subclinical malabsorption (13). Visitors, such as Peace Corps volunteers, to countries where these intestinal changes are common acquire morphological and functional changes similar to those in natives (20); these changes revert to normal when visitors return from the tropics.

In view of thi. idence of the impact of enteric infections on intestinal function, there is sufficient reason to contend that the success of programs directed at the prevention of acute and chronic enteric disease in tropical countries can be measured not only by the reduction in morbidity and mortality from enteric infection but also by improvement in the utilization of foods and in the nutritional status of the people. This should be particularly apparent in those populations on a marginal nutritional intake. Antibiotics exert specific or nonspecific action against bacterial causes of enteritis and diarrhea. They are known to be effective in the treatment of some forms of malabsorption and intestinal bacterial overgrowth syndromes (15, 17). In addition, low doses of antibiotics have had remarkable success in improving nutrition and growth and prevention of infection in animal and poultry husbandry (21).

Antibiotics

The experience in animal husbandry

Low-level antibiotic feeding is an accepted component of modern animal husbandry (21). Feed antibiotics give a measure of insurance against morbidity and mortality and provide increased weight gains with increased feed efficiency; a recent evaluation has shown that their use is economically advantageous (22). Carcass quality is unchanged and a marketable product is obtained in a shorter period of time (23).

Low-level feeding of antibiotics such as bacitracin, penicillin, and the tetracyclines is most effective early in life. Its effects are greatest under conditions in which growth is otherwise poor, morbidity and/or mortality is high, birth weight is low, diet quality is poor, the environment is dirty, and stresses (i.e., unfavorable temperature) are present (24). When any of these adverse conditions are present, feed antibiotics result in a much greater than the 10% average increased meat production (21). Conversely, under ideal husbandry conditions, antibiotics may provide little or no advantage. Antibiotic feeding improves utilization of nutrients present in suboptimum quantity and utilization of low quality proteins (24). In rats, growth promoting effect of antibiotics was inversely related to protein adequacy of diet and was unexplained by changes in appetite or food intake (25).

Animal feed antibiotics promote faster growth and greater feed efficiency by several different mechanisms. Antimicrobial effects of antibiotics include changes in microbic competition with the host for nutrients. The total numbers and kinds of intestinal microbes appear to change without consistent patterns after antibiotic feeding. In studies lasting more than 1 month, bacterial changes revert to pretreatment patterns (24, 26). Other antimicrobial actions include changes in nutrients or toxins, or both, produced by microbes. Feeding antibiotics reduce microbic toxin production; specifically, ammonia (24), Clostridium toxins (24), and the Streptoccoccus factor(s) (27) causing malabsorption are decreased by antibiotic feeding. These changes are consistent with improved performance. Widespread endemic infections have been eliminated. Control of subclinical disease is exemplified by 50% fewer liver abscesses in antibiotic-fed cattle than in the controls (21).

Of special interest is the observation that microbic resistance, when it occurred, was found to revert quickly to the original susceptibility after withdrawal of the antibiotic.

Low levels of dietary antibiotics stimulate growth by direct effects other than antimicrobial (24). This "direct" action was confirmed by growth increment and metabolic changes observed in germfree animals fed antibiotics, by growth stimulation of classic animals fed inactivated antibiotics and nonbacteriostatic compounds, and by the stimulation of microbes and higher plants in pure culture after the addition of dilute concentrations of bacteriostatic compounds. In one study, however, no improvement in growth and an adverse effect on intestinal mucosa was seen with antibiotic feeding to pigs with preexisting protein-calorie malnutrition (28).

The potential risk of long-term daily feeding of antibiotics to humans

Of greatest concern is the observation that protracted use of antibiotics results in emergence of antibiotic-resistant strains of microorganisms that pose a theoretical threat to man. This concern has been expressed by the action of the British Government to disallow use of those antibiotics in animal feeds that lead to reservoirs of resistant bacteria (29). The United States Government has proposed a similar action (30), e.g., the Food and Drug Administration Task Force concluded that while there was not enough evidence to indicate an imminent and immediate health hazard, there was sufficient data to assure there is a potential, if not possible health hazard associated with feeding antibiotics to animals. The position was supported by documentation of the emergence of antibiotic-resistant bacteria in animals that pose a potential risk to humans. The Food and Drug Administration report takes note of the rarity of documented episodes of human infection by resistant organisms attributable to animal reservoirs in the 20 years of experience to date but reiterates the importance of the potential risk to human health.

There are other potential risks of long-term antibiotic feeding. Many antibiotics have such undesirable side effects as toxic or allergic reactions. These are dose related in some instances, and dose independent (idiosyncratic) in others. In the instances in which resistant strains of microorganisms are selected, resistance due to plasmid-mediated mechanisms may spread to other microorganisms and may carry with it additional plasmid-borne factors (e.g., toxins). The extent to which this will happen and the risks of human disease cannot be predicted (30), but reports from India and Central America suggest that the increased use of antibiotics in therapy is increasing the populations of resistant enterobacteriacea significantly. Independent of drug resistance, alterations of the normal intestinal flora as the result of the antibiotic effect and the subsequent invasion by pathogens are possible. Finally, some long-term undesirable effects of the drugs may result from storage in fat and bones.

Experience in prolonged use of antibiotics in infants and children.

A considerable experience in man with the long-term use of antibiotics, largely of the tetracycline group, has been reported. This experience was reviewed in 1956 (31) and again in 1972 (32). Controlled design and statistical analysis has often been lacking. As noted in the summary of the results of these reviews in Table 1, the use of antibiotics has commonly been associated with improved weight gain and, occasionally, decreased moribidity and mortality (33–43). In general,

TABLE 1
Experiments in which chlortetracycline and oxytetracycline were administered daily

Reference	Reason for drug	Year	Dosage per day	Duration	No. of patients	Results
Infants						
(33)	Prematurity	1952	50 mg/kg	Weeks	15	Weight gain Mortality ↓
(34)	Prematurity	1952	50 mg	Weeks	47	Weight gain
(35)	Prophylactic	1957	5 or 50 mg	6–12 months	127	Weight gain
(36)	Malnutrition	1957	50 mg	2–7 weeks	38	Weight gain
(37)	Malnutrition	1956	25 mg	7 weeks	10	Faster recovery
(38)	Prematurity	1963	25 mg/kg	2 weeks		Bone growth
Children						
(39)	Rheumatic fever	1953	500 mg	Up to 20 mos	23	Morbidity ↓
(40)	Poor diet	1955	20 mg	7 months	181	Weight gain[a]
(41)	Poor nutrition	1958	50 mg	15–30 months	184	No sustained effect[b]
(42)	Legg-Calve-Perthes disease	1955	50 mg	8–36 months	25	Improved growth and ossification
(43)	Growth failure	1957	50 mg	12 months	243	Height and weight gain[a]

[a] Smallest children only. [b] Only in one village was a significant increase in height and weight gain associated with antibiotic feeding. Difference from controls, apparent after 18 months of study, were not maintained after suspension of treatment. In other villages, the positive effect of antibiotics were suggestive but inconclusive.

the use of antibiotics was most successful when they were used in the management of children with malnutrition or for the prevention of respiratory disease in children with cystic fibrosis. Positive effects were most prominent in the youngest of the children studied. When antibiotics have been used "prophylactically" for children without disease, the results have been less dramatic and often the positive trends have not reached statistical significance.

Because these studies involve over 900 infants and children treated as long as 3 years, and with the theoretical possibilities that prolonged antibiotic use could have serious detrimental side effects, we have examined these studies for evidence of deleterious effects. With the exception of staining of the teeth in patients with cystic fibrosis on long-term tetracycline therapy (38) and reversible suppression of bone growth in premature infants given chlortetracycline (44), there are few reports of toxic side effects with the use of antibiotics; none with low-dose antibiotic use in the series quoted. It should be noted that most of these studies did not seek evidence of side effects in a systematic way, and long-term evaluation after the studies is not reported. No serious superinfections by resistant bacteria or fungi are reported but neither are there reports of careful studies of bacterial alterations. The lack of toxic side effects in these studies is, therefore, only partially reassuring in view of the superficial nature of most of the study designs.

Of special interest therefore is a recent double blind study to assess the impact of a nonabsorbed antibiotic, colistin, on diarrheal morbidity in Apache children (45). In this study, diarrheal incidence was decreased in the 7 to 13-month age group on antibiotics, but was slightly increased in the 1 to 6-month group. In the 13-week study, neither growth differences nor any evidence of antibiotic side effects were observed.

Antibiotic selection

The reported experience indicates that tetracycline is remarkably safe for chronic use. However, this is one antibiotic whose resistance is transferable to other organisms. The dangers from antibiotic use could be reduced by substances which fulfill the following criteria: *1)* that plasmid transmission of resistance factor be non-existent, and *2)* that the antibiotic not be a first-line drug for use in intestinal infections. Bacitracin fulfills these requirements as it is a poorly absorbed, polypeptide antibiotic with a broad spectrum against Gram-positive organisms and against *Escherichia coli* which is not associated with the development of drug resistance. Zinc bacitracin has been accepted as a feed antibiotic in the United Kingdom based on the criteria set forth in the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (30).

Conclusion

We have attempted to identify the magnitude of the problem faced as well as the seriousness of the dangers involved in the widespread consumption of antibiotics by humans. In the face of the real risk to life that is faced by every infant born in areas of the world where poor hygiene, diarrheal disease, and childhood malnutrition are common, we present the position that additional pilot studies of antibiotic use are justified. Such studies could be directed at the entire high risk population between the ages of 6 months and 2 years or they could be targeted at those who demonstrate recurrent or persisting diarrhea or at those who begin to show growth failure. Although the experience with tetracycline in human studies has not produced evidence of unacceptable risk, the danger of emerging strains of resistant bacteria would be obviated if bacitracin were used as the drug of choice.

References

1. HIRSCHHORN, N. Can small daily doses of antibiotics prevent the cycle of diarrhea, malabsorption, and malnutrition in children? Am. J. Clin. Nutr. 24: 872, 1971.
2. ROSENBERG, I. H., W. R. BEISEL, J. E. GORDON, M. KATZ, G. T. KEUSCH, T. D. LUCKEY AND L. J. MATA. Infant and child enteritis-malabsorption-malnutrition: the potential of limited studies with low-dose antibiotic feeding. Am. J. Clin. Nutr. 27: 304, 1974.
3. SCRIMSHAW, N. S., C. E. TAYLOR AND J. E. GORDON. Interactions of Nutrition and Infection, Monograph Series no. 57. Geneva: World Health Organization, 1968.
4. GRACEY, M. Environmental pollution and diarrheal disease in Jakarta, Indonesia. J. Trop. Pediat. 22: 18, 1976.
5. CAPPARELLI, E., AND L. J. MATA. Microflora of maize prepared as tortillas. Appl. Microbiol. 29: 802, 1975.
6. BEISEL, W. R. Interrelated changes in host metabolism during generalized infectious illness. Am. J. Clin. Nutr. 25: 1254, 1972.
7. ROSENBERG, I. H., N. W. SOLOMONS AND R. SCHNEIDER. Malabsorption associated with diarrhea and other infections. Am. J. Clin. Nutr. 30: 1248, 1977.
8. LUGO-DE-RIVERA, C., H. RODRIGUEZ AND R. TORRES-PINEDO. Studies on the mechanism of sugar malabsorption in infantile diarrhea. Am. J. Clin. Nutr. 25: 1248, 1972.
9. SCHENK, E. A., F. KLIPSTEIN AND J. T. TOMASINI. Morphological characteristics of jejunal biopsies from asymptomatic Haitians and Puerto Ricans. Am. J. Clin. Nutr. 25: 1080, 1972.
10. BAKER, S. J., AND V. I. MATHAN. Tropical enteropathy and tropical sprue. Am. J. Clin. Nutr. 25: 1047, 1972.
11. ROSENBERG, I. H., AND N. S. SCRIMSHAW. Workshop on malabsorption and nutrition. Am. J. Clin. Nutr. 25: 1046. 1226, 1972.
12. SPRINZ, H., R. SRIBHIBHADH, E. J. GANGAROSA, C. BENYAJATI, D. KUNDEL AND S. HALSTEAD. Biopsy of the small bowel of Thai people. Am. J. Clin. Pathol. 38: 43, 1962.
13. EINSTEIN, L. P., D. M. MACKAY AND I. H. ROSENBERG. Pediatric xylose malabsorption in East Pakistan: correlation with age, growth retardation, and weanling diarrhea. Am. J. Clin. Nutr. 25: 1230, 1972.
14. GORBACH, S. L. Microflora of the gastrointestinal tract in tropical enteritis: a current appraisal. Am. J. Clin. Nutr. 25: 1127, 1972.
15. MATA, L. J., F. JIMENEZ, M. CORDON, R. ROSALES, E. PRERA, R. E. SCHNEIDER AND F. VITERI. Gastrointestinal flora of children with protein-calorie malnutrition. Am. J. Clin. Nutr. 25: 1118, 1972.
16. GRACEY, M., SUNHARJONO SUNOTO AND D. E. STONE. Microbial contamination of the gut: another feature of malnutrition. Am. J. Clin. Nutr. 26: 1170, 1973.
17. DONALDSON, R. M. Role of enteric microorganisms in malabsorption. Federation Proc. 26: 1426, 1967.
18. STANFIELD, J. P., M. S. R. HUTT AND R. TUNNICLIFFE. Intestinal biopsy in kwashiorkor. Lancet 2: 519, 1965.
19. SCHNEIDER, R. E., AND F. E. VITERI. Morphological aspects of the duodenojejunal mucosa in protein-calorie malnourished children and during recovery. Am. J. Clin. Nutr. 25: 1092, 1972.
20. LINDENBAUM, J., T. H. KENT AND H. SPRINZ. Malabsorption and jejunitis in American Peace Corps Volunteers in Pakistan. Ann. Internal Med. 65: 1201, 1966.
21. Use of Drugs in Animal Feeds. Proceedings of a symposium. Washington, D. C.: Natl. Acad. Sci., 1969, p. 3.
22. VAN HOUWELING, C. D. FDA Task Force Report—The use of antibiotics in animal feeds. Washington, D. C.: FDA, January, 1972.
23. JUKES, T. H. Antibiotics in Nutrition. New York: Medical Encyclopedia, 1955, p. 28.
24. LUCKEY, T. D. Antibiotics in nutrition. In: Antibiotics, Their Chemistry and Non-medical Uses, New York: Von Nostrand, 1959, p. 174.
25. CHAWLA, R. K., T. HERSH, D. W. LAMBE, JR., A. D. WADSWORTH AND D. RUDMAN. Effect of antibiotics on growth of the immature rat. J. Nutr. 106: 1737, 1976.
26. MCCOY, E. Changes in the host flora induced by chemotherapeutic agents. Annu. Rev. Microbiol. 8: 257, 1957.
27. EYSSEN, H., AND R. DESOMER. Effects of *Streptococcus faecalis* and a filterable agent on growth and nutrient absorption in gnotobiotic chicks. Poult. Sci.

46: 323, 1967.

28. NEUTRA, M. R., J. H MANER AND L. G. MAYORAL. Effect of protein-calorie malnutrition on the jejunal mucosa of tetracycline-treated pigs. Am. J. Clin. Nutr. 27: 287, 1974.
29. SWANN, M. M., K. L. BLAXTER, H. I. FIELD, J. W. HOWIE, I. A. M. LUCAS, E. L. M. MILLER, J. C. MURDOCH, J. H. PARSONS AND E. G. WHITE. Report: Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. London: H. M. Stationery Office, Cmnd. 4190, 1969, p. 83.
30. EDWARDS, C. C. New animal drugs (21 CFR Part 135), Federal Register 37: 2444, 1972.
31. HINES, R. L. An appraisal of the effects of long-term chlortetracycline administration. Antibiot. Chemother 6: 623, 1956.
32. JUKES, T. H. Efficacy and safety of feeding low levels of antibiotics to young animals and children. Philadelphia: Am. Soc. Microbiol. Annual Meeting, April 24, 1972.
33. ROBINSON, P. Controlled trial of aureomycin in premature twins and triplets. Lancet 1: 52, 1952.
34. SNELLING, C. E., AND R. JOHNSON. The value of aureomycin in prevention of close infection in The Hospital for Sick Children. Canad. Med. Assoc. J. 66: 6, 1952.
35. LITCHFIELD, H. R., R. TURIN AND L. ZION. Oxytetracycline and vitamin B_{12} in infant nutrition. Antibiotics Ann. 1957–1958, p. 102.
36. MACDOUGALL, L. G. The effect of aureomycin on undernourished African children. J. Trop. Pediat. 3: 74, 1957.
37. LEWIS, R. A., M. P. BHAGAT, M. A. WAGHE, B. S. KULKARNI AND R. S. SATOSKAR. Antibiotic dietary supplements in the therapy of childhood protein malnutrition. Am. J. Trop. Med. Hyg. 5: 483, 1956.
38. Cohlan, S W., G. Beneländer and T Tiamsic. Growth inhibition of prematures receiving tetracycline. Am. J. Diseases Children 105: 453, 1963.
39. MCVAY, L. V., AND D. H. SPRUNT. Aureomycin in the prophylaxis of rheumatic fever. New Engl. J. Med. 249: 387, 1953.
40. JOLLIFFE, N., G. FRONTALI, G. MAGGIONI, S. CORVO AND O. LANCIANO. Effects of chlortetracycline on weight gain of Italian children ages 6 to 10 on diets relatively low in animal protein. Antibiotics Ann. 1965–1966, p. 19.
41. SCRIMSHAW, N. S., AND M. A. GUZMAN. The effect of dietary supplementation and the administration of vitamin B_{12} and aureomycin on the growth of school children. In: Current Research on Vitamins in Trophology. The National Vitamin Foundation, Nutrition Symposium Series No. 7. New York: The National Vitamin Foundation, Inc., 1953, p. 101.
42. GOFF, C. W. Growth acceleration in Legg-Calve-Perthos syndrome by complementary feedings of aureomycin. Am. J. Clin. Nutr. 6: 430, 1958.
43. LOUGHLIN, E. H., L. ALCINDOR AND A. A. JOSEPH. Extended low-level dosage of oxytetracycline. Antibiotics Ann. 1957–1958, p. 95.
44. WALLMAN, I. S., AND H. B. HILTON. Teeth pigmented by tetracycline. Lancet 1: 827, 1962.
45. HIRSCHHORN, N., W. E. WOODWARD, L. K. EVANS, G. H. CHICKADONZ, R. S. GORDON, R. B. SACK, M. BREUTZMAN, R. A. CASH AND P. D. ZIEVE. Attempted prevention of diarrheal disease in Apache children with a non-absorbable broad-spectrum antimicrobial. Am. J. Trop. Med. Hyg. 24: 320, 1975.