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Infant and child enteritis-malabsorption-malnutrition: the potential of limited studies with low-dose antibiotic feeding[1,2]

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Background

The problem of infant and childhood diarrheal disease

It has been estimated that 25 to 50% of the children born in the developing countries die before the age of 5 years (1). Many of these deaths have been associated with diarrheal disease. 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 (1). 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. 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.

The malnutrition 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. Implicit in most efforts to improve the quality or utilization of food is the assumption that increasing the availability and consumption of these enriched foods in target populations will result in a proportionate improvement in standards of nutrition and health. Perhaps the principal outcome of the recent Workshop on Malabsorption and Nutrition sponsored by the Committee for International Nutrition Programs of the National Academy of Sciences (2) was to qualify that assumption. The Workshop emphasized once again the impact of infectious disease on nutritional status and called particular attention to the potential importance of enteric disease and malabsorption in the development of malnutrition in developing nations. 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. 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 (3).

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[1] The following statement grew out of recent deliberations by a working subcommittee (Subcommittee on Interactions of Nutrition and Infections) of the Committee for International Nutrition Programs–Food and Nutrition Board, National Research Council. The position taken here is the opinion of the authors only and should not be construed as an official document, nor should it be considered the official position of the Committee on International Nutrition Programs, The Food and Nutrition Board of the National Research Council. The position on this very important problem is presented to stimulate discussion and, hopefully, to open new approaches to a most pressing international health program.

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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 (3). This malabsorption in association with acute infection is best documented and most devastating in small children (4).

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. The Workshop confirmed that a morphologic abnormality of the intestine may be observed by biopsy in over 80% of asymptomatic adults in countries where malnutrition is highly prevalent. Defective intestinal absorption of xylose has been reported by clinical tests in 30 to 50% of these individuals. Recent studies in Pakistan indicate that subclinical malabsorption as judged by this criterion is apparent by the end of the first year of life (5). Although the quantitative impact of this malabsorption on a nutritional status is not yet known, preliminary studies indicate a relationship between subclinical intestinal malabsorption and delayed growth in children in Pakistan (5).

4) Although the etiology of this widespread intestinal abnormality is not known, several lines of evidence point to chronic or recurrent intestinal infection or altered microbial ecology as contributing factors:

a) Abnormal bacterial colonization of the small intestine has been demonstrated in patients with this nonspecific intestinal abnormality in tropical countries (6). Bacterial overgrowth in children with protein–calorie malnutrition is greatly diminished after appropriate dietary treatment (7).

b) Bacterial overgrowth in the small intestine is commonly associated with malabsorption in the clinical setting (8).

c) There is clear evidence that the morphologic 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 (7, 9, 10). Preliminary data from Pakistan suggest an association between the frequency of diarrheal disease early in life, and the development of subclinical malabsorption (5). Visitors, such as Peace Corps volunteers, to countries where these intestinal changes are common acquire morphologic and functional changes similar to those in natives (11); these changes revert to normal when visitors return from the tropics.

In view of this evidence 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. The three most obvious approaches to prevention of enteric infection are improvement in: *1*) environmental sanitation, water supply, and personal hygiene; *2*) immunoprophylaxis; and *3*) the use of antimicrobials. Improvements in sanitation, obviously, are of potential long-range importance and are encouraged, but the time lapse before this costly and slow approach will be implemented on a global scale forces consideration of interim intervention techniques. Immunization techniques would be most attractive but techniques for immunization against many of the pathogens involved are not presently available. Further, specific vaccination measures must await identification of etiologic agents and development of reliable vaccines. 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 (8). In addition, low doses of antibiotics have had remarkable success in improving nutrition and growth and prevention of infection in animal and poultry husbandry (12). Unfortunately, the various antibiotics used may be quite ineffective in treatment of much of the diarrhea seen in village populations of developing countries.

Antibiotics, the experience in animal husbandry

Low-level antibiotic feeding is an accepted component of modern animal husbandry (12). 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 (13).

Carcass quality is unchanged and a marketable product is obtained in a shorter period of time (14).

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 (15). When any of these adverse conditions is present, feed antibiotics result in a much greater than the 10% average increased meat production (12). 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 (15).

Animal feed antibiotics promote faster growth and greater feed efficiency by several different mechanisms. Evidence exists supporting a "direct" or non-antimicrobial effect of antibiotic feeding in addition to the expected antimicrobial effects. The latter include changes in microbic competition with the host for nutrients. The total numbers and kinds of intestinal microbes appear to change without consistent patterns following antibiotic feeding. In studies lasting more than 1 month, bacterial changes revert to the pretreatment patterns (15, 16). The antimicrobial action includes changes in nutrients or toxins, or both, produced by microbes. Feeding antibiotics reduced microbic toxin production; whereas specifically, ammonia (15), *Clostridium* toxins (15), and the *Streptococcus* factor(s) (17) causing malabsorption were decreased by antibiotic feeding. These changes are consistent with improved performance. Microbic resistance was found to revert quickly to the original susceptibility following withdrawal of the antibiotic. Widespread endemic infections were eliminated. Control of subclinical disease is exemplified by 60% fewer liver abscesses in antibiotic-fed cattle than in the controls (12).

Low levels of dietary antibiotics stimulate growth by direct effects other than antimicrobial (15). 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 following the addition of dilute concentrations of bacteriostatic compounds.

Reservations have been expressed regarding the wisdom of low-level antibiotic feeding to meat-producing animals in view of possible dangers to man. 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 that lead to reservoirs of resistant bacteria (18). The United States Government has proposed a similar action (19), 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 FDA report takes note of the few 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.

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

Many antibiotics have such undesirable side effects as toxic or allergic reactions.

Resistant strains of microorganisms may be selected. In the instances in which plasmid-mediated resistance develops, it 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 (19).

Alterations of the normal intestinal flora as the result of the antibiotic effect and the subsequent invasion by pathogens are possible.

Some long-term undesirable effects of the drugs may result from the storage in fat and bones.

The drugs will be largely ineffective in the enteric diseases of viral and protozoal origin.

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 variety, has been reported. This experience was reviewed in 1956 (20) and again in 1972 (21). 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 morbidity and mortality. In general, 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 three 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 (32) and reversible suppression of bone growth in premature infants given chlortetracycline (33), 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.

Summary and conclusions

The decision as to whether to recommend a study of the prophylactic use of antibiotics to improve growth and lessen mortality and morbidity in infants and children must be based upon a weighing of: *1*) the seriousness of the problem; *2*) possible alternative approaches; *3*)

TABLE 1
Experiments in which chlortetracycline and oxytetracycline were administered daily

Investigator	Reason for drug	Year	Dosage per day	Duration	No. of patients	Results
Infants						
Robinson (22)	Prematurity	1952	50 mg/kg	Weeks	15	Weight gain *Mortality*↓
Snelling and Johnson (23)	Prematurity	1952	50 mg total	Weeks	47	*Weight gain*
Litchfield et al. (24)	Prophylactic	1957	5 or 50 mg	6–12 months	127	*Weight gain*
Macdougall (25)	Malnutrition	1957	50 mg	2–7 weeks	38	Weight gain
Lewis et al. (26)	Malnutrition	1956	25 mg	7 weeks	10	Faster recovery
Cohlan et al. (31)	Prematurity	1963	25 mg/kg	2 weeks		Bone growth↓
Children						
McVay and Sprunt (27)	Rheumatic fever	1953	500 mg	Up to 20 mos	23	Morbidity↓
Jolliffe et al. (28)	Poor diet	1955	20 mg	7 months	181	Weight gain[a]
Guzman et al. (29)	Poor nutrition	1958	50 mg	15–30 months	184	No sustained effect[b]
Goff (30)	Legg-Calve-Perthes disease	1955	50 mg	8–36 months	25	Improved growth and ossification
Loughlin et al. (31)	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 likelihood of success; and *4*) possible deleterious side effects.

The problem is certainly serious, and there is a need to find workable solutions without delay.

Measures to prevent and correct malnutrition must be encouraged. Unfortunately, despite many considerations given to the problems of infant and child malnutrition during the last decade, with much publicity, and the expenditures of money, time and skill, infant and child mortality rates in developing countries continue to remain high.

Concerning the likelihood of success in man, published studies suggest that limited benefits of short duration often ensue following the use of small-dose antibiotic feeding in infants. This is, however, generally a therapeutic rather than prophylactic effect. Available data from human studies cannot be interpreted to suggest that antibiotic intervention will produce consistently helpful results or that any improvement will be dramatically obvious. Although these studies, in toto, represent a considerable body of experience, many pertinent questions remain unanswered.

Possible deleterious side effects of prolonged, small-dose antibiotic feeding include: toxic or allergic complications and sequellae; altered host flora with overgrowth of pathogens or opportunists; development of antibiotic-resistant organisms; and possible long-term degenerative or genetic effects. The use of prophylactic antibiotics in farm animals or malnourished children could give rise to resistant organisms dangerous to the population-at-large. This danger has been present for the two decades of agricultural experience but seems, in experience, far less of a hazard than those created by therapeutic use of antibiotics in hospitals and general medical practice. Moreover, the large experience with long-term use of antibiotics in infants and children, although inconclusive as to clear positive effects, is at least reassuring in view of the lack of observed complications.

Current medical teaching holds that the prophylactic use of antibiotics will create more problems than it will solve in most clinical situations. However, 5-year mortality rates as high as 25 to 50% of the infant population at risk introduce additional judgment factors that must be considered. With either additional pilot type or field studies of antibiotic feeding, potential risks to the infant and the population-at-large must be weighed against the real risk to life which is faced by every infant born in an area where malnutrition is common.

Upon evaluating the available evidence, we consider it currently unwise and inappropriate to recommend large field trials of small-dose antibiotic feeding in human populations. However, because of the continuing grave problem of high mortality rates in deprived populations of children during the weaning period and because of the relatively small risks to children included in a pilot study or to the population-at-large, it is believed that additional scientific studies of small-dose antibiotic feeding can be justified if they are of limited size, are carefully designed and controlled, and are focused at the groups at maximum risk, i.e., children from 6 to 24 months of age. In addition to evaluating possible benefits on growth, morbidity and mortality, such antibiotic pilot studies should also consider long-term effects with particular emphasis on body composition, intestinal absorption and microbial ecology.

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