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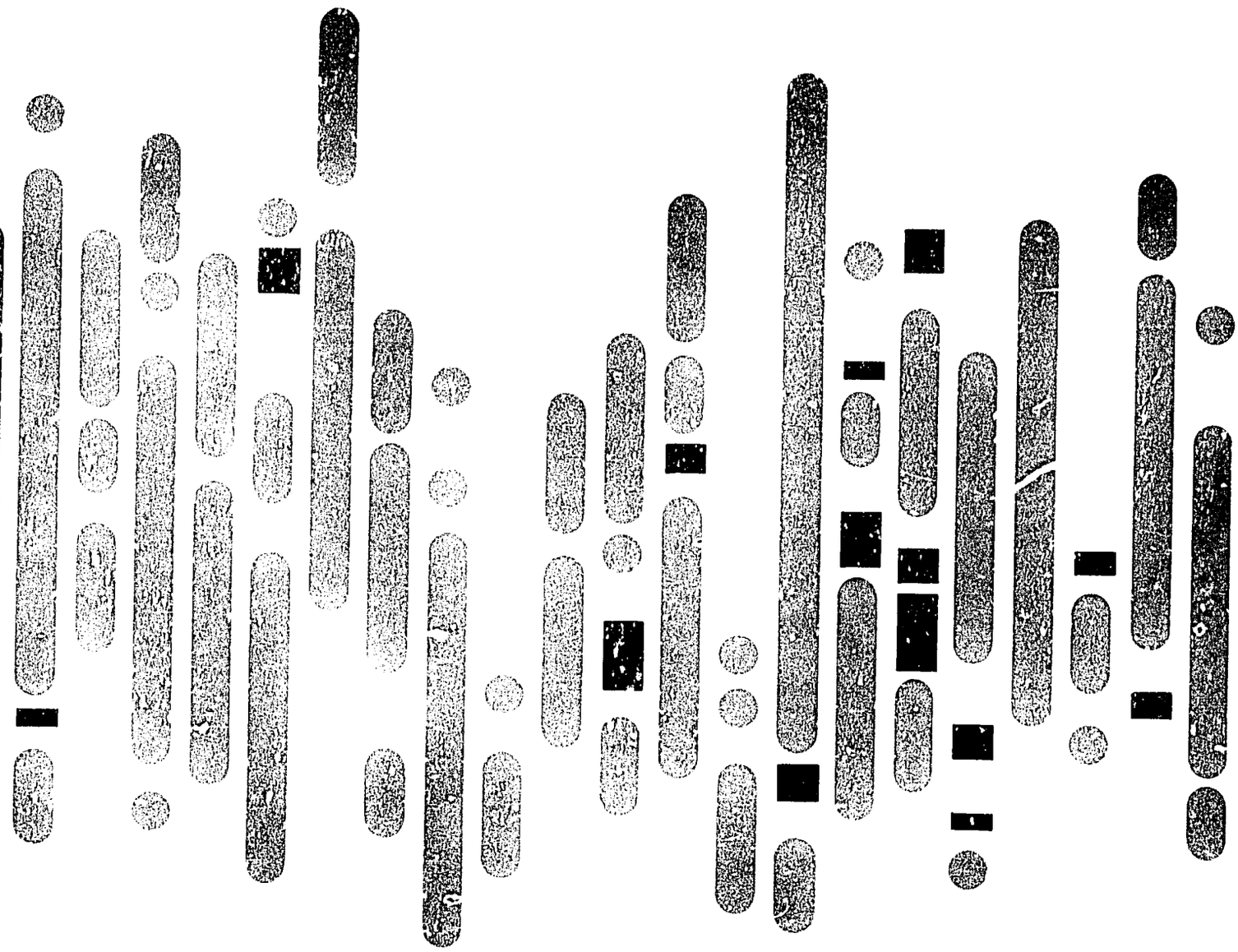

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THE BIOLOGY OF PARASITIC INFECTION

WORKSHOP ON INTERACTIONS OF NUTRITION
AND PARASITIC DISEASES

An International Symposium Held at The Rockefeller Foundation
Conference and Study Center, Bellagio, Italy
September 27-October 1, 1980

Guest Editor: GERALD T. KEUSCH

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Introduction to the Workshop

The relationship between malnutrition and infection has received attention of late from nutritionists, physicians, immunologists, public health professionals, funding agencies, and governments, each of which has its own professional perspective as a bias. In fact, evaluation of programs designed to improve the health of populations in developing countries, particularly the health of preschool children who are highly vulnerable to infectious diseases and experience considerable morbidity and mortality because of them, indicates that both reduction in infection and improvement in nutrition are required for optimal effects. Although an enormous proportion of the world's population is infected by parasitic agents (frequently by several at the same time), parasitic diseases have often been left out of the picture in favor of the acute bacterial and viral diarrheas and respiratory diseases. Quantitative data that demonstrate the importance of these latter diseases in the malnutrition-infection complex have been obtained, and programs of intervention have been developed. However, a similar formulation for the various parasitic diseases has not been undertaken, even though modern chemotherapeutic agents offer the possibility of successful mass control for some infections (those caused by *Ascaris lumbricoides*, for example), and insecticides can be effectively used for others (malaria), at least for a time in some places, primarily because quantitative data linking parasites and nutrition are lacking. In such a vacuum, governmental decisions may be made on a priori grounds and valuable resources wasted on ill-conceived or low-priority programs.

Because of the explosive increase in our knowledge of the biology, pathophysiology, and immunology of the parasitic diseases and the initiation of a number of studies to determine their interaction with nutritional state, the Subcommittee on Interactions of Nutrition and Infection (of the Committee on International Nutrition Programs, Food and Nutrition Board, U.S. National Academy of Sciences–National Research Council) set out to organize a workshop for the exploration of "the state of the art." The Subcommittee was joined in this effort by the Subcommittee on Nutritional Effects of Infection (of the Committee on Nutrition and Infection, International Union of Nutritional Sciences) and the resulting Workshop on Interaction of Nutrition and Parasitic Diseases was convened at the Rockefeller Foundation Conference and Study Center, Villa Serbelloni, Bellagio, Italy, September 27–October 1, 1980.

In addition to producing an up-to-date summary of knowledge, the Workshop hoped to explore a fundamental health policy issue—whether there was a rationale for control of the infections under consideration that would be distinct from the direct benefit of reducing acute and chronic diseases—a rationale based on nutritional benefits. Several questions were thus posed. Was a nutritional gain expected from control of asymptomatic or mild ascariasis or schistosomiasis? Did asymptomatic infections alter host-nutrient requirements? Would programs to control parasites improve nutrition, and, if so, how much? How could control be accomplished? And finally, what do we need to know to assign priorities and to answer the practical, operational questions that follow?

The meeting was jointly supported by the United Nations University (World Hunger Programme), The Fogarty International Center, National Institute of Allergy and Infectious Diseases, National Cancer Institute, and National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases of the U.S. National Institutes of Health, and The Rockefeller Foundation. Additional funding was received from The Wellcome Trust, Merck Sharpe & Dohme, Inc., UpJohn International, and Ross Laboratories. The organizing committee expresses its gratitude for this generous assistance.

Finally, the Chairman wishes to personally thank his fellow committee members for their major contributions to the organization of the meeting: Dr. Nevin Schrimshaw, for his help in bringing it to fruition; Mrs. Wanda Chin-Coker, for her devoted administration of the meeting; Miss Cynthia Heim, for long hours of secretarial work; and Mr. Roberto Celli and the staff of the Villa Serbelloni, Bellagio, Italy, for their attentive care.

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Functional Consequences of Malnutrition

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Human factors likely to be related to dietary intake and regarded as important across cultures and time are disease response, reproductive competence, cognitive function, work output, and social and behavioral habits. Functional failure in these domains is seen as having profound effects on health and demography. Most investigators who have examined issues of food intake and human function have accepted some indicator of an individual's body size as a measure for malnutrition. Anthropometric indicators, such as weight/age, weight/height, or height/age, are most commonly used. Unfortunately, body size reflects many other factors in addition to malnutrition. Because food intake is seldom known, it is difficult to estimate the amount of variation in size due either to nutrition or to other factors. The tacit assumption is that, within a given milieu, conditioning factors are reasonably constant and that differences in size not attributable to conditioning factors are due to differences in intake of nutrients. Thus, persons of larger stature generally appear to function better than persons of smaller stature, with respect to reproductive and disease competencies, work performance, and cognitive ability. Evidence from studies in humans also shows that food deprivation affects ability to produce healthy babies, physical performance, mental attitude, and disease experience, irrespective of body size. Communities that have evolved under conditions of recurrent scarcity will have developed and accepted what are seen to be the lowest-risk strategies for coping with the immediate and longer-range problems of survival. Because the cost of failure is perceived to be high, there will be pressure against innovation. This tendency to avoid risk-taking, in turn, may be among the grave effects of chronic food deprivation, even when deprivation is not severe.

Nutritionists traditionally view questions about nutrition in terms of a model in which intake of a nutrient causes a commensurate status that is definable and quantifiable in terms of certain parameters or indicators, such as body size and conformation, the level in the blood of the nutrient or substances dependent upon it, or morphologic characteristics. Experimentalists have utilized this model effectively to prove the essentiality and to elucidate the function of the 40-50 nutrients required by mammals.

Observations that the same intake does not always produce the same state have led to an elaboration of the model that takes account of conditioning factors or agents that modify the requirement for a nutrient. These may be physiological (pregnancy), dietary (bioavailability), climatic (heat), genetic (lactase deficiency), occupational (heavy work), or environmental (disease vectors). These factors alter the dietary requirement for a nutrient by changing absolute tissue demand, absorption, loss, or the like. According to this model, the requirement for the nutrient is said to be met when the indicator of status is satisfactory under stipulated conditions. The quantitative requirement cannot be absolute because it depends on the selection of the indicator and on the condition of life. Much of the argument surrounding the relationship between nutrition and infection derives from this model. Infection alters the dietary requirement for a nutrient. If parasitism is endemic and will remain so, the recommended intake of the nutrient must be set high enough to take account of the prevailing condition [1].

A more developed model for questions about nutrition widens the range of indicators of status to include relevant capacities, such as the ability to see in dim light or to mount an immunologic defense. Some researchers now refer to these as functional indicators (rather than clinical signs) to differentiate them from the anthropometric and biochemical measurements that indicate tissue status but have limited power to predict the risk of failure of an essential or desirable function. The

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finding of an unsatisfactory functional indicator suggests the need for prompt intervention because of the associated high risk that the affected individual will be unable to perform some function of societal concern. If this were not the effect, the finding of failed dark adaptation would have no greater importance than the finding that plasma vitamin A is <20 μg/dl, for example.

The functions of interest and degree of concern vary because they are culturally and circumstantially determined. A workshop conducted by the National Academy of Sciences (United States) [2] identified five areas of competency likely to be related to dietary intake and to be regarded as important across cultures and time: disease response, reproductive competence, cognitive function, work output, and social and behavioral function. In most societies, the range of concern would extend to the retention of intact function beyond adulthood, i.e., to the duration of productive and satisfying life. Functional failure in any of these domains is seen as having profound consequences for health and demographics, as affecting the pattern of human activity and its material consequences, and as having even broader societal consequences through alterations in individual behavior and psychosocial well being [2]. Governments would surely wish to take corrective measures if they had the means to do so and if they were persuaded that nutrition does affect these functions.

In the past, where governments have decided to provide better nutrition, the programs have usually been viewed as welfare with marginal or no real return expected from the investment. (This view may not apply in socialist countries, but documentation is lacking.) Food distribution has also been used as a political measure, to keep down urban unrest [3]. Perceived as a form of welfare, however, nutrition programs cannot compete successfully with other programs making demands on the welfare budget. Some nutritional programs, e.g., the iodization of salt or nutritional education within established school programs, cost very little and are usually adopted where appropriate, irrespective of demonstrated utility. But most of the malnutrition in the world is due to food deprivation rather than to lack of a specific essential nutrient. To prevent or cure such malnutrition, people must be fed daily throughout their lives.

The prevalent stance reflects the way nutritionists and clinicians have presented the problem of nutrition. In the traditional model, one's own food intake is seen as affecting one's own condition but not the condition of others. While some studies have attempted a definition of the malnutrition of individuals in more functional terms, no study has yet approached the problem fully in the context of a man-environment system.

Throughout this article, the focus is on overall food deprivation and hence, primarily on energy or protein-energy malnutrition rather than on lack of specific minerals and vitamins. Populations that are food-deprived generally lack an array of nutrients, but the deficits, with a few exceptions, are reasonably in balance with the food-energy deficit.

Linking Nutrition and Function

Several difficulties are encountered immediately in any attempt to establish the linkage between nutrition and function. The first is the identification of those whose function may be impaired because of inadequate intake of food. Generally, two types of information are used to determine who is or is likely to be malnourished: a comparison of actual intake of nutrients with recommended levels of intake, or a comparison of some biological measurements with the normative values for a well-nourished population.

Inaccurate knowledge of food intakes is a serious limitation. National data on food disappearance are not reliable estimates of consumption, nor are they valid indicators of malnourishment, because food is not distributed uniformly among people. Adjustment of national average figures according to income distribution improves the estimate of populations at risk, but the question of the reliability of the basic data remains [4]. Intakes of individuals and households have not often been measured over long periods of time or at regular intervals over time. The present methods of assessing food intake are costly and time-consuming, and questions of reliability and validity have been raised [5]. Even if adequate information on food intake were available, comparison with dietary standards is not sufficient proof of individual states of nutrition. As individual requirements for nutrients are neither known nor constant, any comparison of intakes

with dietary standards can only provide an estimate of the risk of inadequacy.

Most investigators who have examined issues of intake and function have accepted some indicator as a surrogate measure of malnutrition. The most commonly used indicators of insufficient total food intake are anthropometric ones (weight/age, weight/height, height/age). Unfortunately, body size is an aggregate reflection of heredity as well as all previous life experiences, including infection, exposure to toxicants, and inattention and neglect, as well as nutrition. Thus, because food intake is almost never known, the amount of variation in size due either to nutrition or to other conditioning factors cannot be estimated. The tacit assumption is that, within a given milieu, conditioning factors are reasonably constant, and the remaining differences in size result from food deprivation.

Illustrative of these difficulties are some longitudinal studies of very young children served by field health stations in Africa [6, 7] (see also [8] for Central American studies). In The Gambia, where marasmus is the typical manifestation of malnutrition, mean weight gain was 98 g per month between ages 0.6 and 3.0 years (mean, 1.62 years), or 45% of the expected rate of 220 g per month. Kwashiorkor predominates in Uganda, where the reported gain was 85% of the expected rate, or 185 g per month. Regression of growth (dependent variable) on prevalence of disease (independent variable) indicated highly significant negative effects of gastroenteritis in both locations; the effect on weight gain was calculated to be −101 g per month in The Gambia and −14 g per month in Uganda. Malaria was very detrimental to growth, but because of its far lower prevalence, the effect on growth was only −8 to −9 g per month. Giardiasis was a significant factor only in The Gambia (−7 g per month), and helminthic infections had no significant effect in either location. Infection, including the attendant withholding of food, anorexia, and intestinal loss, appears to explain most of the deficit in weight gain in these populations, but the authors believe otherwise. When seasonal differences in the growth rate and the prevalence of infection were allowed for in the statistical analysis, the contribution of gastroenteritis was reduced. The investigators believe that availability of food is responsible for the remaining unexplained variance, but they present no supporting data.[1] Neither these nor other investigators reported whether or not individual episodes of disease can be related to the immediately preceding weight to height ratio or growth rate of children. They do, however, report that the same associations hold for individual children as for the group (i.e., a given child's growth falters during episodes of gastroenteritis [9]), and further analysis of their data may yield the information wanted. Resistance is generally considered far less likely to be affected by nutritional state than is response, but the subject of host resistance warrants study.

The ambiguity that has resulted from use of nonspecific indicators has given scope for extended and generally unproductive arguments about the relative importance of food deprivation (in contrast to the general concomitants of poverty) to individual and societal well-being. Much of the argument hinges, as well, on acceptance of the view that being bigger is better than being smaller (and of course, that living is better than dying).

The Significance of Body Size

All other things being equal, persons of small stature should have a clear advantage in resource-limited societies. From this perspective, the limitation of linear growth (stunting) can be viewed as an adaptive response in that adapted individuals can make do with less food throughout adulthood, when total physiologic food demands are highest. Yet this concept runs counter to the common belief and experience of nutritionists, biologists, and clinicians alike.

When laboratory and farm animals are deliberately deprived of food, their growth slows. Clinicians have identified children free of organic disease in whom very short stature has resulted from low intakes of energy, even in privileged circumstances; in these children, growth was shown to accelerate with increased intake of food [11].

Experimentally, whether animals achieve their normal, genetically determined body size depends on the stage of development during which the deprivation is introduced and on the degree and duration of the deprivation [12, 13]. The potential for acceleration and deceleration of growth is substantial, and, unless energy deprivation occurs

[1] See Appendix.

at a particularly critical stage (e.g., during the fourth to seventh month of fetal life in humans, when the hypothalamic nuclei and tracts are being organized [12]), catch-up growth usually occurs and growth continues beyond the age at which it usually terminates in more generously fed animals. British data indicate that early growth may be critical because children tend to remain in the growth channel established by 18–24 months of age [14]. In human populations whose food intake is chronically low, growth may continue into the early 20s but, even so, adults rarely attain the height of similar people with larger food intake.

In the experimental models and in food-deprived human populations, a lag usually occurs in the attainment of physical, developmental markers other than growth (dentition, sexual maturation), but gross functional capacities are preserved. And, rather than being shortened, the life-span of food-restricted animals in a sheltered environment is extended.

On the other hand, smallness may be handicapping. Bigger mothers do have bigger babies, and the incidence of low birth weight (<2,500 g) is considerably higher among babies of short mothers [15, 16]. Babies with low birth weights have increased risk of defective development and death. In fact, low birth weight has been found to be the main determinant of infant mortality when age, race, and socioeconomic conditions are taken into account [17, 18]. The observation that perinatal mortality from all causes is inversely correlated with maternal height led Thomson [19] to conclude that "it looks as if stunting of growth, leading to short stature in adult life, causes impairment of physiological efficiency, as well as physical impairment, so that the baby is more likely to suffer from defective development during early fetal life, growth retardation up to the time of birth, and impaired vitality . . . ." Further studies showed that this relationship holds within all socioeconomic classes. Thomson [19] uncomfortably acknowledged that women who are genetically short ". . . are on the whole less efficient at reproduction. . . ." In reaching this conclusion, however, Thomson reflects a bias in assuming that the height of women of upper economic classes is limited only by genetics, and that height and birthweight are related through inherent physiological/physical processes. It is possible, even likely, that short women eat less than tall women within a given socioeconomic group, and food intake during pregnancy does affect birthweight.

A woman's height can also affect her selection of a marital partner. Thomson [19] cites studies of primigravidae showing that a woman's height is associated with her occupation and the occupations of her father and her husband; women who rose in social status through marriage tended to be taller, and those who fell in status were shorter. English and American data indicate that unmarried women are taller than married women of the same age with no children; mean maternal height varies inversely with the number of children. If these trends are stable and universally true, selection processes favor women of average height; the tallest women are deselected for marriage, and the shortest women, although they bear the most children, also have the poorest reproductive outcomes. In modern Western cultures, obesity is also a deselection factor for marriage. Because deposition of body fat is a survival strategy, a bias against fatness is unlikely in cultures where periods of food scarcity are the norm.

No comparable information relating to male reproductive selection has been noted. Tall men were probably preferred in the past, as being likely to be more successful hunters and warriors. But because women tend to outnumber men and so much of women's social identity is vested in marriage, any man's being rejected on the basis of height alone seems highly unlikely.

Among adults of both sexes, the abilities to perform physical and mental tasks are key determinants of a successful and satisfying life. An important distinction exists here between functional capacity and expressed function. If work productivity is the measure of interest, for example, physiologic work capacity, consumable energy (food or reserves), and the availability of employment are all necessary preconditions.

The capacity for physical work depends on the amount of lean body mass and muscle mass and on oxygen transport capacity. Because taller people tend to have larger lean body mass, their performance capacity tends also to be greater. This correlation is borne out both by an analysis of Olympic performances that showed tall athletes to have a distinct advantage in most events [20], and by standardized work tests of control and undersized Colombian men [21]. Among the Colombian men, the malnourished groups were all of the

same average height, and decrements in performance capacity followed decrements in body weight and urinary excretion of creatinine (indicative of muscle mass) [21].

Studies of three groups of men residing in a tropical lowland area of Nepal found a positive association between performance capacity (maximal oxygen uptake) and weight in indigenes and recent migrants from the Lower Himalayas and revealed a negative association between capacity for work and skinfold thickness (fatness) among the migrants [22]. After controlling for weight, the researchers found no significant effects of any other morphologic characteristic in the migrants. In the indigenous people, however, stature, leg length, and surface area remained strongly associated with work capacity. Among the migrants (recent and first generation residents), performance capacity declined with duration of residence in the jungle, and both groups of migrants performed less well than the indigenous people when weight and stature were controlled. Clearly, factors other than morphology are involved. Training, food intake, and malaria are among those factors.

Work capacity has been correlated with the occupational output of cane cutters [23, 24], and work output in light industry has been shown to be related to body weight [25], but the relation between height and capacity for work has not been examined separately. Other components of performance, such as dexterity, balance, and eye-hand coordination, have received little attention.

Bliss and Stern [26] have taken a different analytical approach in dealing with the manner in which consumption of food and other goods relates to the efficiency of labor. A frontier or boundary describes the limit of an individual's possible performance (defined as a maximal number of feasible tasks), and the analytical question posed was to relate that frontier to intake of energy. The development of a rational model required the concept of a minimal body weight necessary to achieve the frontier. The model could be, but has not yet been, tested empirically.

Cognitive abilities are unquestionably required for all aspects of life, as well as for many work tasks. It is only in recent decades that new conceptualizations and improved methodologies have permitted the demonstration of residual and often subtle damage in experimentally deprived and rehabilitated animals. Comparable changes have been found in retrospective studies of previously malnourished humans, but generally the findings reach significance only for those who have been severely or repeatedly malnourished in early life. In these survivors of marasmus and kwashiorkor, the effects of the various environmental assaults cannot be separated, nor can a value be assigned to either size or to any other causal factor.

Such limited evidence as exists supports the view that cognitive ability is positively associated with stature. Brozek provides a recent review of this literature [27]. Guatemalan studies that utilized discriminatory tests (such as attention span and short-term memory) led to the conclusion that, under conditions in which growth is limited by nutrition and other environmental factors, bigger children are smarter [28]. Older literature, involving conventional measures of intelligence, also indicates that even in richer countries greater height in women suggests at least marginally higher intellectual capacity [29].

The literature relating the body size of children to morbidity and mortality shows clearly and uniformly that in an unsanitary environment the smallest children are the most vulnerable. For example, in a prospective study of one- to two-year-old children in Bangladesh [30], the mortality rate of the lowest decile, according to initial weight-for-age or height-for-age, was about four times the rate of the top decile. In this population, fewer than 10% were within 95% of the Harvard height-for-age norm, and 112 out of 2,019 died during the two-year study; this number indicates poor functional performance indeed.

Enhanced morbidity and mortality are usually ascribed to diminished immunocompetence, which has proved to be a powerful explanatory variable. Studies of Indian children indicate that not all immune responses are affected to the same extent in children with various degrees of growth retardation [31]. Compared with normal children aged one to five years (weight-for-age, >80% of the Indian Council for Medical Research standard), those with mild to moderate malnutrition (weight-for-age was 60%–80% of standard) showed impaired leukocyte phagocytic function. In more seriously deprived children (weight-for-age, <60% of standard), both phagocytic function and cell-mediated immune response were altered, and antibody response to typhoid antigen (but not to diphtheria and tetanus toxoids) was impaired as well.

Indian children whose nutritional status was recorded when they were about five years old were reexamined at ages 13–15 for observation of how immune status relates to long-term protein-energy malnutrition [32]. The 94 five-year-old children were divided into four groups according to height-for-age (in relation to Harvard norms) as follows: normal (within 2 SD of the mean), mild protein-energy malnutrition (>2 but <3 SD below mean), moderate protein-energy malnutrition (>3 but <4 SD below mean), and severe protein-energy malnutrition (≥4 SD below mean). A fifth group was made up of individuals from groups 2, 3, and 4 who had suffered from kwashiorkor or marasmus during early childhood.

Height status at age five was maintained at age 13–15. Weight-for-age relative to the standard was lower in adolescents than it had been in five-year olds, but the difference between groups was maintained. Regarding immunologic status, it was reported that bactericidal activity of leukocytes was insignificantly higher in normal children than in those of the other groups. The number of T lymphocytes and the rate of ^{3}H-thymidine incorporation were significantly lower in children of group 4 than in normal children, a fact indicating that cell-mediated immune response is impaired in chronic severe malnutrition. Values in children with mild and moderate protein-energy malnutrition were essentially normal. In 15 children who had kwashiorkor before the age of five, numbers of T cells were considerably lower, while no such reduction was seen in 10 children who had had marasmus. Counts of B lymphocytes were normal in all the groups except those who had suffered earlier from kwashiorkor. Serum immunoglobulin levels were similar in all five groups of children, and the responses to diphtheria and tetanus antigens were satisfactory and similar in all groups. These results support conclusions drawn from earlier work [31] that immune status is impaired in severe malnutrition.

To my knowledge, no studies of the relationship between adult height and experience with infectious disease have been done. While modern literature is replete with evidence concerning the perils of obesity as regards degenerative diseases, relatively little attention has been paid to chronic underweight, short of anorexia, in the postantibiotic era in Western countries. In the past, it was recognized that thin people were more likely than normal or plump ones to succumb to infectious diseases. There is now ample evidence that chronic severe undernutrition, due usually to malabsorption or injury, results in depressed immune function of hospitalized patients and that this function can be restored by adequate feeding.

Chen et al. [30] carried their analysis of the association between size and disease in Bangladesh one step beyond the usual. They examined mortality of children in relation to maternal height and weight. The correlations did not reach statistically significant limits, but the inclusion of maternal size improved the efficiency of the children's anthropometric measurements for the discrimination of survivorship within the severely malnourished group. Apparently, small women are less able to cope with a poor environment and a sick child.

On the other hand, the view that bigger is better is not universally accepted. South African investigators, for example, are not convinced that "quality of life" differs between lighter and heavier or slower- and faster-growing (the designations are used interchangeably by these authors) black schoolchildren, although their quality of life is clearly different from that of the white population[2] [33]. The measures compared within the black population were the prevalence of schistosomiasis and ascariasis, attendance at school, a 12-min walk-run test, and hematologic indexes. These investigators used school attendance as the most persuasive argument, stating that

> Although education for blacks in South Africa is not compulsory, of those enrolled, the percentage attendance per diem is invariably high, 95–98%. Such data are much the same as those for white schoolchildren. Furthermore, absenteeism among black children is due more often to family reasons than to sickness. . . . Perhaps the most telling observation is that in rural areas, especially in remote parts, a high proportion of black children walk very long distances to attend school; many walk 10 to 15 km a day. Among such children, school attendance is very little affected by bad weather. We insist that this performance, which we have adequately verified, cannot be reconciled with the situation whereby a high proportion of these children are labelled as malnourished specificially on account of non-compliance with growth standards. . . .

The Walkers [33] plead for development of different growth standards for evaluating the need for supplementary feeding:

> While improvements in diet are taking place in measure among the world's developing and less privileged popula-

[2] See Appendix.

tions, in the not so distant future population growth will certainly exceed food supplies. It has been stated that "between 1969-71 and 1985 Africa's food demand would rise by 76% and her food production by only 45%." In consequence, ultimately, there will be greater reliance on plant sources of nutrients, as is already the case with the bulk of the world's population. Hence, the defining of adequate growth, *consistent with environmental circumstances*, in terms of current and future health among such populations, as urged above, takes on crucial importance. It is preposterous to regard the acquiring of this knowledge as an "academic exercise," as Habicht et al. [*Lancet 1*:611, 1974] maintain. Furthermore, it must be appreciated that the need for this information is intensified by (*1*) a lack of knowledge of desirable masses of adults since western norms for body mass are not optimal, and (*2*) the fact that at 50 years and thereafter, South African blacks with their lower prevalences of degenerative diseases compared with whites, have higher survival rates. [Walker, A. R. P. *Postgrad. Med. J. 50*:29, 1974]"

This issue of longevity is an interesting one in that the observation accords with findings from the experimental underfeeding of animals. We, of course, cannot know whether black South African survivors are simply the hardiest of those born, the weaker ones having been unable to withstand the quality of their lives, or if their probable chronic underfeeding is a relevant factor.

Empirical Evidence

Scientists, for the most part, are unwilling to rest the case for nutrition on the ambiguous evidence provided by the acts of nature reviewed above. For some, the only acceptable proof comes from intentional experimentation. Although much of this work has been less than satisfactory, there is no serious discrepancy between the two lines of evidence.

Deprivational studies have been experimentally the cleanest. Benedict's studies at the Carnegie Laboratory involved male college students who were free to continue their usual activities while eating a normal diet but restricted to about 1,600-1,800 kcal per day [35]. In the Minnesota experiment, Keys et al. [36] studied conscientious objectors confined and for 24 weeks given a "semi-starvation" diet typical of reduced wartime rations in Europe; this regimen supplied ~1,600 kcal per day. Both groups of investigators found the expected physiologic adaptation to energy restriction (loss of weight, reduced basal metabolic rate, diminished performance capacity) and important attitudinal changes and behavioral adaptation as well. The men became apathetic, had difficulty concentrating, lost libido, and were less active physically. Unfortunately, these behavioral responses were not documented fully in either study. In general, animals will exhaust their repertoire of behavioral adjustment before the full range of physiologic adaptation is activated; in humans, however, the behavioral responses to food deprivation may have the more lasting functional outcomes.[3]

Field observations are entirely consistent with the evidence from these classic studies. For example, European miners whose rations were severely cut lost weight; they continued to perform under the incentive of wartime defense needs, but the tonnage of coal mined fell [37]. Victims of famine, prisoners of war, and those in concentration camps finally become apathetic and listless, broken in body and spirit [38].

Food supplementation is the other experimental mode used to illuminate the significance of malnutrition. The studies usually are intended to serve dual purposes, i.e., to constitute an experiment and to give direction and impetus to governmental preventive and remedial nutrition programs. As experiments, most of these studies provided at least some proof of the benefit of feeding the malnourished, as measured by such criteria as the birth weight of infants, children's growth, and the physical work capacity of adults. For policy and planning purposes, the studies were less than effective.

These intervention experiments are often criticized, sometimes because the design would have been inadequate under even the best of circumstances, but often because the investigators did not appreciate the full, possible range of human responses. Successful intervention requires a different view of and approach to nutrition questions, a view and approach that take account of how people conduct their lives. For our efforts to affect policies and programs, we must ask different questions in different ways.

The Nutrition Factor: A Construct

Food deprivation is unquestionably the most pervasive problem among humankind. Perhaps it has always been so, and much of the way humans

[3] See Appendix.

relate to one another and their environment may have been conditioned by its continued existence. We should at least consider the hypothesis that cultural styles and malignant poverty and all its concomitants are as likely to be the outcomes of food deprivation as the cause of it.

To aggregate and quantify food deprivation, we must think in terms of energy and, especially, recall that the need for energy has priority over all other nutritional needs. The amount of energy required is largely a function of the level of physical activity. When energy intake is less than is needed to carry out required activities, energy may be obtained from tissue reserves (within physiologic limits) or by the elimination of activities that are, or are seen to be, discretionary. This type of behavioral adaptation to deficient intake occurs even in those who have adequate or excessive tissue stores [40, 41]. Logic suggests that the extent to which activity falls during food deprivation must be determined by some more or less conscious overlay of a physiologic regulatory process.

If the work demanded under conditions of deficient intake is critical to survival, the limits of behavioral adjustment would be reached and tissue would be consumed until the destruction of lean mass rendered further work impossible. In this situation, persons who have larger reserves of fat and lean tissue and are the most adept at regulating their behavior are the ones who will survive. This situation exists in some subsistence farming communities where there is a seasonal loss of body mass during the hungry period, before the crops are ready to harvest.

Families who live in this setting must be efficient managers and strategists. They must be good at predicting the time and quality of harvest and in balancing the remaining food reserves against the foreseen needs of family members and other demands and obligations. Families must make hard decisions about the expendability of whatever resources they have (time, labor, goods, and, in the extreme, persons). Even in situations where women do not usually work in the fields, they may at a critical stage set aside their normal work of preparing food, fetching water and firewood, and caring for children and the house, to turn to field work. Children may be left with food prepared in advance that becomes increasingly less safe to eat, and the younger ones may be left in the care of older children who, because they are at a less advanced stage of socialization than their parents are, may also be less likely to share, and are surely less experienced at managing. A nutrition and health survey made at this time would find variable degrees of thinness among the family members (depending on how that family sees the hierarchy of needs and demands), the apparent anomaly of people being underfed when food is available to the household (stored grain or cassava in the ground, perhaps), and low standards of hygiene (expressed as gastroenteritis, parasitism, etc). In this case, malnutrition of children is to some extent due to their own low intake, but more directly to the way their parents deal with the recurring problem of food deprivation. And if the food deprivation of parents is severe, their inability to provide adequate subsistence for the family and to care for its members is the final malfunction ensuing from malnutrition.[4]

Communities that evolved under conditions of recurrent scarcity have developed and accepted what they view as the the lowest-risk strategies for coping with the immediate and longer range problems of survival. Family structure and members' roles will follow those strategies, and over time behaviors appropriate to those roles became the cultural norm. Because the cost of failure is perceived to be high, there is pressure against innovation. This tendency to avoid risk-taking may be among the higher costs of chronic food deprivation, even where the deprivation is not severe.

Disparity in the amount of food available to families within a community undoubtedly also alters relationships among people. Others' hunger may be seen as a threat to one's own security; cultures have evolved various ways of dealing with this threat. One is to segregate the affected ones ideologically as a class or caste whose deprivation is fated. Other ways are schemes for redistribution ranging from customs of marriage and death to philanthropy and taxation.

To address these societal concerns effectively requires a new conceptualization of the problems of nutrition. This is not to deny the worth of basic science, of meticulous biochemical and biophysical studies of parts of cells, organ systems, and even people; scope exists for all of these. But virtually nothing that the scientific community has discovered about nutrition in this century has al-

[4] See Appendix.

tered the prevalence or severity of the dominant forms of malnutrition. We know a great deal about protein-energy malnutrition, almost everything in fact, except what causes it, how to prevent it, and what it costs society not to do so.

Appendix

[1] These investigators [6, 7] observed that standard curative medical care (reported as equivalent to that of the British National Health Service) was not noticeably effective in dealing with the infection-induced growth failure in these settings. In a search for simple measures suitable to isolated rural Gambian villages and effective against diarrheal disease, water and food were identified as sources of contamination [10]. All well water gave evidence of fecal contamination (depth of wells was 45–60 feet), and most water storage pots were also contaminated. Bacterial counts in cooked food reached unacceptable levels 30 min after preparation in two-thirds of the samples tested. Feeding of children was said to be haphazard, especially when adults were away, working in the fields. Then, cereal gruel was prepared in advance and left for feeding during a period of 8–9 hr.

[2] The authors did not attempt to make a similar case for black preschool children, among whom the smaller ones are clearly more vulnerable than the larger ones. Other South African studies [34] of this age group found that growth of Bapedi children indicates "suboptimal to serious nutrition deficit" in that growth failure occurs ". . . in the absence of endemic malaria or other tropical diseases, the absence of severe parasitic infestation, major forms of anaemia or primary tuberculosis. . . . " A longitudinal study of 110 Bapedi babies in this sample population found 28% to suffer from overt malnutrition between six months and five years of age. Ten percent had lost one or both parents and another 20% had mothers of "low efficiency" as judged by "attitudes, cleanliness, impressionability, care of their other children, general awareness and concern." All of the children in these two groups had hospital admissions for infectious disease (gastroenteritis, respiratory infections) as did 81% of the overtly malnourished (weight/age, <third centile, Harvard norms). The incidence of overt malnutrition was nearly twice as high among children where low maternal efficiency was a factor (52%) as in the group as a whole. During the first six months of life, the growth of these children was not discriminably different from that of the others. There were 12 mentally retarded children in the series, and in 10 of them there was no identified cause; of these 10, three had overt malnutrition, five had mothers with low efficiency, and one was an orphan.

[3] Some evidence indicates that performance may be impaired by missed meals [39]. Not all studies have found these effects, but the point is worth pursuing because missed meals may occur throughout a significant portion of poor children's preschool and school years.

[4] It is well to bear in mind that a cross-country multivariate analysis conducted under the auspices of the World Bank [42] related calorie deficits to life expectancy, child and infant mortality, and child growth. Across 39 countries, calorie deficit had a significantly detrimental effect on life expectancy, growth, and child and infant mortality. The effects of calorie deficiency could not be explained away by income, health care, or education; and calorie deficiency was a better indicator of the outcome variables than was income.

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Synergism and Antagonism of Parasitic Diseases and Malnutrition

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Malnutrition may appear to increase or decrease the severity of a parasitic disease, but the fundamental mechanisms that influence such synergistic or antagonistic relationships have yet to be identified. Several factors must be considered in an evaluation of possible synergistic or antagonistic relationships. They include the species and virulence of the parasite; the nutritional requirements of the parasite; the severity, duration, and type of malnutrition in the host; and lastly, the competence of immune mechanisms and other resistance factors in the host. Because the immune system may be impaired by malnutrition, fails to provide protection against most parasitic infections, and has a known propensity for producing harmful as well as beneficial responses, the immunological functions of the host are undoubtedly key indicators of whether malnutrition will cause an increase or a decrease in the severity of a parasitic disease.

As with other infectious diseases, a complex three-sided interrelationship appears to link parasitic diseases with both the nutritional status of the host and the functions of the immune system (figure 1). Because of its fundamental implications, this concept—that malnutrition has an important impact on the susceptibility and resistance of the host—was included for discussion in the initial session of this Workshop. Nutritional deficits, imbalances, and even excesses can impair the functional competence of the immune system [1]. Both the nutritional status and the immunologic responsiveness of the host appear to exert, by yet uncertain mechanisms, an enhancing or suppressing effect on the pathogenic progression of a parasitic disease; in the opposite direction, a parasitic disease can alter both the nutritional and immunologic status of the host.

The Concept of Synergism and Antagonism

In a World Health Organization (WHO) monograph published 12 years ago, Scrimshaw, Taylor, and Gordon [2] made a detailed attempt to categorize the apparent changes in the severity of an infectious disease process in a nutritionally deprived host. They reviewed a large number of early descriptive studies in animals or man and found that preexisting malnutrition did not always increase the severity of disease. In 325 studies, malnutrition enhanced the severity of infection. However, in 93 studies the infection was less severe in the presence of malnutrition, and in 66 studies the presence of a nutritional deficiency made no apparent difference.

These authors defined synergistic interaction as one in which preexisting malnutrition lowered the resistance of the host to the infection and led to an infectious process of greater-than-expected severity. The opposite or antagonistic type of interaction resulted in an infectious process that was less severe in a malnourished host than in one with normal nutrition. Infections in humans were often made worse by preexisting malnutrition and nearly always increased the magnitude of any coexisting nutritional deficits.

Examples of Synergism and Antagonism

Synergistic or antagonistic relationships appeared to be influenced in animals by the nature of the infectious process, as well as by the type and degree of malnutrition. Most bacterial diseases (83%) were made worse by concurrent malnutrition, but, in contrast, the number of viral infections with reduced severity equalled the number with increased severity in malnourished individuals [2]. The parasitic diseases appeared to fall into an intermediate position in this type of evaluation, with a 63% incidence of synergistic interactions being about

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense (Para. 4-3, AR 360-5).

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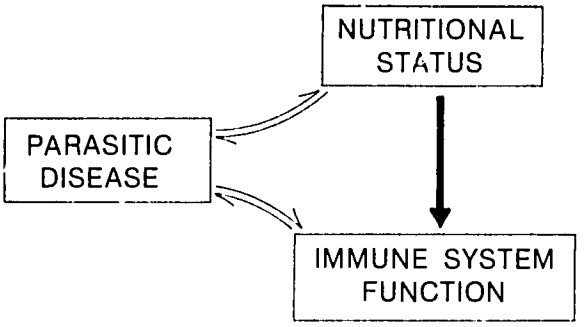

Figure 1. A schematic representation of the factors that cause synergistic or antagonistic changes in the severity of parasitic diseases. Malnutrition in its various forms typically interferes with functions of the immune system, while the nutritional status and immune system competence of the host have reciprocal influences on parasitic diseases.

midway between the findings for viral and for bacterial diseases.

Total starvation in combination with experimentally induced parasitic infections in laboratory animals led to some synergistic or antagonistic interactions [2], but no pattern emerged to indicate that the type of interaction was influenced by the species of either parasite or host. Multinutrient deficiencies in laboratory animals seemed to worsen protozoan infections; but with helminthic infections in rodents, equal number of synergistic and antagonistic interactions were reported.

States of protein deficiency almost always led to synergistic worsening of helminthic infestations, but showed only inconsistent effects on protozoan infections. Infection with *Eimeria tenella* in chickens and infections with *Plasmodium berghei* or *Trypanosoma gambiense* in rats were less severe in protein-deficient animals. A cestode infection due to *Hymenolepis nana* also showed an antagonistic interaction with protein deficiency in mice. Equivocal findings were noted in protein-deficient mice challenged with *Schistosoma mansoni* [2].

Deficiencies of vitamin A enhanced severity of most types of parastic disease, but parasitemia was alleviated in chickens with induced malaria. After being given a large dose of *Trichinella* larvae, rats deficient in vitamin E had lower muscle parasite counts than did controls [2]. *Plasmodium knowlesi* counts in the blood of monkeys deficient in vitamin C were lower than in the blood of controls, and an overwhelming increase in the parasite count of the red cells followed ascorbic acid repletion.

Deficiencies of isolated B vitamins also produced inconsistent patterns of antagonistic or synergistic interactions with a large variety of experimental parasitic diseases [2]. Although only a few studies were reported during deficiencies of riboflavin, niacin, folic acid, and biotin, most of the interactions were synergistic. In contrast, deficiencies of pantothenic acid produced a large percentage of antagonistic responses, especially during experimental malarias. In comparison with other B-group vitamins, a deficiency of pyridoxine is known to lead to the most profound abnormalities in both the histology and the function of lymphoid organs [1]. Despite any accompanying immune system dysfunction, a deficiency of pyridoxine also produced a seemingly patternless array of either synergistic or antagonistic effects during a variety of other experimental parasitic diseases.

Hookworm infections in experimental animals have been made worse by a deficiency in iron. Very little information is available, however, concerning the specific effects of other individual minerals or trace elements on parasite diseases in animals.

Validity of the Concept of Synergism and Antagonism

Although the analysis in the WHO monograph [2] did much to solidify concepts about the occurrence of synergistic and antagonistic interactions, it was based largely on descriptive data. The array of synergistic or antagonistic relationships reviewed in the preceding paragraphs fails to exhibit consistent responses based upon disease or deficiencies of individual nutrients. Clearly, the available evidence is not strong enough to certify the existence of a cause-and-effect relationship between states of malnutrition and the severity of parasitic infections. At the other extreme, the designation of a synergistic or antagonistic relationship may merely reflect a very wide scattering in published old data. Few if any of the older studies were adequately designed to test the hypothesis that malnutrition worsens (or lessens) the severity of an induced parasitic disease. Furthermore, since the WHO monograph preceded the virtual eruptions in immunologic knowledge and

molecular biology that have characterized the past decade, future investigations must seek out the mechanistic explanations for observed events.

In contrast to the hope that interpretable new studies can be designed using experimental animal models is the extreme difficulty of producing a scientifically acceptable demonstration in humans that single nutrient deficiencies, imbalances, or excesses have either a synergistic or an antagonistic effect on parasitic diseases. The number of uncontrollable variables is overwhelmingly large in human disease. Under naturally occurring circumstances, parasitic infections rarely occur as isolated events. Polyparasitism is common; initially infecting doses of parasites are not measurable; exposures are typically recurrent or continuing; and infections are usually chronic. Nutritional deficiencies in man are equally complex in terms of their severity, duration, and multiplicity and are generally influenced by coexisting bacterial or viral infections.

With respect to intestinal parasites, little is known about the effects of local variables that may be pertinent, such as the role of the fiber content, quantity, and variety of ingested foods, the effects of the normal microbial flora of the gut, or the effects of other intestinal pathogens. Intestinal viral infections often occur in children harboring multiple parasites; however, no information is available about how such viral infections might influence a parasitic process, or vice versa. Possible effects on parasitic diseases are equally uncertain with respect to intestinal infections caused by invasive or toxigenic bacterial pathogens.

Interactions may also develop among coexisting parasitic infections. Murray et al. [3, 4] suggested that interactions may occur during malaria and ascariasis if both infections are present in minimally malnourished children. Their studies were conducted on two neighboring islands of the Comoros archipelago in the Indian Ocean. Children of Anjouan were heavily infected (93% of 632 children, ranging from two to 14 years of age) with *Ascaris lumbricoides* but were relatively free of malaria (1.7%), while 237 children on Grand Comore showed a 27% incidence of malaria and a much lower (i.e., 24%) incidence of ascariasis, mostly without heavy worm burdens [3]. The dietary habits of both groups were similar, and the only other detectable parasites included small numbers of ova of *Trichiuris* or *Tricocephalus*, which were found occasionally in the stools of children in both groups [3]. When 37 Anjouan children heavily infected with *Ascaris* but with negative malarial smears were treated with piperazine, more than half of them developed malaria due to either *Plasmodium vivax* or *Plasmodium falciparum* within six to 14 days [4]. Only one of 23 children with light ascariasis developed malaria after receiving piperazine, and only two of 52 children who received a placebo developed malaria [4]. These data were interpreted as suggesting that the suppresion of malaria was a nutritional consequence of severe ascariasis and could represent an "ecological balance" for optimal cosurvival of the host and the two parasites [4]. On the other hand, these descriptive studies have been criticized [5] on several grounds, including the failure to adequately define the nature and magnitude of the children's malnutrition or to show that the *Ascaris* had, in fact, been cleared by the therapy. Nevertheless, the observations raise interesting questions about the nature of any interrelationships among different types of parasitic diseases in the same host.

Effects of Parasites on the Nutrition of the Host

The influence of parasitic diseases on the nutritional status of the host must also be considered. This influence may be virtually nil in asymptomatic patients with relatively small parasite burdens or it may reach life-threatening proportions in untreated, severe malaria [6, 7]. As an acute febrile illness, malaria resembles other generalized acute infections of bacterial, viral, or rickettsial origin in many of its metabolic and nutritional sequellae [8]. As in other generalized infections, nitrogen balance becomes negative [6, 7]; there is increased urinary excretion of nitrogenous compounds and diazo- reactants; plasma albumin and the A/G ratio are decreased; and acute-phase reactant proteins are produced in excess by the liver [8]. However, malaria is unlike other generalized infections in several unique ways. The proliferation of parasites requires the availability within red blood cells of amino acids and all other substrates needed for organism replication; the content of various amino acids is, in fact, markedly increased within parasitized red blood cells [9, 10]. Further, iron released from red blood cells because of hemolysis may virtually saturate the iron-binding

capacity of plasma; this pattern contrasts with the lowered concentration of iron in plasma that typifies most other infections [8]. In malaria the intravascular release of hemoglobin is followed rapidly by the formation of hemoglobin-haptoglobin complexes; removal of these complexes through phagocytic uptake by reticuloendothelial cells leads, in turn, to a fall in plasma haptoglobin values, rather than to the rise that characterizes other acute infections [11].

Parasitic diseases may influence the nutrition of the host in additional ways that differ from those of most other infections. Because of their very bulk, some parasites require sizeable quantities of nutrients, which must be obtained from the same sources available to host cells [7]. The competition for available nutrients is best illustrated by the requirements of fish tapeworms for vitamin B_{12}, which can lead to the development of megaloblastic anemia in the host [7, 12]. Further, the chronic nature of a parasitic disease can lead to progressive, continuing malnutrition that may feed back to impair the competence of the immune system and other systemic host defensive mechanisms. Such decrements can, in turn, reduce the abilities of the host to control the malnutrition-initiating parasite. In short, a self-contained vicious cycle could emerge on the basis of a symptomatic persistent parasitic infection in a manner analogous to that seen during an untreated chronic bacterial disease such as tuberculosis.

Nutrition-parasite interrelationships must also be evaluated in the reverse direction. Malaria may be considered an illustration in humans of an antagonistic interaction between severe malnutrition and a parasitic disease. During severe droughts, many starving African desert nomads, adults and children, were observed to have low-grade malarial parasitemia, but manifested no symptoms of illness [13, 14]. Refeeding of Nigerian nomads with a whole-grain diet [13] and the inclusion of oral ferrous sulfate therapy in a refeeding regimen in Somalia [14] were followed by an increase in iron concentrations in plasma, by near saturation of the iron-binding capacity of plasma already lowered by malnutrition, and in many patients, by an abrupt onset of symptomatic malaria. The malaria became severe and was sometimes of the cerebral variety with parasites often present in more than half of the red blood cells [13, 14]. One cannot determine from the published data whether the reemergence of symptomatic malaria was a direct effect of the increased availablity of iron as a key nutrient for parasite replication, or whether important iron-requiring cellular enzymes and defensive responses of the host became functional at different rates and, perhaps, in an unbalanced manner during the refeeding regimens.

Effects Caused by the Immune System

These concerns lead naturally to questions about the third major aspect of the three-sided interrelationship under discussion, i.e., how the immune system responds to malnutrition, parasitic diseases, or both variables in combination. The immune system is highly complex, involving multiple cell-to-cell interactions, specific and nonspecific control signals, amplification capabilities, feedback loops, and memory properties. Its highly adaptable responsiveness involves both its humoral and its cell-mediated arms, along with the supporting activities of factors, such as complement, divalent cations, lymphokines, phagocytic cells, and hormones. Although immune responses are directed toward specific antigenic targets, they do not always serve to protect the host. Immune-mediated problems include the development of allergies, anaphylactic or serum sickness reactions, formation of antigen-antibody complexes that may precipitate on cell membrane surfaces, or the initiation of cell-destroying reactions. Severe, generalized malnutrition leads to atrophy of lymphoid tissue and functional inadequacies of immune system competence [1]. Each aspect of the immune system may respond to some form of malnutrition in a different manner, and the delicately balanced interactions among immune system components may be upset. Although most of these acquired dysfunctions can be restored by correction of the initiating malnutrition, recovery of the functions of different immune system components may take place at different rates; thus, additional transient imbalances may develop during refeeding programs. These possibilities may account for some of the apparent patternless arrays of synergistic and antagonistic relationships in malnourished hosts.

Little is yet known about the details of the responsiveness of the host immune system in parasitic diseases, and still less about the possible nutritional influences on these responses. In his recent

review, Playfair [15] characterizes immune system achievements against protozoa and worms as "pitiful" in contrast to the abilities of immunologic mechanisms to control bacterial and viral infections.

Playfair [15] identified only "a few rodent protozoa, usually in unnatural hosts, a handful of worms in cattle, and human cutaneous leishmaniasis . . ." as the parasitic diseases that could be terminated by an adaptive immune response capable of maintaining resistance thereafter. Parasites seem capable of protecting themselves from immune defenses by gaining an intracellular location, forming cysts, covering their surfaces with material derived from the host, or developing surface antigens closely resembling those of the host. Blocking antibodies may also contribute to the progression of parasitic infections in which soluble antigens are often produced in large amounts [15]. Although a great variety of easily measured serum antibodies are formed during malaria, they do not appear to be of major effectiveness in generating resistance, and their contribution to protective immunity remains unclear.

An array of immune responses to parasitic antigens was identified by Playfair as being harmful to the host [15]. These include the hepatic cirrhosis of schistosomiasis, which begins as a T-lymphocyte-dependent (type 4) hypersensitivity reaction to egg antigens; the nephritis of malaria, which results from deposition of complement-fixed, antigen-antibody complexes (type 3) on glomerular basement membranes; or the IgE-mast cell interaction (type 1) which gives rise to the wheezing of tropical eosinophilia [15].

A myriad of possibilities for nutrient effects on antigen-specific immune system responses thus emerges as mechanisms that could account for synergistic or antagonistic interactions during parasitic diseases. To these must be added the possibilities for nutritional effects on nonspecific or generalized aspects of host resistance [1, 8, 16].

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Immune Responses in Parasitic Diseases. Part A: General Concepts

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Parasitic infections are incredibly varied and distinct in terms of interactions between hosts and pathogens as well as in complexity of life cycle, host range, vector or intermediary host requirements, forms of reproduction, and elicited response. A number of protozoan parasites are intracellular pathogens capable of surviving and mutiplying within microbicidal cells such as macrophages. In contrast, nematodes generally do not multiply within the host, a trait that dramatically alters the epidemiologic, clinical, and immunologic consequences of infection. Parasites have acquired apparently effective mechanisms for escape from normal host defenses and clearance. These mechanisms may be classified as antigenic mimicry, antigenic depletion, antigenic variation, immunologic indifference, immunologic diversion, and immunologic subversion. A determination of the importance and relevance of these subterfuges to parasitic infection in humans and to therapeutic or prophylactic strategies is of the utmost urgency.

The outcome of the encounter between a pathogenic microorganism and a mammalian host depends on many factors. These include the size of the inoculum (infectious dose), the state of innate or natural resistance (whether of specific immune nature or nonspecific nature), the multiplication rate of the pathogen within the host, the mobilization of host defenses to meet the challenge and the ability of the organism to multiply or overcome these protective host responses, and the virulence factors possessed by the invader.

Playfair [1] has recently categorized the events in parasitic infections into six levels of interaction (table 1). The limited success in the development of effective vaccines against most of these agents can be attributed not only to those features of the host-pathogen interaction that permit continuing infection in the "immune host," but in many instances also to features that circumvent, modulate, or turn off the immune response [2]. A number of recent papers have reviewed these problems [1-6]. The purpose of this paper is to provide a conceptual framework for an understanding of the uniqueness of parasitic infections and the immune response.

Immune Mechanisms: General Overview

Elegant studies in recent years have amply demonstrated the complexity of the immune systems of mammalian hosts. Instead of the simple division of the immune response into humoral and cellular arms that was once accepted, there exists a multiplicity of soluble factors and cell populations and subpopulations, each with regulatory and modulatory controls. These factors and cell types interact with one another in sometimes mysterious ways, largely through signals received at the cell surface. Thus, the complexity stems not only from the large number of distinctive components involved, but also from the fact that various types of cooperation may be required to perform different immunologic tasks (or specific reactions, as measured in systems in vitro). Moreover, from a clinical point of view, the system is redundant; several responses may individually produce significant protection. On the other hand, a summation of effects from different effector mechanisms may well be essential to an adequate host response. "Experiments-of-nature" immunodeficiencies provide examples of these principles.

Clear, quantitative relationships also exist between immune functions, as assayed in isolated systems in vitro or in the in vivo milieu, and susceptibility to infection. However, these relationships are not necessarily linear, for there are both thresholds for functional consequences at one end of the spectrum and "functional reserve" at the opposite end, not to mention amplification and feedback loops. In the context of the interaction of parasitic agents and the immune system, however, the net result may be significant protective immunity, failure of effective immunity, irrelevant

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Table 1. Classification of events in parasitic infections.

Level	Characteristics	Example in human host
1	No invasion: natural resistance	*Trypanosoma brucei*
2	Colonization, mutual benefit: symbiosis	Gut flora
3	Colonization, no disease: commensalism	*Entamoeba coli*
4	Invasion, disease, cure: sterilizing immunity	*Leishmania tropica*
5	Invasion, disease, no cure, resistance to reinfection: concomitant immunity	*Plasmodium* species
6	Invasion, disease response, no resistance or cure: ineffective immunity	*Trypanosoma cruzi*

NOTE. Data are adapted from [1].

immunity, concomitant immunity, or even immune pathogenesis of disease.

Parasitic Infections and Diseases: General Overview

It must be emphasized that the classifying term parasites, as commonly used, is meaningless. The agents usually encompassed by the term come from two distinct subkingdoms, the protozoa and the metazoa, that have little or no physical, biologic, or physiologic similiarities. Even among themselves the members of these individual subkingdoms vary enormously with respect to complexity of life cycle, range for either definitive or intermediary host (if required), forms of reproduction, requirement for arthropod vectors, and immunologic responses.

Three features of the protozoa and metazoa are particularly relevant to the immunologic responses of the host. First, some of the virulent forms of the protozoans are (apparently) obligate intracellular pathogens, surviving and multiplying within cells where they are protected from immune attack by either humoral or cellular elements. Indeed, in the case of *Leishmania*, the organisms proliferate within the macrophage, a professional phagocytic and microbicidal cell whose normal task is the destruction of, not the support of, pathogenic microorganisms. This observation raises the issue of the ability of certain parasites to evade the immune response of the host. Second, with a few exceptions, the metazoan parasites of humans do not replicate within the host. The clinical, immunologic, and epidemiologic implications of this fact are enormous [7]. Parasitism involving these agents is a manifestly quantitative phenomenon, dependent on the number of invading or ingested infective forms that survive within the host, the antigenic burden that worm load imposes on the immune system, the physiologic consequences on the functions of the target tissue (asymptomatic infection vs. overt disease), and the number of infective forms present in the environment. In some examples (e.g., the hookworms, *Schistosoma mansoni*, and *Ascaris lumbricoides*), the majority of human hosts are in fact lightly infected, completely or relatively asymptomatic, and nonimmune [8]. The acquisition of immunity is usually critical for the survival of the host following infection with multiplying pathogens, but it may have little or no impact on the response of the host to nonreplicating helminths. Third, parasitic agents may undergo dramatic transformations accompanied by changes in size, shape, and surface characteristics within the human host [9]. Thus, acquired immunity to one form may have no effect on another stage in the life cycle of the organism.

Immune Responses of the Host to Parasites

Immune responses of helminths sufficient to result in the expulsion of worms and cure can be documented in a few animal systems. These mechanisms may involve secretory IgA (as against *Taenia taeniaeformis* and *Nippostrongylus brasiliensis*) [10, 11], IgG (as against *Hymenolepis nana*) [12], B cells (as against *Trichinella spiralis*) [13], T cells (as aganist *N. brasiliensis*) [14], several of the above [15], or the generation of a marked inflammatory response in the intestinal tract [3], which may also be immunologically mediated and involve eosinophils (as against *T. spiralis*) [16]. However, helminthic infections of humans are long-lasting, chronic processes, and immune mechanisms, if present, cannot be very effective.

In the case of *S. mansoni*, the immune response

to eggs released into the liver is the basis of the disease symptomatology. The critical problem results from the formation of granulomas around the eggs [17]. Studies on microcirculation in living animals experimentally infected with *S. mansoni* show minimal effects on the circulation of eggs impacted in the portal venules early in disease, but dramatic alteration of blood flow when the granulomas form [18]. The formation of these granulomas is a cell-mediated immunologic reaction, in which specific egg antigens interact with sensitized T cells to release lymphokines affecting macrophages and eosinophils, the major constituents of the granulomas. The disease caused by *S. mansoni*, hepatosplenic schistosomiasis, is thus immunologically induced. The immune response may also be responsible for the fibrosis that results; Wyler et al. [19] have demonstrated fibroblast proliferation in response to soluble factors from granulomas stimulated by soluble egg antigens.

Another immune response well illustrated by schistosomiasis is concomitant immunity, in which the host infected with adult worms becomes resistant to cercarical challenge. That this resistance is induced by the adult can be demonstrated by the transplantation of adults to a virgin host, which then also becomes resistant to cercariae without ever having been exposed to them before [20]. However, this resistance does not result in immune expulsion of the adults.

Evasion Mechanisms of Parasites

A number of organisms have evolved distinctive mechanisms for avoiding the consequences of the immune response of the host (table 2). These mechanisms appear to play a major role in the survival of the parasite [21].

Antigenic mimicry refers to the ability of the pathogen to display host antigens on its surface and thus masquerade as "self;" this phenomenon is demonstrated by *S. mansoni* [22, 23]. In a fascinating experiment, adult worms were grown in mice and transferred to rhesus monkeys that had been preimmunized against either mouse or gerbil erythrocytes [20]. The fact that the adult schistosomes were able to survive except in those monkeys previously sensitized to mouse antigens suggests the presence of murine antigens on the surface of the mouse-grown worm. Acquisitions by worms of host constituents, such as blood group antigens, occurs over a period of days following penetration of the skin by the invading schistosomula [22]. Sher et al. [23] have also shown that murine major histocompatibility complex (MHC)-antigens were present on the mouse-grown worms. Another example of antigenic mimicry is the ability of certain organisms to split immunoglobulins and to coat themselves with immunoglobulin fragments, such as Fab [24], or to bind the Fc portion of immunoglobulin and expose Fab still capable of anti-

Table 2. Escape mechanisms of parasites from protective host responses.

Escape mechanism	Nature of response	Example
Antigenic mimicry	Incorporation of host "self" antigens into parasite surface	*Schistosoma mansoni*
	Coating of parasite by Ig fractions (fabulation)	*Tetrahymena pyriformis* *Trypanosoma cruzi* (?)
Antigenic depletion	Shedding of tegument	*S. mansoni*
	Capping and shedding of surface antigens	*Leishmania*
Antigenic variation	Sequential adoptive phenotypic variation	African trypanosomes
Immunologic indifference	Intracellular survival within macrophages	
	(*a*) failure of lysosomal fusion	*Toxoplasma gondii*
	(*b*) escape from lysosomes	*T. cruzi*
	(*c*) resistance to microbicidal events	*Leishmania donovani*
Immunologic diversion	Polyclonal B-cell activation	*Plasmodium* species
Immunologic subversion	Immunosuppression	
	(*a*) humoral	*S. mansoni*
	(*b*) cellular	*S. mansoni*

gen recognition [25]. This ability both masks parasite antigens and presents a screen of host "self" antigens to the immune system.

Antigenic depletion refers to the stripping of antigens from the surface of the parasite by a shedding mechanism, such as that observed for the tegument of *S. mansoni* [26], or the capping and shedding of surface antigens, such as that described for *Leishmania enriettii* [27]. In the latter example, antibody capping and shedding reportedly results in the insensitivity of the organism to the addition of fresh antibody and complement [21]. Whether this mechanism is of real importance to the survival of intracellular organisms like *Leishmania* is unknown, but it might be very important to extracellular organisms, such as nematodes.

Antigenic variation is the term used in describing the periodic shifts in surface antigenic composition of the African trypanosomes [28]. Infection with these organisms is characterized by waves of parasitemia associated with variant surface glycoproteins. Cloning experiments have demonstrated that this phenomenon is not due simply to selection of antigenic variants by antibody-induced selective pressure from an initially mixed population, because single clones undergo antigenic transformation in sequence in vitro in the absence of antibody [29]. Antigenic variation has also been described in a number of hemoprotozoa, including other genera such as *Plasmodium* and *Babesia* [30].

Several protozoa have apparently learned to survive within the macrophage, either by preventing lysosomal fusion [31] or by escaping from an already formed phagolysosome [32]. The situation that results may be called immunologic indifference. As in the example of *Leishmania*, these remarkable organisms continue to grow within the phagolysosome [33], even though the macrophage is sufficiently activated to eliminate certain facultative intracellular pathogens such as *Listeria monocytogenes* [34]. The capacity to survive within activated macrophages is clearly a unique property of some, but not all, intracellular pathogens. Among the parasites, *Leishmania* appear to be the most efficient in this ability, but the mechanism by which this occurs is not understood.

Recently, the trematode fluke, *Fasciola hepatica*, has been shown to evade the effective immunity it induces in rats by means of excretory/secretory products that are toxic to host lymphocytes and other immunocompetent cells [35]. The categories of immunologic diversion, such as polyclonal B-cell activation [36, 37], or of immunologic subversion, such as humoral or cell-mediated immunosuppression [38, 39], may aid the parasite in its struggle against host defenses. However, the meaning and importance of these observations to the pathogenesis of disease are uncertain. Much more remains to be done at the laboratory level, but direct extrapolation of these results to the human situation poses difficulties, which can be expressed as the dual danger of the "nonmodel" model and the "model nonmodel." For example, infection of mice with *Plasmodium berghei*, unlike infection of humans with malaria, entails an overwhelmingly virulent organism which, nonetheless, relatively easily induces solid immunity. In these features the system qualifies as a "nonmodel" model. As a "model nonmodel," the rodent nematode, *N. brasiliensis*, can be cited. This worm causes a limited infection of the small bowel in rats that is self cured by a T-cell-dependent, mast-cell-mediated mechanism of worm expulsion that results in immunity to reinfection. In contrast, nematode infections of humans are characterized by their longevity and by the continuing susceptibility of the host to repeated infection. This is not to say that immunity does not occur, but rather that it is not acquired with ease. In both types of system an important distinction exists between questions relevant to human infection that can be studied and questions that can be studied but are irrelevant.

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Immune Responses in Parasitic Diseases. Part B: Mechanisms

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A number of host defenses provide variable resistance against parasites. From the biological point of view, invading parasites must not eliminate the susceptible host population; therefore, antiparasite immunity plays an essential role in limiting the invasion and proliferation of parasites. Several differences exist between immune responses to parasites and immune responses to other microorganisms. Effector mechanisms include T lymphocyte-mediated inflammatory granuloma formation and encapsulation involving the deposition of fibrous tissue. In some instances, passive immunity can be transferred by serum antibodies. Antibodies may act via complement fixation, granulocyte adhesion, opsonization, inhibition of invasion, or mast cell degranulation. Of the nonspecific factors, macrophage activation, natural killer cells, and serum factors other than antibodies are critical in the battle against parasites. The net result of these immune responses may be antiparasitic, proparasitic, of no consequence to either host or parasite, or harmful to the host.

The diversity of parasites potentially capable of infecting humans makes it inconceivable that any one antiparasitic effector mechanism could be responsible for protective immunity. Thus, a variety of immune responses can be mobilized to restrain invasion and proliferation and to eliminate parasites.

Understanding of immunity to parasites is still limited and most data are derived from studies using laboratory host-parasite systems. Knowledge of the precise mechanisms of protection and how they fail in certain instances is not only of intrinsic interest, but is also essential for the development of strategies of control. Several general concepts must be considered in relation to host responses to parasites: (*1*) parasitic agents are heterogeneous; (*2*) chronicity is a characteristic of most parasitic infections, and persistent antigenic stimulation is a major factor in host-parasite interactions; (*3*) the mechanisms of evasion differ substantially from those involved in prevention of reentry or in rejection of the parasites; (*4*) the immunologic accompaniments of chronic parasitic infection, e.g., immunosuppression and hypergammaglobulinemia, may by themselves have important functional consequences; (*5*) many parasites are in a state of evolution and undergo significant genetic and antigenic variation within a relatively short time; (*6*) striking, genetically-determined variation in innate immunity exists in natural hosts; and (*7*) humans, as well as monkeys, mice, rats, and other laboratory animals differ widely in their ability to handle complex antigens such as those found in parasites.

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Host Resistance to Parasites

Resistance can be passively transferred from one individual to another with antibodies and specifically sensitized lymphocytes (table 1). There is good evidence that spontaneous cure depends on thymus-dependent immune response. Athymic animals (nude mice, neonatally thymectomized murine models) exhibit increased susceptibility to infection, as manifested by heavier burdens of parasites, increased proliferation of parasites, prolonged infection, failure to develop immunity, or death. However, this greater susceptibility is not invariable. Also, protection cannot be correlated with the extent of cell-mediated immune response or levels of circulating antibody. The protective effect of vaccination against many parasites provides evidence for the role of immune responses in host resistance. However, resistance need not and does not have only an immunologic basis. Moreover, the search for effective vaccines is thwarted by protozoa using antigenic variation as a parasite-protective strategy and by those relatively sequestered in protected sites such as inside cells, cysts, or skin. The four tiers of resistance to para-

Table 1. Some examples of spontaneous cure and underlying mechanisms of immunity to intestinal helminths in mouse and rat.

Parasite	Transfer of protection with immunologic process			
	Lymphocytes*	Serum	Inflammation	Reaginic antibody
Trichuris muris	+	+	–	–
Trichinella spiralis	+	+	+	+
Aspiculuris tetraptera	±	±	–	–
Nippostrongylus brasiliensis	+	+	+	+
Hymenolepis diminuta	–	–	–	–
Strongyloides ratti	+	+	+	+

* Often using mesenteric lymph node cells or thoracic duct lymph cells.

sites in vertebrate hosts are presented in table 2. The net result of these responses may be (*1*) antiparasitic (or host-protective), (*2*) proparasitic (or parasite-protective) and of no use to the host, (*3*) of no consequence to either host or parasite, or (*4*) definitively harmful to the host and resulting in pathology and disease manifestations. In this paper, the subject of immune response to parasites is briefly reviewed, with selected examples of the extreme variety of effector mechanisms that the host employs against parasites.

Effector Mechanisms

The chronicity of many parasitic infections and the paucity of sterile and reinfection immunity have led to the belief that several parasites are poorly immunogenic. However, the use of sensitive techniques has shown that immune response occurs during all parasitic infections. The main components of parasite-destructive processes, such as T cells, antibodies, phagocytes, and inflammatory response, are presented in table 3.

T lymphocytes. The process of granuloma formation around metazoan parasites is T-cell dependent. It involves fibrous tissue deposition and localized cellular infiltrate in which a variety of inflammatory cells participate. For example, the inflammatory response to *Schistosoma mansoni* eggs is a delayed hypersensitivity reaction [11–13]. Lymphocytes, monocytes, and giant cells accumulate. Deficiencies of protein, the B group of vitamins, and vitamin C reduce the size and cellularity of the granuloma. The practical implications of the nutritional modulation of granuloma formation in regard to the incidence of clinically manifest disease in areas of the world where both undernutrition and schistosomiasis are rampant are not known.

The reactions to *Nematospiroides dubius* larvae in the gut wall [14, 15] and to *Mesocestoides corti* larvae in the liver [16] are other examples of T-cell-dependent encapsulation. The T-cell subpopulation involved is not known. In the case of infection with *M. corti* in mice, at least seven steps of the host-parasite interaction are T-cell dependent, including eosinophilic infiltration in the peritoneum, malabsorption, hepatic encapsulation, antibody response, elevation of serum IgG1 levels, restriction of parasite proliferation, and ultimately the survival of the host [17].

The sequestration achieved by the walling off of the parasite has a protective effect. The survival of the host is promoted by the encapsulation of harmful substances produced by the parasite [18]. The proliferative rate of the parasite also may be

Table 2. Types of resistance to parasites.

Innate resistance	Induced immunity	Modulating immunity	Curative immunity
Natural. Does not permit establishment of infection.	Affords relative resistance to reinfection with homologous parasites in already parasitized hosts.	Modifies parasite antigenic expression.	Eliminates parasite.

Table 3. Effector mechanisms of protection against protozoa.

Parasite	T-cell cytotoxicity [1, 2]*	Delayed hypersensitivity [3]	Antibodies: Complement-fixing, neutralizing, and agglutinating [4-6]	Antibodies: Blocking [7, 8]	Antibodies: Opsonizing cytotoxic [9, 10]
Malaria	–	+	+	+	+
American trypanosomiasis	?	+	+	?	+
African trypanosomiasis	?	?	+	?	?
Leishmania	–	+	+	?	+
Toxoplasma	–	+	+	?	+

* Representative examples of each type of effector response can be found in the references cited.

reduced [19]. On the other hand, the encapsulation may lead to manifestations of disease. This is best illustrated by the response of tissue to Schistosoma eggs [20]. Involvement of both antibody-mediated inhibition of T cells and T suppressor cells has been proposed. Blast transformation response is markedly depressed in the presence of immune sera [21]. The contribution of various T-cell subsets and the nature and effects of various lymphokines in the regulation of immunoparasitologic responses is not yet delineated.

Mucosal responses to intraluminal parasites also are T-cell dependent. Depletion of T lymphocytes results in reduction in accumulations of eosinophils, mast cells, and goblet cells. The action may be initiated and mediated by lymphokines or T-dependent antibodies. Some evidence suggests that T cells and gut mast cells have a common lineage. There is a paucity of data on the route of absorption of parasite antigens and the mechanisms by which the gut changes to a secretory organ in the parasitized host. Elimination of intestinal metazoan and protozoan parasites in mice is a T-cell-dependent process (table 1). Homing of T cells and B lymphoblasts destined to become IgA plasma cells is enhanced during intestinal parasitic infections. The expulsion of some intestinal worms, e.g., *Trichinella spiralis*, may require complementary action by both lymphocytes and antibody. In nude mice, both metazoan and protozoan parasites persist for a long time. In multiply infected hosts the complex interplay of factors may enhance or retard the expulsion of one parasite and at the same time have the opposite effect on another parasite. Rejection of parasites is promoted by T-cell-dependent antibodies and T-cell-dependent inflammatory response. In infection with *N. dubius*, the susceptibility of individual strains of mice to chronic parasitism is an important variable. Repeated exposure to third-stage larvae or the systemic implantation of adult worms induces T-cell-dependent worm expulsion and resistance to reinfection in the females in some strains but not others [22].

Antibodies. Against some parasites, complete immunity can be achieved by passive transfer of immune serum. The complement-fixing antibodies, particularly IgG2, are effective against the early stages of parasites, that is, oncospheres and larvae. For example, in the infection of rodents with the larval cestode *Taenia taeniaeformis*, complement-fixing IgG antibodies mediate host protection [23]. Interestingly, host resistance of different inbred strains correlates with ability to mount a rapid antibody response. On the other hand, the production of anticomplementary activity in the cyst promotes the evasion of immune response [24]. Purified IgG2 antibodies from immune sera transfer protection from reinfection to nude recipients. Similar effects may be achieved by IgG1 antibodies from sera of infected animals; this influence may be mediated by neutralization of anticomplementary activities in the larvae or by destabilization of mast cells. The result is an increase in vascular permeability for other antiparasitic molecules and cells.

A second mechanism by which antibodies provide protection against parasites depends on granulocytes. The binding of leukocytes to antibody-coated larvae is an important first, though not always essential, step prior to phagocytosis. Enzymes released by granulocytes can destroy early stages of parasites. Young larvae of *S. mansoni* and *T. spiralis* are extremely susceptible to IgG-dependent eosinophil-mediated damage [25, 26].

In these responses, complement components may act enhancing molecules promoting the efficiency of kill. The combination of antibodies (possibly anticuticular IgM) and granulocytes has a synergistic effect for the destruction of *Dipetalonema viteae* microfilariae in hamsters [27].

Antibodies over mucosal surfaces may prevent the attachment of infectious agents to the epithelial cells and impair antigen absorption. IgA as well as other isotypes of immunoglobulins may be active, as is particularly evident in the case of intestinal cestodes. For example, local IgA antibodies protect mice against infection with *T. taeniaformis* [23]. Colostrum-derived anti-oncospheral IgA antibodies prevent mucosal penetration by hatched and activated oncospheres. On the other hand, IgG but not IgA antibodies are protective when given parenterally.

Antibodies can also inhibit the invasion of red cells by protozoan parasites such as *Plasmodium* [28] and *Babesia*. Antibody-mediated neutralization of enzymes and other destructive molecules released by parasites may be protective. Finally, reaginic IgE antibodies are often elevated in parasitized hosts; these are considered helpful in the elimination of parasites, presumably via mast-cell degranulation and immediate hypersensitivity responses. In the case of many intestinal parasites, e.g., *Nippostrongylus brasiliensis*, the initial damage by antibody is followed by T-cell participation resulting in expulsion of the worm.

Recent studies have shown that a rheumatoid factor-like IgM may confer protection by enhancing IgG response. Rats infected with *Trypanosoma lewisi* respond by producing an ablastin IgG antibody that inhibits reproduction of the parasite by blocking cell division and that lacks cytotoxicity. The antibody induces metabolic and morphologic changes. IgM antibody response occurs late in the course of disease and terminates the infection, leaving the animals with lifelong immunity. The serum of lactating rats that have never been infected with the parasite also contains the rheumatoid factor-like IgM autoantibody [29].

Other defense mechanisms. These protective processes do not depend upon the recall of a specific immune response initiated by a previous exposure. Nevertheless, these mechanisms do show some measure of specificity in that they distinguish between different types of organisms. In this context, it may be more appropriate to use the term "natural resistance." At the very outset, we should recognize the natural immunity is strongly modulated by genetic factors. The successful establishment of parasitism is possible only in a restricted number of host species, strains, and breeds [30]. For example, susceptibility to infection by *Leishmania donovoni* in mice is governed by alleles at a single or closely linked locus, mapping away from the major histocompatibility locus and situated on the same chromosome as the locus governing susceptibility to *Salmonella typhimurium* [31].

Innate immunity may depend upon the environmental conditions within the potential host. For example, different species of *Plasmodia* invade different stages of erythrocytes presumably related to variations in the intracellular environment [32], including hemoglobin, glucose-6-phosphate dehydrogenase, etc. In addition various cellular and humoral factors confer natural resistance. Some of these factors are also modulated by environmental influences.

Macrophages. Macrophages participate both in antigen-specific and nonspecific immune responses, but principally in the latter. Phagocytes of the host provide a home for the survival and proliferation of many protozoa, e.g., *Toxoplasma gondii*, *Trypanosoma cruzi*, and *Leishmania* species. The parasites evolve methods of dealing with the intracellular environment, which is generally inimical to pathogens. In fact, for some parasites pathogenicity may depend on the ability to grow in activated macrophages. In specific instances, there is failure of phagosome fusion with lysosomes (for example, *T. gondii*), escape into cytosol, (for example, *T. cruzi* and *Mycobacterium leprae*), resistance to lysosomal enzymes, and reduced expression of surface H-2 molecules (for example, *Leishmania* species).

The initial steps in the interaction between macrophages and parasites involve recognition, adhesion, and phagocytosis. The activation of complement by parasites may generate chemotactic molecules that attract phagocytes at the site of action. For some organisms, e.g., *Leishmania* and *Trypanosoma*, ingestion in vitro can proceed in the absence of serum factors [33, 34]. Pretreatment of phagocytes with chymotrypsin, which does not influence complement-mediated phagocytosis of red cells but blocks the attachment and phagocytosis of *T. cruzi*, suggests that C3b recep-

tors are not essential for ingestion. Recent data [35] contradict earlier suggestions that parasites must be oriented in a specific manner during the process of engulfment. However, the formation of a microfilamentous mesh is an important prerequisite because this step is blocked by cytochalasin B.

The parasitophorous vacuole is lined by a membrane derived essentially from the plasma membrane of the host cell. The size of the vacuole relative to that of the parasite can vary considerably. Fusion of vesicles as well as influx of fluid into secondary lysosomes can alter the size of the vacuole, but the significance of these processes and of vacuole size for the survival of intracellular parasites is not known.

The next steps of fusion with primary or secondary lysosomes, generation of microbicidal activity, parasite inactivation, and digestion or extrusion are enhanced by macrophage activation. Certain parasites, on their part, have evolved mechanisms for evasion of the lethal effects of phagosome-lysosome fusion. Some of these mechanisms are inhibition of phagolysosome formation, resistance to the intralysosomal milieu, and escape to extravacuolar spaces. The cytotoxic mechanisms of macrophages include hydrolytic enzymes and synthesis of highly reactive oxygen metabolites including the superoxide anion, hydrogen peroxide, singlet oxygen, and hydroxyl radicals. Moreover, activated macrophages release factors or induce other cells to release products that inhibit cell membrane transport processes.

Natural killer (NK) cells. Recent investigations have shown that certain populations of lymphoid cells from nonimmunized donors exhibit cytotoxicity against a variety of target cells, including parasites and parasitized host cells. The heterogeneity of the NK cells is becoming apparent. They vary in size from small to medium lymphocytes and have poorly detectable surface immunoglobulin and C3 receptors and low density of Thy-1.2 antigen. The activity of NK cells is independent of a functioning thymus; in fact, some evidence suggests that the thymus may have a suppressive effect on NK cells. Natural cytotoxicity is significantly controlled by genetic factors. The role of NK cells in hemoprotozoan infections is indicated by the observation that the mouse strains extremely vulnerable to *Plasmodium chabaudi* and *Babesia microti* infections are those with the lowest NK cell activity [36, 37]. An increase in the activity of NK cells can be observed in the spleens of those infected animals who survive the parasite challenge. Inoculation of infected nude mice with spleen cells from syngeneic, recovered, normal littermates permits the recipients to eliminate the parasite rapidly [36]. Since depletion of B cells and adherent cells by nylon-wool columns, depletion of T cells by anti-Thy 1 antiserum and complement, and immune serum have no influence on this phenomenon, the protection must depend on NK cells. Furthermore, recruitment of precursor cells via interferon or other mechanisms may further increase cytotoxicity.

Serum factors. Fresh serum from nonsensitized animals may be toxic for various parasites [38]. However, if parasites rapidly penetrate host cells, they are protected from serum damage. The mechanisms of serum toxicity are not clear. Both natural antibodies and complement may participate [39, 40]. Parasites themselves can activate complement by both alternate and classical pathways [25].

Other factors. Other antiparasitic effector mechanisms are involved in nonspecific protective immunity induced by substances such as bacille Calmette-Guérin vaccine. The identification and

Table 4. Some mechanisms of evasion adopted by protozoa.

Parasite	Intracellular localization	Antigenic change	Immunodepression	Polyclonal activation
Malaria	+	+	+	+
American trypanosomiasis	+	+	+	+
African trypanosomiasis	±	+	+	+
Leishmania	+	?	?	±
Toxoplasma	+	?	?	?

characterization of these mediators, many of which are derived from inflammatory cells, are the focus of current studies.

Concluding Remarks

In the struggle between humans and parasites, the various host protective mechanisms are important determinants of the final outcome: disease or survival. The repertoire of immune responses mounted by humans is often matched by the canny mechanisms of survival and proliferation shown by parasites (table 4). Studies have demonstrated that protective immunity is compromised when the host is malnourished or has multiple or repeated infections. These problems are especially common in developing countries with rampant poverty and poor sanitation. Moreover, we must recognize the profound immunodepressive effects of parasitic infections, which by themselves may allow infection to persist. Several mechanisms have been suggested, including nonspecific suppressor effects mediated through macrophages and the generation of suppressor T lymphocytes.

The recent application of modern immunologic concepts and techniques to parasitic infections has yielded important fundamental and practical knowledge [41-51]. there remain many unresolved, pertinent problems, such as the purification of the relevant parasite antigens, the role of lymphocyte subsets in protective antiparasite immunity, the production of effective vaccines, etc. Ideally, judicious application of the available information ultimately will result in effective control of the parasitic diseases of man and domestic animals, with resultant profound economic and health consequences across a wide belt of Asian, African, and American countries.

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Intestinal Physiology and Parasitic Diseases

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This paper reviews the major steps in alimentation, digestion, and absorption, which must be intact as a basis for normal nutrition, and discusses evidence relating parasitic infection in humans to effects on intestinal physiology. Parasites, with their ability to induce systemic toxicity and fever, to release active and toxic substances into the intestinal lumen, to compete for certain nutrients, to cause both functional and structural changes in the intestinal mucosa, and to stimulate hypermotility, which lessens the time available for digestion and absorption, can influence the alimentary process at almost every one of its steps. However, parasitic infection is likely to exert its most important impact at the very first step of the alimentary process, by adversely affecting the intake of food through any of a variety of mechanisms.

In order to influence the nutritional status of the host, parasites must affect one of the following processes: the intake of food, its subsequent digestion and absorption, the final disposition of nutrients in body structure and metabolism, or the maintenance of nutrient pools. The structural and functional impact upon the digestive tract is obviously a critical determinant of the extent to which parasitic infection influences the nutritional status of the host [1-3]. Table 1 provides some examples of the effects of various parasitic infections on intestinal physiology. This paper reviews the relevant digestive physiology with special attention to those functions that are or might be influenced by infection with helminths or protozoa. The highly variable range of effects, from minimal to grave, on host physiology directly reflects the variability in the intensity of infection or parasite load.

An Overview of Alimentary Physiology

A brief overview of alimentary physiology may serve as a useful introduction to a discussion of the altered physiology caused by parasitic infection. This physiology can be conveniently divided into four arenas: (*1*) appetite and eating behavior; (*2*) events in the gastrointestinal lumen, beginning with swallowing, which leads to the mixing of food with gastric, pancreatic, biliary, and intestinal secretions, then progressing to digestion and propulsion to appropriate locations in the intestine for absorption; (*3*) cellular events in the intestinal mucosa, including the terminal digestion of sugars and proteins, the uptake of nutrients from the intestinal lumen, the processing of nutrients (as in the resynthesis of triglycerides during fat absorption or in the conversion of vitamins to coenzyme forms), the release of nutrients for return to the circulation, the generation and release of hormones, which may influence not only gastrointestinal secretions but also motility and even the subsequent disposition of nutrients: and (*4*) circulatory events, including the return of nutrients to the circulation in either the mesenteric venous circulation or the intestinal lymphatics, and also the subsequent enterohepatic circulation. The enterohepatic circulation involves nutrients, endogenous substances, or drugs that perfuse the liver in the portal circulation, are taken up and excreted in the bile, and then reabsorbed and returned in the portal circulation. Our understanding of the importance of this enterophepatic circulation for the maintenance of circulating nutrient pools is growing.

Food Intake and Anorexia

An area of great importance for this or almost any discussion of the effect of disease on nutritional status is one about which we have incomplete physiological understanding: the control of appetite and the cause of anorexia. Discussions of individual parasitic infections often refer to effects

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Table 1. Some examples of the effects of parasitic infection on intestinal physiology.

Stage or site	Effect	Parasite
Food intake	Anorexia	Most protozoa and helminths
Swallowing	Achalasia	*Trypanosoma cruzi*
Stomach	Achlorhydria/hypochlorhydria	*Giardia lamblia, Diphyllobothrium latum*, hookworm
Liver	Biliary obstruction	*Ascaris lumbricoides*
Pancreas	Obstruction	*A. lumbricoides*
	Impaired protein digestion	*G. lamblia, A. lumbricoides*
Intestine	Altered motility	*Trichinella spiralis*
	Competition for nutrients	*D. latum*
	Bacterial overgrowth	*G. lamblia*
	Local irritation (damage) and nutrient malabsorption	*A. lumbricoides* (heavy load), *G. lamblia, Isospora hominis, Capillaria philippinensis, Strongyloides stercoralis*
	Mucosal damage resulting in endogenous losses	*C. philippinensis, S. stercoralis*, hookworm
	Obstruction of lymphatics	*Schistosoma mansoni*
	Diminished venous return	*Plasmodium knowlesi*

on appetite and food intake without much insight into the mechanism. Space does not permit a discussion here of current concepts of the control of appetite and satiety in man, but it is pertinent to our discussion that, in addition to psychological factors, the intake of food is influenced both by events in the central nervous system and by local events in the gastrointestinal tract, most importantly those related to propulsion and motility.

Systemic effects of parasitic infection, including fever, toxicity, and metabolic and hormonal alterations, can certainly influence the central nervous control of appetite and local aspects of gastric emptying, and the mass effect or irritation from intestinal parasites can influence intestinal propulsion and motility. Whatever the mechanism (and we need to learn more about the mechanism by which parasitic infections and infections in general influence feeding behavior), the lowered intake of nutrients, contrary to the common caricature of the hyperphagic host with intestinal tapeworms, may be the most common and most important cause of deficits of calories and other nutrients in the presence of parasitic infection. Virtually every parasite considered in this workshop influences food intake by either a systemic effect or perhaps a local effect on the gastrointestinal tract.

Dietary intake has generally not been measured as an independent variable, nor has intake been controlled in most studies of nutrition and infection. In the United States, the nutritional status of relatively well-nourished children seemed little affected by infection with *Ascaris* [4]. In contrast, in rural Nigerian children intakes of energy and protein decreased significantly as the severity of parasitic infection increased [5]. In fact, the intake of energy decreased significantly with only a moderate, single infection [5]. Experimentally, heavy infection with *Ascaris suum* produced a significant reduction in rates of growth and intake of food in young protein-deficient pigs, with impaired digestion of fat and retention of nitrogen [6]. The nutritional impact and the benefits of treatment are likely to be greatest for those with heavy parasite burdens and preexisting marginal intakes of protein and/or energy.

Events in the Gastrointestinal Lumen

We might begin by noting the capacity of one parasite to influence the function of swallowing. Chronic infection with *T. cruzi* (Chagas' disease) destroys the neural plexuses in the esophagus and produces a swallowing disorder almost indistinguishable from idiopathic achalasia. Anatomically, the next potential locus of interference in luminal events is in the stomach, which functions both in the secretion of acid and pepsin and in the

mixing and emulsification associated with the churning movements of that organ. Achlorhydria or hypochlorhydria has been discovered in patients with parasitic infection [7]; such a diminution in the production of gastric acid could influence subsequent digestion and release of hormones. Loss of gastric acid could also interfere with the maintenance of a relatively bacteria-free intestinal lumen because a low pH is one of the important factors in the suppression of intestinal bacterial overgrowth [8]. Whether parasites influence the secretion of gastric acid by direct damage to the parietal cells or the antral cells that produce the hormone gastrin or by other metabolic or systemic events has not been established. A most important consideration is that most studies that have demonstrated effects of intestinal parasitic infection on the secretion of gastric acid have been carried out in patients with multiple infections and considerable degrees of malnutrition. In such cases, it is unclear whether the infection or the malnutrition or the combination of the two is responsible for the changes in gastric physiology.

The controlled release of food from the stomach into the proximal small intestine, a process that is critical to normal digestion, may also influence feeding behavior. Protozoa such as *Giardia* or helminths such as *Ascaris*, which cause irritation and hyperactivity of the proximal intestine and the gastric pylorus or a mass effect in the lumen, could be responsible for anorexia as well as for altered digestion, especially when they are migrating in response to irritant food or fever.

The secretion of bile by the liver is a complex of synthetic, metabolic, secretory, and circulatory events. This process can be influenced by damage to the circulatory system or to the hepatocyte, as in late-stage schistosomiasis, or by interference with the mechanical release of bile into the intestinal lumen, as in the obstruction of the biliary duct in infection with *Clonorchis* or *Ascaris*. Similarly, in severe ascariasis, obstruction to the flow of pancreatic juice, bicarbonate, and enzymes may impair the digestion of fats, starches, and protein [9]. While little current evidence suggests that parasitic infection produces direct damage to or inhibition of pancreatic acinar cells or of the flow of pancreatic fluids [10], some reports indicate that certain intestinal parasites, *Giardia* and *Ascaris* for example, produce enzymes capable of interfering with or even digesting pancreatic proteases such as trypsin and chymotrypsin [11]. One enzyme produced by *Ascaris* is called "ascarase."

Intestinal motility deserves some emphasis here since the process of digestion in the lumen of the intestine requires not only the release of biliary and pancreatic juices, but also proper mixing with the food in the proper location for subsequent absorption of the products of digestion. An additional intraluminal factor is the time available for digestion and absorption of nutrients. Good studies of motility are lacking, but the impression is that some intestinal helminthic infections result in intestinal hyperactivity, which may lead to anorexia and, perhaps equally important, limit the time available for digestion and absorption. Rats infected with *Trichinella spiralis* experienced significant speeding of intestinal transit with increased propulsive activity [12].

Another important aspect is the impact of luminal parasites or associated bacterial overgrowth on the nutrition of the host. In addition to producing metabolites or proteins that can interfere with the digestive enzymes in the lumen of the intestine, the parasite may compete with the host before the absorption, assimilation, and utilization of nutrients from the lumen. The competition of the fish tapeworm *Diphyllobothrium latum* for vitamin B_{12} [13] is the best demonstration. Clearly, such competition is more significant for micronutrients, which are present in the diet and in the lumen in microgram amounts, than for macronutrients, of which the small uptake by the parasite might make only a miniscule difference in the overall distribution of the nutrient between host and parasite. When the content of the parasite and its products are measured in the stool as an index of the utilization of nutrients, the percentage of total utilization of protein is calculated to be small [14], except in the case of heavy loads of *Ascaris* [15]. The potential for competition for micronutrients, including trace metals, beyond the well-documented loss of iron due to bleeding from hookworms, deserves further study.

An interesting association has been made between giardiasis and other intestinal parasitic infections with intestinal bacterial overgrowth [16]. When bacterial overgrowth is severe, it can produce significant disruption of both digestion

and absorption of fat as a result of effects on luminal bile salts and of competition for micronutrients such as vitamin B_{12} [17, 18]. The unsettled question here is whether the bacterial and parasitic infections are related causally. Few studies have been done in which the two kinds of infection have been controlled independently. Certainly some of the intraluminal effects that have been attributed to intestinal parasites and even some of the therapeutic effects of metronidazole (which is also potent against anaerobes) in giardiasis may well be due to effects on intestinal bacterial overgrowth in the same populations [19].

Morphology and Function of the Epithelium

The direct toxic effects of intestinal parasites on the gastrointestinal epithelium are unclear because, once again, these effects can be attributed to the parasites, to associated bacterial overgrowth, or to associated malnutrition. The degenerative and inflammatory morphologic changes in the intestinal or gastric mucosa that have been observed in the presence of intestinal parasites may be related to other factors, bacterial or nutritional, or to endemic tropical enteropathy in the underlying population, rather than to the parasites themselves. Note that most of the studies demonstrating diffuse morphologic changes in the intestine at biopsy have not used adequate controls for the underlying tropical enteropathy in these populations; good morphologic studies before and after deworming are very difficult and rare.

In certain cases, however, the direct effects of the parasites on the mucosa are well established and well studied. Examples include *Giardia lamblia*, which appears to attach itself to the intestinal mucosa and to produce local damage [20], and severe infection with *Strongyloides*. Other intestinal parasites probably produce some damage to the intestine both by local irritation [21] and, perhaps more importantly, by the production of toxic metabolites.

Functionally, toxic effects on the intestinal epithelium are reflected not only in absorptive but also in digestive abnormalities. The brush border of the intestinal mucosa, which faces the lumen, is responsible for critical terminal events in digestion, including the digestion of disaccharides and oligosaccharides, as well as the digestion of peptides, which are the products of pancreatic protease action. Thus, damage to the intestinal brush border surface results in inability to digest lactose, sucrose, to some extent maltose derived from starch, and the peptide products of protein digestion, in addition to the inability to absorb amino acids, sugars, vitamins, and minerals [22]. Damage to the distal small intestine uniquely impairs the intestinal absorption of vitamin B_{12} and the recirculation of bile salts. Evidence is increasing that certain minerals may be absorbed throughout the small intestine, in which case lesions confined to the distal intestine may be less important in the overall mineral balance. Extensive damage to the enterocyte impairs its ability to take up, store, transport, and process nutrients for release into the circulation.

One other feature of the direct toxicity of parasites to the intestinal epithelium is the loss of the mucosal integrity, with the subsequent leakage of nutrients into the intestinal lumen and their later loss in the stools. This process is well documented in the case of hookworm, in which the loss of blood is the basis for iron deficiency and also the vehicle for the loss of other trace metals and micronutrients. Sufficient damage to the intestinal epithelium may cause substantial loss of plasma, which may produce a protein-losing enteropathy with an impact on protein balance more important than the impact on protein malabsorption [23, 24]. Intestinal parasites may, by direct irritation or by the production of toxins, produce intestinal secretion of water and electrolytes, which results in diarrhea and mineral deficits [3].

Entero-Systemic-Hepatic Circulation

Finally, the absorbed and processed nutrients must enter the mesenteric or lymphatic circulation for return to the systemic circulation. Intestinal lymphatics are the most important for the return of fats and some fat-soluble vitamins, but recent research indicates that the mesenteric venous circulation is an important route of return for certain lipid substances and certainly for water-soluble materials. Schistosomes that invade intestinal lymphatics and cause lymphatic obstruction [25] may impair the return of fats to the circulation and

thus cause malabsorption of fats. Malarial parasites may cause constriction of the mesenteric microcirculation, which in turn causes a backup of nutrients in the intestine, with coincident malabsorption [26].

Certain nutrients, including some of the vitamins, are involved in an enterohepatic circulation that depends on the integrity of the liver, the biliary tree, and the intestine for maintenance of the circulating body pool [27]. The effects of parasites on this enterohepatic circulation have not been studied but could also affect the nutritional status of the host.

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Adverse Metabolic Effects of Antiparasitic Drugs

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Several drugs are available for mass campaigns against enteric helminths. Mebendazole and pyrantel pamoate are quite effective against ascariasis and reasonably effective against the hookworms. Only mebendazole is effective against trichuriasis. Two drugs have recently been introduced for mass therapy of schistosomiasis, but they remain experimental, pending further evaluation. Other drugs are mentioned, and possible adverse metabolic effects are discussed. The fundamental question remaining is whether the eradication of certain parasites will improve the nutritional status of the infected populations.

This review presents an analysis of adverse effects on the metabolism of the host of otherwise beneficial therapy against parasites. Since the issue here concerns the prevention of malnutrition and not clinical medicine, I discuss only those drugs that are likely to be used in mass campaigns against parasites. I do not consider, therefore, the highly toxic drugs used in individualized therapy of certain parasitic infections. Neither do I deal with some of the older drugs that have been used in the recent past, because they have been supplanted by better ones.

Two exceptionally effective anthelminthics are mebendazole and pyrantel pamoate. Against *Enterobius vermicularis*, the ubiquitous pinworm or threadworm, either drug is effective; against *Trichuris trichuria*, only mebendazole is effective. Against roundworms and hookworms, both are effective, but the advantage of a single dose of pyrantel pamoate over two daily doses for three days of mebendazole is obvious.

Pyrantel pamoate [1] is a pyrimidine type of drug, available as a crystalline salt; it is virtually insoluble in water or alcohol and is poorly absorbed. At least 85% of the administered drug can be recovered in the stool; the remainder appears in the urine, either intact or partially metabolized. It has a nicotinic action in the helminths, depolarizing the myoneural junction and thus paralyzing the worms in a spastic state. Moreover it inhibits the cholinesterases. Piperazine, the drug once commonly used against *Ascaris lumbricoides* but now largely supplanted by the other drugs, acts by causing hyperpolarization of the myoneural junction, paralyzing the worms in a flaccid state. These two drugs are antagonistic and should never be used together.

In the conventionally prescribed doses, pyrantel pamoate is truly free of side effects for the host. When given experimentally to rabbits in excessive doses, it does to them what it does to the worms; i.e., it causes neuromuscular blockade. A similar effect could probably be induced in humans, but the necessary toxicity could be achieved only through parenteral administration; an oral toxic dose would be virtually unconsummable, and a smaller but still excessive dose would induce nausea and vomiting long before causing neuromuscular blockade.

Mebendazole [2], one of the benzimidazoles, also dissolves with difficulty and is poorly absorbed. Only 10% of the administered dose is recovered in the urine. Its mode of action is quite different from that of pyrantel pamoate: it irreversibly inhibits glucose uptake by the helminth without in any way inhibiting glucose uptake by the host, even if given in very large doses. Most important, it has shown no toxic effects even in malnourished and anemic children [3].

A drug to be used with caution is thiabendazole [4]. Although unlikely ever to be used in mass campaigns, thiabendazole may well be administered under supervision to some populations with strongyloidiasis because, although far from an ideal medication, it is the only drug available for this infection. The mode of action of thiabendazole is unknown. It is insoluble in water but

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easily dissolves in acids and alkali and, therefore, is readily absorbable. Only 10% of the ingested dose is excreted in the stool; the rest is excreted in the urine. Thiabendazole causes a number of troublesome side effects. Nausea and anorexia are frequent, although not longlasting because the therapy is brief. The drug also causes some parenchymal liver damage, as indicated by the rise in level of hepatic enzymes in the serum. It is probably contraindicated in patients with liver disease, but no guidelines exist. Two anecdotal reports have attempted to correlate use of thiabendazole with Guillan-Barré syndrome [5], keratoconjunctivitis sicca, and cholestatic jaundice [6].

Therapy of infections with most tapeworms can be effectively accomplished with niclosamide [7], which is appropriate for mass campaigns. Insoluble in water and unabsorbable, it acts by interference with glucose uptake by the worm, but has no adverse effects on the host.

Mass therapy against schistosomiasis in selected populations may soon be possible. Two drugs are now available and each is a good candidate for such therapy. Oxamniquine [8], an hydroxytetrahydroquinoline, cures schistosomiasis at rates approaching 90% when it is administered im. Oral therapy gives cure rates of 70%-90% in adults, but of only 30% in children. Larger doses in children achieve cure rates of 80%. This drug is toxic to the central nervous system and induces dizziness, drowsiness, and even hallucinations. Although these side effects are not frequent, their seriousness must be assessed before the drug can be accepted for general use.

Metrifonate [9], an organophosphate, is also quite effective against schistosomiasis, producing 50% cure rates and substantial reduction of egg output in 90% of the recipients [10]. It has a potential for toxicity because of its action against the cholinesterases, but its indirect effect is achieved through a product of metabolic transformation, dichlorovos. Like oxamniquine, it requires evaluation before it can be recommended for mass therapy.

There are currently no agents that could be used as prophylactics against amebiasis or giardiasis. Nor are there agents that could be useful in therapeutic campaigns. Nevertheless, *Giardia lamblia*, by causing malabsorption, can be responsible for malnutrition in individual patients, and supervised treatment of groups of people may be necessary. Either metronidazole or quinacrine can be used for this purpose, although because both drugs are associated with troublesome side effects, they are far from ideal. Moreover, metronidazole has the theoretical danger of oncogenicity because it has been shown to be mutagenic to bacteria [11] and oncogenic in rodents [12]. Still, each drug cures 80% of infected individuals.

Chloroquine, which can be used in mass campaigns against malaria, is relatively free of toxicity as long as it is used in the small doses appropriate for antimalarial prophylaxis. In an experimental study [13] in animals and in vitro, chloroquine was shown to inhibit gastric motility. There is no evidence that this phenomenon has a parallel in man. One recent report has indicated that chloroquine enhances the expression of Epstein-Barr virus [14].

Pyrimethamine and the related antagonists of folic acid used in therapy of malaria have the potential to induce megaloblastic anemia. However, when used in the prescribed doses, these drugs have not caused any clinical problems attributable to their effect on hematopoiesis.

Finally, we must briefly address the potential toxicity for man of those insecticides used for the eradication of vectors of diseases and, in topical administration, as therapy against ectoparasites. Chlorophenothane (DDT) has a half-life of several decades. When used in the environment, DDT permeates all mammalian tissues, becomes part of the food chain, and is excreted in human milk. Experimental administration of this chemical to animals has resulted in a myriad of toxic effects, ranging from liver damage through the development of ependymomas to disturbances in the estrous cycle and reduction in libido. In humans, too, it has in sporadic instances caused serious idiosyncratic reactions, such as polyarteritis nodosa and aplastic anemia. Yet there is no objective evidence that it has caused direct adverse effects in human populations [15]. The other insecticides are less problematic, although some, e.g., benzene hexachloride (Lindane®) may be toxic if they are absorbed through the skin.

Before closing, I must raise for our consideration certain recent activities, particularly in Southeast Asia, directed toward mass campaigns against helminthic parasites. These campaigns are

based on periodic mass administration of anthelminthics to large segments of the infected populations. Although the use of either pyrantel pamoate or mebendazole alone at intervals of four to six months has been reasonably effective [16], this form of therapy has not been wholly satisfactory against hookworm and *T. trichuria*. Consequently, recent trials have combined these two drugs [16]. For economic reasons, certain indigenous herbs can also be tested as possible anthelminthics. Although both types of programs may well turn out to be quite effective, we must be alert to the possibility that a combination of two drugs, each of which is considered safe when given alone, can be toxic, and that the use of any new drugs without proper facilities for the assessment of their toxicity is risky.

In summary, my message is rather optimistic. There are effective drugs against many parasites of humans and in most cases these drugs are relatively safe. Indeed, the risk : benefit ratio, for once, seems favorable to our cause! The fundamental question remaining is whether eradication of some of these parasites will improve the nutritional status of the infected populations.

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Schistosomiasis: Host-Pathogen Biology

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Schistosomes are helminths of the class Trematoda that alternate generations, with a sexual phase in definitive mammalian hosts and an asexual phase in intermediate snail hosts. In humans, these blood flukes reside in the mesenteric and vesical venules. They have a life span of many years and daily produce large numbers of eggs, which must traverse the gut and bladder tissues on their way to the lumens of the excretory organs. Many of the eggs remain in the host tissues, inducing immunologically mediated granulomatous inflammation and fibrosis. Heavy worm burdens may produce hepatosplenic disease in schistosomiasis mansoni and japonica and urinary tract disease in schistosomiasis haematobia. Since both the schistosomes and the eggs utilize host metabolites, and since the host responses to the parasite are affected by its nutritional status, malnutrition may strongly affect both the parasite and the complex host-parasite relationship.

Schistosomes are helminths. These organisms differ from all other infectious agents in that most of them do not multiply within the definitive host, a category that includes humans. The consequences of this situation are enormous. Helminths are distributed (in humans) in a highly clumped or over-dispersed manner; therefore, most infected individuals carry low worm burdens. Manifestations of disease cluster in the small proportion of those with heavy worm burdens. In this group genetic factors may also affect susceptibility to disease. Lack of multiplication in the definitive host also has profound consequences with respect to immunity, treatment, control, and the effects of nutritional deficiencies.

Schistosomes belong to the class Trematoda and are also known as flukes. There are lung flukes, liver flukes, intestinal flukes, and the group that comprises the schistosomes—blood flukes. In the name of each type of fluke the modifying term refers to the final habitat of the adult worm. All flukes have a unique life cycle involving alternation of generations, with a sexual phase occurring in the definitive host and an asexual phase in the intermediate host. In all cases, the intermediate host is a particular species of snail.

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Life Cycle

Schistosomes are known as blood flukes because the habitat of the adult worm within the definitive host is the blood vessels, usually the mesenteric and vesical venules. Within the blood vessels, the thread-like female schistosome lies within a cleft in the body of the male worm, remaining in a state of *copulo* for many years, during which it produces between 300 and 3,000 eggs daily. The embryo, protected by the egg shell, develops within six days into a ciliated organism called a miracidium and begins to secrete proteolytic enzymes, which are emitted via ultramicroscopic pores in the egg shell. These enzymes enable the eggs to pass out of the venule through the tissues and into the lumen of the intestine or urinary bladder, and thence into the outside environment. However, well over 50% of the eggs remain within the body of the definitive host. If the egg enters fresh water, it hatches and the miracidium emerges, swims about, and if possible, penetrates the soft tissues of a susceptible snail. Inside the snail, it develops locally into a mother sporocyst, which soon produces multiple daughter sporocysts. These organisms migrate from the area of penetration to the hepatopancreas, the digestive gland of the snail. After several weeks, cercariae begin to form. When these fork-tailed larval forms reach maturity, they issue from the snail either in small numbers or in thousands daily, depending on the species of schistosome. Immersion of definitive hosts in water enables the cercariae to penetrate

the intact skin, an action that they accomplish in a matter of minutes by means of both enzymes and vigorous movement. Immediately on entering the skin, these organisms undergo drastic anatomic, physiologic, and biochemical changes in order to become schistosomula. These young schistosomes remain in the skin for a few days and then migrate to the lungs via the bloodstream and lymphatic system. Almost all species then pass through the bloodstream or tissues to the liver, where they mature into adult worms, mate, and move to their particular final habitats in the mesenteric or vesical venules. This occurs four to 13 weeks (depending on the species) after the time of skin penetration. The adult schistosomes do not replicate within the definitive host, and their average lifespan seems to be between three and eight years.

Contrary to general belief, waters containing schistosome-infected snails are not continuously and highly infective. Even in heavily endemic areas, usually <1% of the snails are infected. Cercariae are emitted by snails infected with *Schistosoma mansoni* or *Schistosoma haematobium* for a relatively short period around noon and by those infected with *Schistosoma japonicum* in the evening [1]. Most cercariae survive under natural conditions for only a few hours. Even at peak periods, uptake of cercariae on filters reveals concentrations that are usually <1/10 liters [1]. Thus, the cercariae are present for only relatively short periods of time and are widely dispersed in large volumes of water or by currents of streams or rivers. Furthermore, there are usually marked seasonal variations in the numbers of snails in the various bodies of water. The prevalence and, particularly, the intensity of infection in the human population are clearly related to the time and degree of water contact. Children usually have the greatest amount of water contact and, consequently, have the greatest intensity of infection [1]. The intensity of infection declines in later life, except in those with occupational exposure such as fishing, because the mean life span of the schistosomes appears to be five years or less [1, 2]. There is no definitive evidence that immunity plays a significant role in controlling the prevalence or intensity of the three major schistosome species that infect humans [1].

Cercariae penetrate a wide variety of animal tissues, both living and dead [3]. Various proportions of cercariae of *S. mansoni* perish while penetrating the skin of different hosts; a significant number (10%) die even in excellent hosts, such as hamsters. Approximately 33% die in the skin of mice, which are also good hosts; 50% die in the skin of rats, which are poor hosts [4]. The yield of adult worms from a given number of cercariae is lower still, being approximately 50% in hamsters, 40% in mice, and 25% in rats. Rats, however, undergo a self-curing phenomenon that results in loss of most of their worms within six weeks [5]. Most primates studied, including chimpanzees, do not develop high worm yields from cercarial exposure. This finding may be true for humans as well.

In the process of skin penetration, during which the cercariae change into schistosomula, the organisms switch exceedingly rapidly from aerobic to anaerobic metabolism and from fresh-water to salt-water physiology, and their surface membranes undergo a drastic change. Within a few hours, the schistosomula acquire host antigens (red cell [6], immunoglobulin [7], and histocompatibility [8]) on their surfaces. These antigens, together with surface modification [9] and a high rate of turnover, protect the schistosomula from the immunologic mechanisms of the host, a phenomenon which has been called concomitant immunity [6]. After migration to the lungs and then to the liver, the adult male and female worms remain in the blood vessels of the intestinal and urinary excretory organs. They utilize enormous amounts of glucose in glycolysis (15%–26% of their dry weight per hour), and the end product produced in the greatest amounts is lactic acid [10]. The schistosomes ingest red blood cells and regurgitate (they have a blind gut) insoluble pigments, the products of a specific globinase [11]. Both uptake and output of amino acids by adult worms have been demonstrated in vitro [12].

Each pair of adult *S. mansoni* worms produces ~300 eggs daily and each pair of *S. japonicum* produces ~3,000. The eggs, which contain no embryos when laid, undergo both growth and development over a period of six days in the host tissues, and the egg shells have ultramicroscopic pores [13]. These findings suggest that the eggs may utilize host metabolites. Biochemical studies of schistosome eggs maintained in vitro have re-

vealed the uptake of tritiated thymidine and its utilization in DNA synthesis. RNA synthesis was shown with tritiated uridine. Large amounts of ^{14}C-labeled isoleucine and ^{14}C-labeled arginine were incorporated into the egg's protein. Little glycolytic activity was demonstrated after prolonged incubation with ^{14}C-labeled glucose. A high rate of catabolism of amino acids to CO_2 was observed, as was a very high rate of acetate metabolism. Degradation of radiolabeled glutamate after incubation with ^{14}C-labeled acetate revealed labeling consistent with metabolism by the Krebs cycle [14].

In addition to their involvement in the uptake of metabolities, the pores also play a role in secretion of enzymes by the eggs. This secretion and the peristaltic motion of the host organs enable the eggs to work their way out of the blood vessels, through the tissues, and into the lumens of the excretory organs. However, more than 50% of the eggs never leave the body; they remain trapped in the primary organ or break free into the bloodstream and pass to the liver (in the case of *S. mansoni* and *S. japonicum*) or to the lungs (in the case of *S. haematobium*) [15].

Pathogenesis

The egg secretions are antigenic and cause severe granulomatous inflammatory reactions that have been demonstrated to be cell-mediated in the cases of *S. mansoni* [16] and *S. haematobium* [17]. In both types of infection, living schistosome eggs have been isolated from the tissues of infected animals and injected intravenously into the lungs of mice [16, 17]. On secondary exposure following a primary intraperitoneal injection of eggs, accelerated, augmented granuloma formation occurs. This anamnestic reaction has been shown to be both species- and stage- (with respect to cercarial and worm antigens) specific and to be transferable from infected animals by means of lymph node or spleen cells but not by serum [16, 17]. With respect to the granuloma caused by *S. mansoni* eggs, marked suppression of the inflammatory reaction has been achieved with measures that inhibit cell-mediated immunologic reactions, such as neonatal thymectomy and injection of lymphocyte antiserum; no effect was seen with measures that suppress antibody-mediated responses [18]. The response to *S. japonicum* eggs appears to be different, however, and may be due largely to antibody-mediated mechanisms [19]. Lymphokines secreted by specifically sensitized lymphocytes in the presence of schistosome eggs or schistosome egg antigens have been demonstrated; these include macrophage migration inhibitory factor [20], eosinophil stimulation promoter [21], and a factor that stimulates fibroblasts [22]. The production of large amounts of collagen in infected liver tissues and isolated granulomas is demonstrated by the uptake of radiolabeled proline and its incorporation into collagen as radioactive hydroxyproline [23]. Thus, it has been shown that schistosomiasis is essentially an immunologic disease characterized by granuloma formation and fibrosis induced by the schistosome eggs [24].

The occurrence of disease following schistosomal infection is related to the number of schistosome eggs in the tissues and the degree of the host's inflammatory response to them [24]. In the latter case, suppression of granulomatous hypersensitivity prevents or ameliorates the disease [24]. The rate of egg production is related to the numbers of worm pairs in the animal, but the rapid destruction of eggs by the host occurs both in infected animals and in uninfected animals after the injection of eggs [25]. Studies in vitro [26] have shown that eosinophils play a major role in the destruction of eggs. Recently, studies in vivo have shown that administration of eosinophil antiserum reduces the rate of egg destruction and exacerbates disease [27].

Immunity

Acquired immunity has been demonstrated in experimental animals but is not complete, usually averaging about 50%. Studies of immunologic mechanisms in murine models first revealed passive transfer by antibody but not by cells [28]. Investigations in vitro then found that schistosomula were killed when both antibody and cells were added, and that the principal killer cell was the eosinophil [29]. This finding was confirmed in vivo by experiments showing that eosinophil antiserum abrogates immunity but that neutrophil, lymphocyte, and macrophage antisera do not [30]. Further studies show that complement is a factor in the antibody-mediated response, both in vitro

[31] and in vivo [32], and that macrophages may be responsible for a small degree of natural immunity (i.e., killing of schistosomula in previously uninfected hosts) [33].

Clinical Considerations

Another host-parasite factor worth mentioning in this context is the effect of schistosomiasis on intestinal absorption, especially when caused by *S. mansoni* and *S. japonicum*, which reside in the mesenteric venules. Studies of *S. mansoni* in mice revealed that the small intestines were heavily involved in the disease process; they weighed considerably more than the small intestines of normal animals and had large numbers of eggs throughout their length [34]. Granuloma formation and fibrosis were marked in the muscularis and serosa but were slight in the mucosa. The villi and mucosal epithelial cells appeared to be relatively unaffected by the disease process. When, in groups of infected and control mice, the entire small intestine was perfused with various concentrations of glucose, methionine, or sodium propionate, no difference was observed in absorption between infected and uninfected animals [34]. In infections due to *S. japonicum* the intestines are not widely involved; the worms tend to remain localized and produce large masses of eggs in particular areas [35], a situation that may cause intestinal obstruction.

Advanced chronic schistosomiasis mansoni and schistosomiasis japonica result in the hepatosplenic syndrome involving hepatomegaly, splenomegaly, and portal-systemic collateral circulation [36]. This syndrome is due to periportal fibrosis induced largely by the inflammatory and fibrotic response to schistosome eggs trapped in the presinusoidal portal venules. Hepatic blood flow remains within normal limits because of a compensatory increase in hepatic artery flow. Liver function also remains relatively normal because the parenchymal cells are not directly involved and sinusoidal perfusion is unimpaired. The major complication of this syndrome is hematemesis from esophageal varices; because liver function is good, hepatic coma is rare and death occurs primarily from exsanguination [36]. A syndrome of decompensated hepatosplenic disease is not uncommon and may be due to associated malnutrition or hepatitis.

Schistosomiasis haematobia, which involves the urinary tract, is associated with hematuria, problems stemming from lack of distensibility of the bladder due to calcified eggs and fibrosis, and hydronephrosis resulting from blockage of urine flow through the uretero-vesical junction or ureters [15].

Schistosomiasis can be treated with relative ease today since a number of good drugs, several of which are taken orally, have become available. The response to some of the drugs may differ markedly according to geographic location. For instance, a much higher dose of oxamniquine is required for treatment of *S. mansoni* infection in Africa than in South America or the Caribbean. Many factors, including genetics and nutrition, could be responsible for this difference.

The biology of schistosomiasis indicates that malnutrition of various types could affect the parasite, the host, and the relationship between them. The likelihood of any of these diet-induced changes is based on the biochemistry of the various parasite stages and of the host cells and membranes that interact with them.

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Schistosomiasis: Nutritional Implications

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Most studies on the interactions of nutrition and schistosomiasis have involved experimental animals. Generally, these studies show that schistosomiasis may be alleviated by severe malnutrition, especially calorie deprivation. However, nutritional modulation of schistosomiasis in experimental animals is observed only when severe deficiencies are induced during the acute disease. Except during overt famine, in humans such severe forms of malnutrition occur mainly in the young, who are not yet exposed to heavy burdens of schistosomal infection. Older individuals, who may be heavily infected, are usually not so severely malnourished. Therefore, the nutritional rehabilitation of severely malnourished children, which should improve immune function, is unlikely to exacerbate the immune-mediated pathogenesis of schistosomal disease. Nutritional interventions can be planned independently of the prevalence or intensity of schistosomiasis in the population. Heavy infection with *Schistosoma mansoni* can cause both direct nutritional losses and severe disease manifestations. These constitute two important reasons for the administration of mass chemotherapy to the heavily infected segment of a population. Both of these adverse effects can be corrected by a reduction in the intensity of infection; complete cure is not necessary.

Current efforts to combat malnutrition in developing countries by an increase in the amount of land used for food production have had an important impact on the spread of schistosomiasis in areas where the disease is endemic. New dams and irrigation projects have helped to increase opportunities for human infection [1]. In 1946, Stoll conservatively estimated that about 114 million persons were suffering from schistosomiasis: *Schistosoma japonicum* infected 46 million persons, *Schistosoma haematobium* infected 39 million persons, and *Schistosoma mansoni* infected 29 million persons [2]. Current conservative estimates of the number of persons infected with schistosomiasis worldwide indicate 200–300 million.

Although malnutrition reduces the general resistance of the host, particularly for bacterial infections [3], available evidence suggests that poorly nourished individuals are not necessarily more susceptible to helminthic infections such as schistosomiasis [4]. Furthermore, whereas infectious diseases exaggerate existing malnutrition in the host, chronic infections such as schistosomiasis relate less clearly to malnutrition.

In experimental infection with *S. mansoni*, evidence indicates that nutrition and infection interact synergistically or antagonistically, depending on the phase of the disease [5]. Direct extrapolation of these results to human schistosomiasis is difficult for several reasons. For example, the clinical symptoms and severity of schistosomiasis vary greatly from country to country and according to the intensity of infestation [6]. Hence, while symptoms and manifestations may be severe in hyperendemic areas and in heavily infected individuals, they may be fairly mild in places with lower endemicity or in individuals with light infection. This variation should affect the type and intensity of any associated nutritional consequence. Clinical variation is related to intensity of infection. In a longitudinal study of infected school children in hyperendemic areas of St. Lucia, children who had a regression of liver enlargement over four years of observation showed statistically higher mean egg outputs than those children who either had no liver enlargement at all or had transient enlargement only [7]. The development of hepatomegaly is slower in light than in heavy infections [8]. Variations in the type and severity of malnutrition itself may modify disease manifestations as

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well. Moreover, the stage of the disease at which the nutritional insult occurs must be considered. Since nutritional status can vary in seasonal fashion and in relation to other superimposed infections, the assessment of impact is exceedingly difficult. Finally, the additional factor of the coexistence of schistosomiasis and other parasitic infection in humans living in endemic areas can be important. For example hepatosplenomegaly is more severe when malaria and *S. mansoni* occur together than when either disease alone is present [9].

Schistosomiasis can be considered primarily an immunologic disease in response to the deposition of ova in tissues. As a tissue parasite, the worm relates to the nutritional status of the host more in terms of the function of immunologic processes than do intestinal parasites. That is, consideration of the nutritional implications of the disease essentially focuses on the impact of nutrition on the immune response of the host.

Three distinct clinical syndromes occur in schistosomiasis: swimmer's itch, which occurs in response to cercarial penetration of the skin; Katayama fever, which accompanies the onset of egg laying by the newly mature worms about 30–60 days after infection, especially in patients infected with *S. japonicum* or with a large number of *S. mansoni;* and hepatosplenic schistosomiasis (*S. mansoni* or *S. japonicum*) or fibrosis of the urinary bladder (*S. haematobium*), which may occur many years later. The first 10 weeks of infection is generally considered the acute stage of the disease, during which swimmer's itch and Katayama fever occur. Nonspecific symptomatology includes fatigue, abdominal pain, and diarrhea, but the relationship of these symptoms to the disease has not been supported by controlled epidemiologic studies in the field [1]. The symtoms do coincide with the onset of the formation of granulomas around eggs in the tissue of the host. The chronic phase of schistosomiasis covers the subsequent course of the disease during which fibrosis occurs around schistosome eggs and produces increasing portal fibrosis in infections with *S. mansoni* or *S. japonicum*. This phase is related clinically to the development of portal hypertension, hepatomegaly, splenomegaly, and esophageal varices [8].

Although they suspected that the nutritional status of the host might modulate the clinical manifestations of schistosomiasis, earlier workers concentrated on the demonstration of etiologic relationships between malnutrition and infection with *S. mansoni*, with little success. Laboratory studies on the effect of nutrition on the interaction of host and parasite in experimental schistosomiasis were devoted to the effect of malnutrition on the host or the parasite but not on the interaction between them. Moreover, few studies were performed during the chronic stages of the disease that predominates in the populations of endemic areas [5].

Studies with Animals

Experimental studies reported in the English language literature have dealt primarily with *S. mansoni*. It is a reasonable assumption that conclusions from those studies would apply to *S. japonicum*, which has similar though more intense disease manifestations in humans. *S. hematobium*, on the other hand, might present a somewhat different picture because of its less intense hepatic and gastrointestinal involvement.

Available evidence shows that host-parasite responses in schistosomiasis may be modified by the nutritional status of the host. While cercarial penetration and the number of worms that develop in the host do not seem to be affected by the nutritional status of the host [5–10], schistosome maturation and egg production may be retarded by severe malnutrition [5]. The mechanism by which such retardation occurs is poorly understood. However, both DeWitt [10] and De Meillon and Paterson [11] have suggested that malnutrition in the host causes direct damage to the reproductive systems of the worms. Retardation of somatic development is observed only if malnutrition occurs during the early stages of the disease. Malnutrition during the chronic stage does not seem to produce any reduction in worm size because the somatic development of the worms is already complete. Regardless of the stage of the disease, however, egg output decreases progressively as the severity of malnutrition increases [4, 5]. Knauft and Warren [5] showed that the egg load in the liver also decreases as dietary protein is further decreased from 8% to 4%; inhibition was greatest with a 50% calorie-deficient diet. Akpom and Warren demonstrated a similar effect at the

chronic stage of the disease by the use of the oogram technique [4].

Different types of nutritional deficiencies not only interrupt egg output, but also lead to the laying of defective or abnormal eggs. Akpom and Warren [4] found that a significant proportion of the eggs recovered from mice fed on 4% protein deficient and 50% calorie-deficient diets were not viable. The viability of newly produced eggs increased with the nutritional repletion of the host. Malnutrition of the host is, therefore, harmful to the parasite because it results in diminished egg production, the laying of defective eggs, and apparent residual damage to the reproductive capacity of the severely malnourished worm. These factors indicate that malnutrition is antagonistic to the parasite, for the development of hepatosplenic disease from infection with *S. mansoni* is a consequence of the granulomatous response of the host to schistosome eggs trapped in the liver. If fewer eggs are produced, disease is less likely to result.

For the host, the combination of malnutrition, especially severe protein malnutrition, and schistosomiasis exacerbates several parameters of acute or chronic schistosomiasis, including serum protein concentration and parenchymal cell function. While calorie deficiency at the acute stage of the disease is associated with considerable amelioration of hepatomegaly, splenomegaly, portal pressure, anemia, and changes in serum protein [5], these effects do not seem to occur at the chronic stage of schistosomiasis [4]. These findings indicate that malnutrition and schistosomiasis act synergistically to the detriment of the host.

Although it has negative effects on both the host and the parasite, malnutrition (especially calorie deficiency) apparently reduces the mortality from schistosomiasis. In the study by Akpom and Warren [4], infected mice fed a 50% calorie-deficient diet showed a significantly lower cumulative mortality (9%) than did the control group (29%) or those fed on a 4% protein diet (31%).

Studies by Knauft and Warren [5] on mice infected with *S. mansoni* and by Akpom and Warren [12] using the von Lichtenberg technique have demonstrated that various nutritional deficiencies inhibit the formation of granulomas around eggs in the tissue of the host. The degree of inhibition induced by protein deficiency varies according to its severity. Deficiencies of calories, thiamine, riboflavin, or vitamin C were all found to suppress primary granulomatous responses to the egg. Various forms of malnutrition in the mouse lung granuloma system were also found to delay the temporal course of granulomatous reaction. Depression of cell-mediated immune responses by the various types of malnutrition was considered the basis for these effects.

Two studies in poor models of *S. mansoni* in

Table 1. Parasite response to nutritional deficiencies during the acute stage of infection with *Schistosoma mansoni*.

Phase	Nutritional Deficiency: Type	Nutritional Deficiency: Effect	Experimental animal	Intensity of infection	Reference
Cercarial penetration	Severe protein, severe calorie	None	Mouse	Moderate	5
Worm burden developed	Severe protein, severe calorie	None	Mouse	Moderate	5
	Torula yeast diet	Increased	Mouse	Heavy	16
	Vitamin A	Increased	Rat	Heavy	13
Somatic development and maturation	Severe protein, severe calorie	Impaired	Mouse	Moderate	5
					11
	Torula yeast diet	Impaired	Mouse	Heavy	16
Egg Production					
Quantity	Severe protein, severe calorie	Depressed	Mouse	Moderate	5
					11
	Torula yeast diet			Heavy	16
Quality	Severe protein	Defective eggs	Mouse	Light	17
	Torula yeast diet		Mouse	Heavy	16
	Vitamin C		Guinea pig	Heavy	13
Viability	Vitamin C	Questionable viability	Guinea pig	Moderate	13

Table 2. Parasite response to nutritional deficiencies during the chronic stage of infection with *Schistosoma mansoni*.

	Nutritional Deficiency	
Phase	Type	Effect
Worm burden	Severe protein, severe calorie	None
Somatic development and maturation	Severe protein, severe calorie	No gross anatomic change
Egg Production Quantity	Severe protein, severe calorie	Depressed
Egg maturation		Impaired
Egg viability		Diminished

NOTE. The experimental animal was the mouse; the intensity of infection was light. All data adapted from [4].

rats and guinea pigs should be mentioned for completeness. Eosinophilic responses to adult worms in the livers of rats and the subsequent destruction of the worms was severely depressed by induced deficiency of vitamin A [13]. In scorbutic guinea pigs, adult worms were unaffected, but granular disintegration and erosion of the shells of the eggs occurred, with death of the embryos [14].

Concerned with the effects of schistosomiasis on nutritional status, DeWitt [15] studied the utilization of nutrients in mice infected for eight weeks with *S. mansoni*. Their efficiencies of utilization of dietary fat and proteins was lower than those of control mice. DeWitt suggested that this difference probably resulted from the diminished digestive functions of the liver and/or acute inflammation of the intestinal tract due to the deposition of large numbers of eggs.

Experimental animal studies indicate that the nutritional status of the host influences disease manifestations in schistosomiasis. Specific findings concerning the intensity, the stage of infection, and the type of deficiency are shown in tables 1–4. Various aspects of disease parameters may be antagonistic or synergestic, or show a balance between synergism and antagonism; however, since the major effect of moderate malnutrition is the inhibition of egg production, which is the main pathology-inducing factor, the net effect of malnutrition on schistosomiasis seems to be amelioration of the disease. Severe protein malnutrition may have debilitating effects that are independent of schistosomiasis, but because the overall mortality of malnourished hosts may be significantly lower than that of better nourished hosts, the postulate of a protective effect seems reasonable.

Studies with Humans

Although observations similar to those described for experimental animals have not been made with humans, there are two major important questions. What are the direct interactions between nutrition and schistosomiasis in humans? What are their implications for feeding programs in regions where the infection is endemic? Of the many epidemiologic studies on the nutritional status of schoolchildren or village populations infected with

Table 3. Effects of nutritional deficiencies in mice on clinical parameters of infection with *Schistosoma mansoni*.

		Effects		
Factor	Type of deficiency	Acute phase	Chronic phase	Reference
Anemia (hematocrit)	Severe protein	Exacerbated	Exacerbated	5
Low serum albumin	Severe calorie	Ameliorated	Exacerbated	
Damage to hepatocyte	Severe calorie	Ameliorated	Exacerbated	
Hepatomegaly	Severe calorie	Ameliorated	Exacerbated	4
Splenomegaly	Severe calorie	Ameliorated	Exacerbated	
Ascites	Severe protein		Exacerbated	4
Esophageal varices	Severe protein		No worse	4
	Severe calorie		No worse	
Portal hypertension	Severe protein	No worse	No worse	5
	Severe calorie	Ameliorated	Exacerbated	4
Cumulative mortality	Severe protein		No worse	4
	Severe calorie		Reduced	

Table 4. Nutritional deficiencies associated with inhibition of granuloma formation in infections with *Schistosoma mansoni*.

Type of deficiency	Experimental animal	Study technique	Reference
Caloric	Mouse	Infection	5
		von Lichtenberg	4
Protein	Mouse	Infection	5
		von Lichtenberg	4
Vitamin C	Guinea pig	von Lichtenberg	4
Riboflavin	Mouse	von Lichtenberg	4
Thiamine	Mouse	von Lichtenberg	4
Pyridoxine	Mouse	von Lichtenberg	4

schistosomiasis in developing countries that are reported in the English language literature, very few can be used or are designed to address these questions.

Information on the effect of nutrition on the manifestation of either the swimmer's itch or Katayama fever is scanty. The former is a sensitization phenomenon, and the latter is probably a form of hypersensitivity or an allergic phenomenon [8]. Thus, a reasonable speculation is that nutritional deficiencies severe enough to produce anergy in the host result in diminished manifestation of these syndromes.

DeWitt et al. [18] used prisoner volunteers to study the influence of nutrition on humans naturally infected with *S. mansoni*. One group of young men with poor dietary histories infected with *S. mansoni* for not less than two years' duration was provided with an enriched diet for a period of nine months. Similarly undernourished and infected male prisoners served as a control group. Treatment with stibophen (Fuadin®, Winthrop Stearns, New York, N.Y.) was given nine months after the patients started the enriched diet. An overall improvement in the nutritional status and general health of the experimental group of patients followed the provision of an enriched diet. The egg output of *S. mansoni* was monitored throughout the experimental period in both the experimental and the control groups, but the fluctuation in egg count obtained from the two groups was such that "interpretation was difficult or impossible." Response to treatment was equally good in both groups. Similarly, no difference due to the effect of diet was detected in serologic tests (fluorescent antibody, slide flocculation, complement-fixation, and circumoval precipitin tests).

Nutrition and Chemotherapy

Two studies examined the influence of nutrition on chemotherapy in schistosomiasis. Luttermoser and DeWitt [19] treated three groups of mice with stibophen. One group was fed a complete purified semisynthetic diet; another was fed a semisynthetic diet low in protein and lacking in choline, inositol, folic acid, and Vitamin B_{12} (fatty-liver-inducing diet); and the third group was fed a standard commercial diet (control diet). All groups were fed ad libitum for four weeks prior to infection and thereafter. Untreated controls were established for each group. Two weeks after the completion of treatment, necropsy was performed and the efficacy of treatment was determined by the average numbers of live and dead worms per mouse recovered by perfusion. Stibophen was much more effective against *S. mansoni* in mice fed the semisynthetic diet than in mice fed the normal control diet. No difference was observed between mice on the complete purified semisynthetic diet and mice on the fatty-liver-inducing diet, although the latter produced moderately severe fatty liver changes. Weight gain of the mice during the 13 weeks of experimentation was reported to be similar for all mice except for those on the fatty-liver-inducing diet; weight gain in this group was considerably less. Rates of survival were better in all treated groups, irrespective of diet, than in untreated mice. In summary, the effectiveness of stibophen was enhanced by the purified semisynthetic diet even when the diet was deficient in protein, choline, inositol, and Vitamin B_{12}.

Bell [20] reported the results of treatment of 36 Asiatic boys, aged 13–20 years, with im injection of sodium antimony dimercaptosuccinic acid (Astiban®). Eleven of the boys were vegetarians; 25 were not. A significantly higher proportion of nonvegetarians than of vegetarians was cured. The author, though unable to identify the factors responsible for these results, suggested that dietary habits do influence the outcome of treatment.

Effect of Nutritional Status on Severity of Disease

Little is really known about the nutritional implications of schistosomiasis in humans, or about the relevance of nutritional modulation of experimental disease for the human situation. If the central policy question is the implication of mass feeding

Table 5. Some reported nutritional implications of schistosomiasis in human clinical studies.

Implication	Intensity of infection	Reference
Daily blood loss from gastrointestinal tract or bladder (*Schistosoma mansoni*, 13 ml; *Schistosoma haematobium*, 23 ml)	Heavy (colonic polyposis)	21*
Daily iron loss (*S. mansoni*, 4 mg; *S. haematobium*, 7 mg)	Heavy (colonic polyposis)	21*
Daily albumin loss (*S. mansoni*, 2.2 g)	Heavy (colonic polyposis)	21*
Loss of trace elements or vitamins, especially albumin-bound ones, e.g., zinc and vitamin A	Heavy (colonic polyposis)	21*
Low D-xylose excretion	Heavy (colonic polyposis)	21*
Elevated fecal fat	Heavy	22*
Glucose intolerance	Heavy	23
Subnormal levels of serum carnitine	Heavy	24
No effect on treatment	Moderate	18
No effect on exercise tolerance	Moderate	25
Predisposal to later complication	Moderate	7

* Information is available in many other sources as well as in the reference cited.

programs on morbidity from schistosomiasis, available information suggests that clinically meaningful effects occur mainly in the treatment of nutritional deficiency severe enough to induce immunosuppression. On a large scale, such a situation exists only during states of famine in human populations, for which there are more pressing reasons for mass feeding than the effects on schistosomiasis. Under conditions of malnutrition commonly encountered in the adult populations of developing countries, DeWitt et al. [18] were unable to demonstrate more severe manifestations of the disease. Admittedly, malnutrition is more severe in children than in adults in such countries. However, children are usually not yet heavily infected, and the level of malnutrition at which the modulating effect begins is not yet clear. On the basis of what is known about the development of relative immunity in infected, moderately well-nourished inhabitants of endemic areas, nutritional rehabilitation by mass feeding programs is unlikely to aggravate the disease in human populations.

Effect of the Severity of Disease on Nutritional Status

Table 5 shows some reported associations of schistosomiasis with clinical nutritional status in humans. The single consistent fact that stands out from the literature is that abnormal findings generally occur in subjects with heavy infection. For example, in a subgroup of the population in Egypt where colonic polyposis from heavy parasitic load occurs in farmers in the Nile Valley, structural damage of the gastrointestinal mucosa leads to loss and malabsorption of nutrients [21]. Chemotherapy targeted at disease suppression (defined in terms of reduction of parasite load) should reduce the nutritional effects and morbidity of schistosomiasis in heavily infected individuals living in endemic areas. Such patients should, therefore, receive periodic drug therapy in combination with ongoing nutritional rehabilitation.

Veterinary Implications

A complete consideration of the nutritional implications of schistosomiasis must include the indirect effect of veterinary infection on a population's food supply from animals. Veterinary infections involve species of schistosomes that do not infect humans. Because weight gain of chronically infected animals is usually less than that of uninfected animals, there is both economic loss and decrease in the total yield of agricultural products such as meat and dairy products. However, just how much food wastage results from these animal infections is unknown.

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Discussion: Schistosomiasis and Malnutrition

Schistosomiasis is a disease prevalent in low socioeconomic levels of populations. In Brazil it is common for patients with schistosomiasis to have concomitant hookworm infection, ascariasis, giardiasis, and/or amebiasis. Therapy of these associated parasitic infections may improve gastrointestinal symptoms experienced by such patients [1]. In the case of infection with *Schistosoma mansoni*, particularly in patients with the hepatosplenic form of the disease, an association with prolonged bacteremia due to *Salmonella* is not rare [2]. Such patients are usually more wasted, more anemic, and have lower serum albumin levels, often with accompanying edema and ascites, than patients without bacteremia. In addition, renal involvement with proteinuria sometimes occurs. The combination of viral hepatitis and schistosomiasis may be an important factor in deterioration of liver function. Several investigators have stressed the high frequency with which hepatitis B antigens and antibodies are found in the blood of patients with the hepatosplenic forms of infections with *S. mansoni* [3]. Neither the importance of persistent hepatitis antigenemia nor the role of associated hepatitis in exacerbation of malnutrition in such patients is yet defined. Alcoholism may also be a contributing factor in aggravating malnutrition and the severity of liver involvement in humans infected with *Schistosoma*. Finally, patients with portal hypertension who undergo portacaval shunts may experience a deterioration of their clinical status; weight loss, signs of wasting, and clinical manifestations of liver deterioration are noted [1].

Malnutrition is most marked in infants and young children in areas where schistosomiasis is endemic; however, the clinical manifestations of the infection are generally mild or inapparent in this age group. Malnutrition is usually a chronic process, fluctuating in intensity and involving multiple nutrients. Schistosomiasis itself may vary tremendously in intensity and duration. Therefore, it is not easy to assess malnutrition, the severity of the infection, or the interaction of the two. The difficulties in clinical assessment needed for interpretation of interactions of the factors and variables described are compounded by the lack of good medical facilities in areas where schistosomiasis and malnutrition commonly occur.

Some of these relationships have been explored in the experimental studies reviewed in the preceding papers. However, it must be recognized that the situations created experimentally are artificial and the direct extrapolation of such data to human disease is questionable. A few additional studies should be cited. Bhattacharyya [4] fed a 4% protein diet to mice and rats infected with *S. mansoni* and found evidence of perilobular cirrhosis in these animals. De Meillon and Paterson [5] studied mice fed a modestly restricted (8%–12%) protein diet. Development of schistosomes was impaired and oviposition occurred less frequently. Maldonado [6] used a diet with low-quality protein (deficient in methionine and tryptophan) and found an increased mortality due to *S. mansoni* infection. Coutinho-Abath [7] observed a delay and a decrease in the inflammatory reaction at the penetration site of cercariae in mice fed a low-protein diet; he also noted an impairment of hepatic regeneration and a decrease in the inflammatory response in the livers of infected mice [8]. The influence of "regional diets" (diets prepared with the food consumed by humans in a region endemic for *S. mansoni*) were compared with control diets in the experimental model [8]. Animals on regional diets developed signs of malnutrition and an increase in hepatic lesions that were unrelated to the infection. However, there were also increases in portal fibrosis and inflammatory changes in the livers of malnourished and infected mice as compared with infected mice on a normal-protein diet.

There have been very few relevant clinical studies that explore the interaction between infection and nutritional state. Coutinho [8] studied patients from two endemic areas in Pernambuco, Brazil. Clinical signs of malnutrition and subnormal weight for height were more common in patients infected with *S. mansoni* than in uninfected persons. Symptoms attributable to this infection were exacerbated in malnourished patients. However, there was no correlation between low serum albumin levels and infection, while the presence of anemia correlated with malnutrition but not with *S. mansoni* infection.

Thus, while severe malnutrition may alter some host resistance factors, the parasite may also be affected; atrophy, reduction in oviposition, and production of altered eggs may result. The end result is probably biologic neutrality. Observation of a few cases of severe schistosomiasis in the same endemic area, or even within the same family, among many clinically mild cases, does not favor a role for nutritional factors in the natural course of the disease. Even in patients dying from severe schistosomiasis, liver changes attributable to malnutrition (e.g., fatty liver) are not frequent. Concurrent malnutrition, however, may exacerbate the development of clinical manifestations (such as weight loss, weakness, anemia, hypoalbuminemia, and edema), in patients with *S. mansoni* infection. The associated pathology commonly found in patients with concomitant malnutrition and schistosomiasis makes it impossible to define the true interaction of these elements in humans. Animal models have been used for such studies, but extrapolation of such data to humans may not be valid. There is, therefore, a need for long-term prospective and controlled field studies.

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Malaria: Host-Pathogen Biology

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The development of resistance to insecticides by anopheline mosquito vectors of malaria and of resistance to drugs by *Plasmodium falciparum* pose new challenges for malaria control programs. The establishment of methods for the continuous cultivation in vitro of plasmodia provided an important new tool for research into the cellular biology and metabolism of these parasites. The molecular basis of the parasite's attachment to and entry into erythrocytes in the host is being elucidated. The impact of the intracellular parasite on erythrocyte metabolism is being explored, and the recognition of the role of plasmodia as an oxidant stress suggested a molecular basis for certain forms of genetic resistance to malaria. In addition, the consequences of parasitization are being studied with regard to alterations in erythrocyte antigenicity, rheologic properties, and the transport of nutrients and antimalarial drugs. The host's immune response to malaria is being assessed with regard to both protective and immunosuppressive effects. The rapid accumulation of new knowledge of host-parasite biology could provide the basis for the design of novel pharmacologic and immunologic methods for the control of malaria.

Malaria continues to be a major cause of morbidity and mortality in many developing nations. The World Health Organization (WHO) estimates the incidence of malaria at ~100 million cases per year with nearly one million deaths, mostly of children under the age of 14 [1]. Sadly, the situation in a number of countries is deteriorating as the prevalence of malaria increases.

When vector control and chemoprophylactic drugs were applied in the malarial eradication program initiated by WHO, optimism was great. WHO officially declared the program a failure in the mid 1970s, however, because the problem was much more complex than was originally envisioned. Political unrest and poor local administration, for example, were frequent complications. Two biological factors in particular contributed to the difficulties: the widespread development of resistance to DDT by the anopheline mosquito vectors, and increasing awareness of strains of *Plasmodium falciparum* resistant to the 4-aminoquinolines such as chloroquine, which are the mainstay of chemoprophylaxis. The alternative residual insecticides available are all petroleum products, and economic developments in the petrochemical industry have placed huge financial burdens on the limited budgets of developing nations. Moreover, it is increasingly apparent that resistance to insecticides in mosquitoes as well as resistance to drugs in *P. falciparum* may involve a continuous process of selection. Thus, the replacement of one agent with another may not, in the long run, prove to be the ideal approach to disease control. Novel approaches are needed, and considerable efforts are now being directed toward the development of a vaccine for malaria [2].

In this review I will focus attention on the more recent discoveries relevant to the molecular biology of malaria. Several of these studies were facilitated by techniques developed by William Trager and James Jensen of the Rockefeller University [3] for the continuous cultivation in vitro of *P. falciparum*. For a more detailed description of the biochemistry of plasmodia, the reader is referred to a recent review by Sherman [4]. The details of membrane pathobiology in malaria were also summarized recently [5]. Several aspects of the biology of parasites and immune response to malaria are reviewed elsewhere [6–9].

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Life Cycle of *Plasmodium* Species

Infection is initiated when sporozoites that have developed in the mosquito are injected into the host during a blood meal. Sporozoites rapidly cir-

culate to the liver and develop within hepatocytes as exoerythrocytic forms. After a period of about one week, merozoites are released from the liver into the circulation to invade erythrocytes. In the erythrocytes, the parasites grow and replicate in a process referred to as schizogony; within 48–72 hr (depending on the species of *Plasmodium*) the infected erythrocytes rupture, liberating six to 24 merozoites, each capable of invading other erythrocytes. The life cycle is completed when a small percentage of intraerythrocytic parasites develop into the sexual stages known as gametocytes and are taken up by susceptible feeding anopheline mosquitoes. In the mosquito's gut, infected red cells lyse, releasing male and female gametes that unite to form the zygote, which subsequently develops as an oocyst in the gut wall. Sporozoites released from the mature oocyst migrate to the salivary glands of the mosquito, whence they are injected into the host during a blood meal.

Disease results solely from the asexual erythrocytic parasites; neither sporozoites, hepatic exoerythrocytic forms, nor gametocytes cause illness. Although a large variety of nonspecific symptoms may accompany malaria, the hallmark of the disease is debilitating fever that may be very high. There is a direct relationship between the density of parasites and morbidity and mortality [10]. Thus, it is not surprising that *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*, species restricted to development in a subpopulation of erythrocytes of different ages, generally cause nonlethal disease, whereas *P. falciparum*, which can grow in erythrocytes of all ages, initiates pathologic processes that may be lethal.

Invasion of the Erythrocyte by the Merozoite

The merozoite is an obligate intracellular form of the parasite that can survive in an extracellular milieu for only short periods of time. Since extracellular cultivation of the parasite has been achieved with very limited success [11], little is known of its metabolism, and indeed characterization of the merozoite membrane is just beginning. The organism is surrounded by an electron-dense surface coat [12] that extends ~20 nm from the merozoite membrane and most likely is composed of protein or glycoprotein [13]. This surface coat is antigenic, and antibodies that react with the coat can agglutinate merozoites [13] and possibly interfere with the process of the invasion of erythrocytes [14]. Some researchers speculate that merozoites undergo antigenic variation in a manner analogous to that described for *Trypanosoma* and, specifically, that alterations in the antigenic composition of the surface coat might account for this variation. Electron micrographic studies of the merozoite revealed specialized organelles that may be important in the process of invasion. At one pole of the merozoite (apical region) is a pair of flask-shaped structures called rhoptries, flanked by smaller micronemes.

The interaction of merozoite and host cell is highly specific. Merozoites attach to and invade erythrocytes selectively. Specificity also restricts the interactions of plasmodial species to erythrocytes of susceptible species of hosts [15, 16]. Some species of plasmodia (e.g., *Plasmodium berghei* in the rat and *P. vivax* in man) invade only the young erythrocytes of the susceptible host. In addition, within a species, genetic host determinants may dictate the susceptibility of the erythrocyte to invasion. Thus, for example, blacks are generally resistant to malaria caused by *P. vivax*. These considerations suggest that the initial interactions between parasite and host cell entail recognition of specific surface receptors.

Interactions between merozoites and erythrocytes were carefully studied by use of real-time Nomarski interference microscopy [17]. Merozoites attach to susceptible erythrocytes via their apical end and induce marked deformations in the erythrocyte membrane; waves of deformations spread out from the initial site of attachment. Thereafter, the merozoite enters the erythrocyte by a process resembling endocytosis and comes to reside in a parasitophorous vacuole created by the invaginated erythrocyte membrane.

Miller et al. observed that merozoites of the simian malarial parasite *Plasmodium knowlesi* (which can also infect man) attach in vitro only to erythrocytes of simian or human origin [16]. Human erythrocytes pretreated with chymotrypsin or pronase, but not with neuraminidase or trypsin, lost their susceptibility to infection by *P. knowlesi* [16] and indeed failed to permit the initial attachment phase. This result suggested the presence of a chymotrypsin-sensitive receptor, possibly a glycoprotein, on the surface of the erythrocyte.

Since blood group substances are the best-defined surface components of erythrocytes, these

substances were suspected to be receptors for the merozoite. In screening a large number of erythrocytes of different blood groups, Miller et al. observed that erythrocytes lacking the Duffy blood group determinants (i.e. FyFy) were not susceptible in vitro to invasion by *P. knowlesi*. Furthermore, treatment of Duffy-positive erythrocytes (Fy^a Fy^b) with chymotrypsin removed these determinants (but not Fy^3) and with them the susceptibility to invasion. In addition, anti-Fy^a antisera blocked invasion [18]. However, trypsin- or neuraminidase-treated Duffy-negative erythrocytes were invaded by *P. knowlesi* even though they still lacked the Duffy determinants [19]. Taken together, these observations suggest that the Duffy blood group system is not the receptor for *P. knowlesi*, but that a still undefined Duffy-associated determinant may act in triggering invasion. The relevance of these findings to human malaria derives from observations that blacks shown to be resistant to *P. vivax* were all Duffy negative [20]. Since the majority of African blacks are Duffy negative, the factor that confers natural resistance to *P. vivax* in this population is probably related to the Duffy blood group system. The finding that erythrocytes from rare nonblack individuals who are Duffy negative (presumably because of spontaneous mutation) resist invasion by *P. knowlesi* suggests that the relationship of invasion to the Duffy system is not one of genetic linkage.

The concept of the specificity of the erythrocyte invasion is corroborated by observations that Duffy-negative erythrocytes, though resistant to invasion by *P. knowlesi*, are nonetheless susceptible to invasion by *P. falciparum*. Duffy-positive cells treated with chymotrypsin escaped invasion by *P. knowlesi*, whereas those treated with trypsin were infected. Conversely, Duffy-positive cells treated with chymotrypsin suffered invasion by *P. falciparum*, whereas those treated with trypsin did not [21]. These in vitro observations parallel the clinical recognition that blacks resistant to *P. vivax* are nonetheless fully susceptible to *P. falciparum*.

The process of invasion itself is complex, rapid (complete in 20 sec in vitro), and, in view of the nonphagocytic nature of the erythrocyte, must represent a relatively unique form of entry. Aikawa et al. [22] provided electron micrographic evidence indicating that, upon contact between the apical end of the merozoite and the erythrocyte surface, the erythrocyte membrane becomes thickened, forming a circumferential site of attachment, and the membrane invaginates. As the invagination deepens, the attachment site is no longer at the apical end, but moves along the circumference of the merozoite so that, as the parasite enters, the site of attachment remains at the entry point of the invagination. Finally, the junction fuses at the posterior end of the merozoite, and the outer erythrocyte membrane reseals. A parasitophorous vacuole created by the internalization of host membrane envelops the merozoite. The mechanism by which the junction "slides" over the merozoite is presently unclear, and whether its energy requirements are derived solely from the parasite or also from the host is unknown. It has been postulated that the histidine-rich protein that may be contained in the rhoptries might empty through a common duct during the invagination process and might somehow alter the erythrocyte membrane to permit the deformations involved in the process of invasion. One consequence of invasion is that the merozoite surface coat is excluded from the developing parasitophorous vacuole and is shed.

Life Within the Erythrocyte

Once inside the parasitophorous vacuole, the merozoite loses its rhoptries, micronemes, and pellicular membrane [23] and is transformed into an ameboid trophozoite. The plasma membrane comprising the parasitophorous vacuole, which derives from the erythrocyte plasma membrane, also undergoes alterations. As revealed by freeze-fracture studies, intramembranous particles of the parasitophorous membrane are reduced [24], and apparently the enzyme constituents of the membrane are rearranged. Membrane ATPase (adenosine triphosphatase) is normally located on the inside and NADH (nicotinamide adenine dinucleotide, reduced form) oxidase on the outside of the erythrocyte membrane. Because the parasitophorous vacuole forms by invagination of the erythrocyte membrane, one would expect an opposite orientation of these enzymes in the vacuolar membrane: ATPase oriented outward and NADH oxidase oriented inward. Yet Langreth [25] found, by histochemical techniques, that the distribution of these enzymes in the vacuolar membrane was

the same as in the erythrocyte membrane: ATPase oriented inward and NADH oxidase oriented outward. While neither the mechanism for nor the physiologic significance of this finding is known, it does suggest a potential major effect of the parasite on the reorganization of the parasitophorous vacuolar membrane.

The metabolic activity of the parasite within the erythrocyte has been studied largely in short-term culture, and results were summarized recently by Sherman [4]. As Sherman points out, interpretation of results in many of these studies is difficult because of inadequate controls and problems involving the distinction between the metabolism of the host cell and that of the parasite. Several attempts have been made to isolate the parasite from the erythrocyte by a variety of techniques, but it is unknown whether these methods adequately preserve the metabolic integrity of the parasite. Extracellular cultivation in vitro of *Plasmodium lophurae* (a *Plasmodium* that infects ducks) was achieved [11], but extracts of duck erythrocytes are required in the medium for the development of the parasite from trophozoite to schizont stage. Thus, metabolic studies utilizing this system are complicated by the lack of adequate definition of the substrates present in culture. Moreover, because the extracellular parasites appear to be "leaky," an accurate assessment of substrate pool and transport is impossible.

One aspect of the biochemistry of parasites that is very important for chemotherapy and potentially important for host nutrition is that of folate metabolism. Plasmodia synthesize folate cofactors de novo and cannot utilize exogenous folate in the same way that mammalian cells can. Sulfonamides, by virtue of their structural similarity to *p*-aminobenzoic acid, block the enzyme (dihydropteroate synthetase) involved in the synthesis of dihydropteroate, an intermediate in the synthesis of dihydrofolate. Plasmodial dihydrofolate reductase, a key enzyme in the formation of tetrahydrofolate, was found to have a binding affinity for pyrimethamine two to three orders of magnitude greater than that of the host cell. Thus, pyrimethamine and other antifolate agents bind avidly to the parasite enzyme and act as excellent antimalarial agents. The synergistic effects of the sulfonamides and the inhibitors of dihydrofolate reductase provide an important approach to chemotherapy for malaria. From the nutritional viewpoint, it is interesting that animals placed on milk diets deficient in folate substrates experienced less severe malarial infection than those receiving diets containing *p*-aminobenzoic acid [26, 27].

The recent establishment of a technique for continuous cultivation of certain species of *Plasmodium* clearly improved the prospects for gaining insights into the dynamics of the intracellular host-parasite relationship. One aspect of this relationship studied with the new methods of culture is the role of oxygen in parasite growth, and particularly the relationship of erythrocyte hemoglobin composition and oxygen tension to parasite development. Interest in this area was engendered in part by the long-standing clinical observations that patients with sickle hemoglobin are protected from malaria caused by *P. falciparum*.

Allison [28] demonstrated that people with sickle hemoglobin are protected from infection with *P. falciparum* (i.e., they have lower levels of parasitemia than people without the sickle trait), but not from infection with *P. malariae*. He proposed that, according to the genetic principle of balanced polymorphism, such protection from lethal infection accounts for the high incidence of the sickle trait in areas where *P. falciparum* is endemic. In an effort to provide a molecular explanation for the earlier clinical and epidemiologic observations, Friedman [29], Pasvol et al. [30], Roth et al. [31], and Friedman [32] subsequently examined in vitro the infection with *P. falciparum* of erythrocytes containing sickle hemoglobin. They determined that erythrocytes containing AA, SS or SA hemoglobin were invaded at similar rates under aerobic conditions, but invasion was slightly reduced in SA cells and dramatically reduced in SS cells under conditions of low oxygen tension (pO_2 = 35 mm Hg). Reduction of invasion did not depend on sickling of the erythrocytes. In addition, intraerythrocytic development was retarded in both SA- and SS-containing cells under conditions of low oxygen tension. Infected erythrocytes containing SA hemoglobin sickled more readily at low oxygen tensions than did uninfected erythrocytes. Loss of intracellular potassium from infected sickled cells may have resulted in death of the parasite. Since erythrocytes containing *P. falciparum* are sequestered in venous beds of certain organs during late stages of schizogony, one would expect that conditions of low oxygen ten-

sion analogous to those studied in vitro might prevail in vivo. Controversy exists, however, as to whether the protection afforded by sickle hemoglobin results primarily from the enhanced death rate of mature parasites, or from inhibition of invasion, or of intraerythrocytic development of young parasites.

Epidemiologic evidence suggests that other erythrocyte variants might also protect against fatal infection with *P. falciparum*. The gene frequencies of glucose-6-phosphate dehydrogenase deficiency (*G6PD*$^-$) and thalassemia (*thal*) tend to be most common in areas originally endemic for *P. falciparum* malaria [33]. This observation suggests that these traits might protect against lethal malaria and therefore impart a selective advantage. The evidence for a protective role of *G6PD*$^-$ and *thal* is less compelling than the data presented for sickle hemoglobin. This topic was recently reviewed [34]. Certain studies suggest that individuals with *G6PD*$^-$ are indeed more resistant to malaria. Other studies, however, failed to establish differences in the severity of disease (clinical complications and magnitude of parasitemia) between normal and *G6PD*$^-$ individuals [35]. Bienzle et al. [36] observed lower levels of parasitemia in heterozygous females (Gd^{A-}/Gd^{B} genotypes) than in nondeficient or homozygous females; they concluded that the high frequency of the *G6PD*$^-$ gene was maintained mainly by the selective advantage against malaria imparted to heterozygous females. An earlier study by Luzzatto et al. [37] of heterozygous females infected with *P. falciparum* demonstrated a greater frequency of parasitization of erythrocytes with normal levels of glucose-6-phosphate dehydrogenase (*G6PD*) than of deficient erythrocytes. However, the subsequent discovery that *P. falciparum* preferentially invades young erythrocytes leaves the interpretation of these observations open to question. In type A *G6PD* deficiency (as occurs in Africa), young erythrocytes have normal levels of the enzyme, which decrease as the erythrocytes age. Thus, the findings of Luzzatto et al. may have been simply a result of preferential invasion of young erythrocytes by *P. falciparum;* if so, their observations provide no direct insight into the cellular aspects of the hypothesis that *G6PD*$^-$ genes protect against malaria.

The growth of *P. falciparum* in *G6PD*$^-$ and *thal* erythrocytes was recently investigated by means of in vitro techniques. *G6PD*$^-$ erythrocytes, as well as *α-thal* and *β-thal* cells, failed to support replication of the parasite in vitro under conditions of oxidant stress. Although high O_2 tension (30%) inhibited multiplication of the parasite even in normal erythrocytes (60% reduction), this inhibition was more pronounced in *G6PD*$^-$ (85%), *α-thal* (82%), and *β-thal* (81%) cells [38]. The variant red cells were also rendered more susceptible to damage by the addition of other exogenous oxidants (such as menadione and riboflavin), which retarded parasite multiplication more in the variant cells than in infected normal erythrocytes. The antioxidant dithiothreitol, which reduces glutathione, prevented the adverse effects of riboflavin on replication of the parasite in *G6PD*$^-$ cells, but not in *β-thal* cells. On the other hand, vitamin E, which prevents free-radical-mediated lipid peroxidation, prevented oxidant damage to *β-thal* cells but not to *G6PD*$^-$ cells.

The role of oxidant stress in the development of the parasite has also been assessed for *P. berghei*, which produces malaria in rodents. Etkin and Eaton [39] have presented evidence suggesting that the parasite itself generates oxidants during intracellular maturation and also incapacitates the ability of the infected erythrocyte to repair or prevent damage due to exogenous oxidants such as ascorbate. Etkin and Eaton postulate that this incapacitation results from parasite-mediated oxidation of erythrocyte NADH and/or NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) with the consequences of increased intracellular methemoglobin, decreased pentose shunt activity that hinders regeneration of reduced glutathione from oxidized glutathione, and excess production of H_2O_2. It follows from this notion that *G6PD*$^-$ cells would be more susceptible to the oxidant stress of plasmodial infection because their ability to regenerate NAD(P)H and glutathione is impaired as a consequence of the enzymatic lesion. The inherent inability of these cells to repair oxidant-induced membrane damage might theoretically result in the death of the parasite and the resultant protection of the host from lethal infection with *P. falciparum*. However, the conflicting clinical data on the protective role of *G6PD*$^-$ may necessitate the proposal of a third factor in the hypothesis concerning *G6PD*$^-$ and malaria.

As suggested by Friedman [38], dietary oxidants

or a deficiency of antioxidants might be necessary in vivo in order for *G6PD*⁻ cells to exert an inhibitory effect on replication of the parasite. Martin [40] proposed the interesting hypothesis that the consumption of fava beans (which contain oxidants that cause hemolysis in *G6PD*⁻ deficient individuals) in certain areas originally endemic for *P. falciparum* may have provided the necessary dietary oxidant to permit the protective effect of *G6PD*⁻ in malaria. This might help to explain the high gene frequency of *G6PD*⁻ in areas where favism occurs.

The notion that oxidant stress might be important in malaria has also been indirectly tested in vivo. Mice given a diet deficient in vitamin E experienced less severe infections with *P. berghei* than did mice receiving the same diet supplemented with vitamin E [41]. Perhaps other dietary antioxidants or oxidants, such as ascorbic acid, niacin, and selenium, have important effects on the course of malaria, but I am unaware that these agents have been directly investigated. The role of iron in malaria is reviewed elsewhere in this symposium, but I wish to mention here that iron may be important to the survival of the intracellular parasite by virtue of the potential role that catalase plays in scavenging H_2O_2 produced by plasmodia. Thus, theoretically, iron deficiency could result in decreased intracellular catalase activity and parasite suicide, with protection of the host as a consequence.

Effects of Parasitism on the Host Erythrocyte

A number of changes in the structure and function of erythrocytes follow invasion and parasite growth, although the physiologic significance of some of these changes is unclear at present. Because the alterations in erythrocyte membrane were recently reviewed [5], I will discuss only those changes that have apparent immunologic or pathophysiologic significance for the host.

Invaginations in the erythrocyte membrane can be found by electron microscopy of cells infected with certain plasmodial species. Erythrocytes infected with *P. vivax* and *P. ovale* have invaginations on their surfaces called caveolae and are surrounded by small vesicles [42]. The number of caveolae increases as the parasite enlarges, and they can be recognized as Schuffner's dots by light microscopy following staining with Giemsa stain. Although the function of the caveolae is unknown, they may engage in micropinocytosis. The binding of the caveolae to horseradish peroxidase-labeled antibody from monkeys chronically infected with *P. vivax* indicates that these sites are antigenic [43]. In addition, erythrocytes infected with other species, such as *P. falciparum*, may display slitlike structures (Maurer's clefts) within their cytoplasm that are believed to be extrusions of the parasitophorus vacuole membrane.

Infection with some species of plasmodia (e.g., *P. falciparum* and *P. malariae*) is associated with the presence of electron-dense knobs on the surface of the erythrocytes. The knobs of *P. falciparum* schizonts form junctions with venous endothelial cells and appear to be the basis for sequestration of the late developmental stages in the deep venous beds. In *P. malariae*, the knobs do not serve the same function because deep vascular schizogony (sequestration) is not a feature of infection with that species. Antibody prepared against *P. falciparum* has been shown to bind to the knobs [44], but not to areas of the erythrocyte membrane lacking knobs. Although the biochemical significance of interaction between the parasite and the endothelial cell is unknown, an interesting speculation is that antibody produced by the host against knob antigen might somehow protect by interfering with this cell-cell interaction.

A number of biochemical consequences of the parasitization of erythrocytes may be important to the altered rheology and physiology of the cell. After infection, the total cholesterol content of an erythrocyte increases, but the ratio of cholesterol to phospholipid decreases both because of cholesterol loss from the erythrocyte membrane and because of a disproportionately greater content of parasite phospholipid than cholesterol [4]. The adenosine triphosphate (ATP) content of infected erythrocytes is increased, as is the sodium content, whereas the amount of intracellular potassium is decreased [45]. It is of interest that increased sodium content has also been found to be a feature of the uninfected erythrocytes of the malarious host [46]. These changes might be ascribable to modification of the erythrocyte membrane lipid-protein structure with an effect on the ATP-dependent sodium pump [5]. Such changes may help to account for the observation that infected erythrocytes are less deformable than uninfected cells [47]. This alteration in the

rheologic property of the infected cell may be important in the microvascular obstruction that occurs in infection with *P. falciparum*, and it may also form the basis for splenic trapping of infected erythrocytes.

Infection may alter the ability of the erythrocyte to bind or transport substances. A particularly interesting observation by Fitch et al. was that accumulation of the antimalarial agent chloroquine is markedly enhanced in erythrocytes infected with *P. berghei* [48]. Increased accumulation was observed in erythrocytes infected with a chloroquine-sensitive strain of the parasite; chloroquine-resistant strains accumulated less of the drug. Protease treatment of erythrocytes infected with the resistant strain demonstrated patterns of accumulation of chloroquine similar to those of untreated erythrocytes containing the sensitive strain. Chou et al. presented evidence [49] that the receptor for chloroquine is ferriprotoporphyrin IX (FP), a degradation product of hemoglobin found in malarial pigment. FP is found in the pigment of chloroquine-sensitive strains of *P. berghei;* in resistant strains pigment is diminished in amount or absent. Reversion to chloroquine sensitivity is associated with the reappearance of pigment and chloroquine binding. Protease digestion of hemoglobin appears to result in the production of FP, which binds chloroquine; the complex then may result in parasiticidal alterations in the membranes of the host or the parasite [50]. Greater understanding of the basis of resistance to chloroquine may aid in the design of new antimalarial drugs.

The parasite also profoundly alters the antigenic composition of the erythrocyte membrane. Antibody produced by rhesus monkeys in response to infection with *P. knowlesi* can agglutinate schizont-infected erythrocytes in vitro [51]. This effect indicates the presence of parasite and/or altered-self antigen on the cell surface. Interestingly, good evidence suggests that the repeated waves of parasitemia (recrudescences) experienced by the host, which are characteristic of this malaria, are associated with variations in the antigenic composition of these surface determinants. Each new wave of parasitemia represents an antigenically distinct population of infected erythrocytes, to which the host responds by synthesizing antibody directed at the new population [52]. However, whether antigenic variation represents actual changes in the parasite or only sequential selection of subpopulations of parasites is unclear.

Furthermore, although whether antigenic variation occurs in human malaria is unknown, the antigenic heterogeneity of *P. falciparum* isolates in a distinct endemic area may be considerable [53]. Evidence suggests that certain antigenic determinants may be conserved among species of the genus *Plasmodium* [54].

Recent evidence indicates that new antigens appear in the plasma membrane of infected erythrocytes and cross-react neither with membrane preparations from uninfected erythrocytes nor with free parasites [55]. It is postulated that these antigens are ultimately of parasite origin and are intercalated into the host membrane. The possibility that, in addition, the antigenic composition of the host erythrocyte membrane might be altered enzymatically by products of the parasite has not been examined carefully. If such a process occurs, it could result in altered "self" antigens that might be immunogenic, or in the exposure of hidden determinants not present on the surface of normal erythrocytes.

Host Responses to Malarial Infection

The hallmark of clinical malaria is fever. Fever occurs at the time of schizont rupture [56] in sychronized infections in which all the parasites are at about the same stage of maturation. Thus, the fever pattern is related to the time required for schizont maturation (schizogony): ~ 48 hr for *P. falciparum*, *P. vivax*, and *P. ovale*, and ~72 hr for *P. malariae*. Although indications are that a pyrogen might be released during schizont rupture, none has been identified. One may speculate that mononuclear phagocytes (in particular, Kupffer cells) ingest debris of parasite or erythrocyte origin released during schizont rupture and are stimulated to release endogenous pyrogen. This hypothesis has not as yet been directly tested, however.

The pathophysiology of malaria has been most carefully studied in infections of nonimmune individuals with *P. falciparum* [57, 58]. At present, the following sequence of events during severe infection with *P. falciparum* is plausible.

Schizonts of *P. falciparum* become attached to the surface of endothelial cells in venules of a variety of organs, including the brain, lung, heart,

intestines, kidney, spleen, and placenta. This attachment seems to be mediated by the presence of the electron-dense knobs on the surface of the infected cell. In addition, the decreased deformability of the infected cells contributes to a decrease in local microcirculation in these organs (or "sludging" of blood [59]) and results in local hypoxemia. As a result, the endothelial integrity is breached and transudation of fluid into the interstitial space occurs. This sequence is readily observed pathologically in the acute pulmonary edema of malaria. If sufficiently severe, this process may ultimately lead to local microscopic hemorrhage, as is seen, for example, in cerebral malaria, or to cell death, as is observed in acute tubular necrosis associated with malaria due to *P. falciparum*. Of potential nutritional importance are the alterations in intestinal microcirculation during malaria, although the impact of these changes on intestinal absorption have not been fully investigated [60].

The vasodilation secondary to fever results in a decrease in "effective" plasma volume and initiates homeostatic mechanisms aimed at restoring plasma volume. Secretion of antidiuretic hormone and aldosterone increases [58] and causes a decrease in free-water clearance. When the degree of renal water resorption exceeds sodium conservation, hyponatremia results.

A variety of hematologic abnormalities may result from malaria. Anemia occurs as a consequence of the rupture of erythrocytes during schizogony, but the degree of anemia frequently exceeds that attributable to the degree of parasitemia [61].

The basis for the excess anemia is unknown but to date little evidence suggests that defective erythropoiesis occurs in human malaria. Although an autoimmune mechanism has been postulated, Coombs reactions can rarely be demonstrated in nonimmune patients with malaria [62]. In contrast, evidence of Coombs reactions has recently been presented in a study of individuals living in a region where malaria is endemic [63]. Some of these individuals were Coombs test-positive both during acute infection and after treatment. The significance of these observations to the pathogenesis of the anemia of malaria awaits elucidation.

Thrombocytopenia and granulocytopenia frequently accompany malaria, but spontaneous bleeding and increased susceptibility to bacterial infection are rare complications. The basis for the thrombocytopenia seems to be the sequestration of most platelets in the enlarged spleen [64]; the basis of the granulocytopenia is less clear, but might be similar. Abnormalities in the concentration of humoral clotting factors also may accompany infection, and chemical evidence for disseminated intravascular coagulopathy is not rare. However, pathologic evidence of intrasvascular coagulation may not accompany these chemical abnormalities [65]. The basis for depression in the clotting factors and the presence of circulating fibrin degradation products is uncertain, but might result from the triggering of the intrinsic clotting pathway by thromboplastins released from erythrocytes following schizont rupture.

Immune Response in Malaria

Malaria initiates a number of specific and nonspecific immunologic responses, some of which are significant for host defense. Characteristically, infection stimulates polyclonal antibody synthesis resulting in hypergammaglobulinemia. Only a small portion of the antibodies produced appear to have antiplasmodial specificity [66]. Some of the antibody has been shown to have specificity against autoantigens [67], although autoimmune disease does not result. The basis for the polyclonal stimulation is imprecisely understood but may include nonspecific stimulation of T cells by mitogens present in plasmodia [68]. If the T cells stimulated by these substances include helper lymphocytes, these might in turn activate a large number of B-cell clones. Using the rodent malaria model of *Plasmodium yoelii* in mice, Wyler et al. showed that macrophages of infected mice secrete supernormal amounts of the monokine lymphocyte-activating factor [69], which might theoretically enhance the sensitivity of helper T cells to other immunologic signals (e.g., parasite-derived mitogens) and thereby participate in the polyclonal stimulation of B cells.

Another manifestation of nonspecific stimulation is a dramatic hyperplasia of the spleen associated with a marked increase in the macrophage population [70], as well as reorganization of the distribution of splenic lymphocytes [71]. The consequences of splenomegaly include sequestration of platelets and enhanced trapping of parasitized erythrocytes. O'Conor postulated that

the "reticuloendothelial hyperplasia" resulting from malaria plays a role in the development of Burkitt's lymphoma in patients from malaria-endemic regions who are infected with Epstein-Barr virus and in the development of so-called "tropical splenomegaly syndrome" [72]. The latter is characterized by massive splenomegaly, hypergammaglobulinemia, anemia and neutropenia, and a characteristic lymphocytic infiltration of hepatic sinusoids [73]. Although patients with this disease frequently lack demonstrable parasitemia, they often respond to treatment with antimalarial drugs [74]. The etiology of the disease is unknown, but its geographic distribution is restricted to malarious areas, and malaria is believed to play some role in its pathogenesis.

In addition to nonspecific stimulation of certain immune responses, malaria may also result in immunosuppression [75]. Children with high levels of *P. falciparum* in the blood were found to have subnormal seroconversion rates when immunized with tetanus toxoid [76] or polysaccharide antigens [77] and to experience decreases in numbers of circulating T cells [78]. In addition, a variety of blunted humoral and cellular immune responses both in vivo and in vitro have been observed in rodent malaria. It is unclear whether and in what manner immunosuppression might be clinically important in children with malaria. Although these children are considered to be at greater risk for intercurrent infections (e.g., diarrhea, pneumonia), this belief has not been adequately documented in controlled studies. Whether the immunosuppression somehow interferes with the induction of important antimalarial immune responses in children is also unknown. If it exists, such a mechanism might help to explain why protective immunity develops slowly in children living in endemic regions [79].

Specific immune responses to plasmodia include synthesis of antibodies to the parasite [80] as well as generation of specific T cells [81]. Although no correlation exists between antibody titer or T-cell responsiveness and resistance to challenge with the homologous strain of *Plasmodium*, Cohen et al. clearly demonstrated in humans [82] (and it has also been shown in experimental animals) that transfer of γ-globulin from immune donors can protect recipients from malaria. Similarly, transfer of spleen cells [83], as well as transfer of specificially immune T cells, can protect rodents from challenge with plasmodia. The precise mechanism of protection is less well defined, however. One possibility is that antimerozoite antibody might block the invasion of erythrocytes. Unfortunately, the presence, in the circulation of rhesus monkeys, of antibodies that blocked invasion in vitro did not correlate with the ability of these animals to resist challenge with the homologous strain of *P. knowlesi* [14]. Indirect evidence [84] suggests that transfer of hyperimmune serum to nonimmune rats protected them from challenge with *P. berghei* by blocking the invasion of erythrocytes. Another possible protective mechanism afforded by antibody is opsonization of infected erythrocytes. Although observations in vitro suggest that antibody to plasmodia can promote ingestion of infected erythrocytes by macrophages [85], studies of clearance of ^{51}Cr-labeled *P. berghei*-infected erythrocytes in rats do not support this notion [86].

Whether and in what manner complement participates in host defense mechanisms is unclear. Although cyclic alterations in complement components (C1, C4) have been observed in relation to schizont rupture [87], depletion of the later complement components by treatment with cobra venom factor or early components with shark factor had no effect on the course of infection with *Plasmodium coatneyi* in monkeys [88]. Little is known about the role of cellular immune mechanisms in this disease. Preliminary observations suggest that leukocytes capable of damaging parasitized erythrocytes might exist, but these have not been clearly indentified [89]. An interesting hypothesis originally proposed in the 1940s and recently revitalized [90] suggests that soluble leukocyte (macrophage?) products might be able to alter the transport of nutrients into parasitized erythrocytes and thereby inhibit the intracellular maturation of plasmodia in immune animals. The validity and importance of such a defense mechanism remains to be established.

A particularly striking feature of host defense in malaria is the critical role of the spleen [91]. Splenectomy may have a markedly deleterious effect on the course of infection in both nonimmune and immune animals. In what way the spleen exerts a salutary effect in malaria remains a mystery. Recent evidence suggests that the function of the spleen in trapping rigid erythrocytes, such as those infected with plasmodia, may be important in

malaria. This trapping function, which interacts with erythrocytes on the basis of their altered rheology rather than on the basis of erythrocyte sensitization by antibody, changes during the course of acute malaria [92]. Resolution of the acute infection appears to result from a sudden increase in the ability of the spleen to remove rigid erythrocytes from circulation.

Finally, an interesting immunopathogenic process occurs occasionally in children infected with *P. malariae*. These children develop nephrotic syndrome and, at renal biopsy, are found to have either focal or diffuse glomerulonephritis. Deposition of immune complexes on the glomerular basement membrane have been identified by indirect tissue immunofluorescence techniques [93], and plasmodial antigens have been identified in these immune complexes [94]. These complexes may arise following the deposition of parasite antigens in the glomeruli or could result from sequestration of circulating immune complexes.

Summary and Conclusions

The biology of the host-parasite relationship in malaria is highly complex and only recently has received broad attention from molecular biologists and immunologists. The specificity of receptors on erythrocytes for merozoites has been demonstrated and attention has been drawn to the complex nature of the endocytic process. Isolation and characterization of the erythrocyte receptors is needed, and the alterations in erythrocyte membrane structure during and after invasion are under study.

The new technique for continuous in vitro cultivation of *P. falciparum*, currently being applied to careful investigations of the metabolism of the intracellular parasite, may provide insights useful in the development of new chemotherapeutic agents. The role of the parasite as an oxidant stress on the erythrocyte and the impact of genetic variants of erythrocyte hemoglobin and enzymes on the development of the parasite are being elucidated. The possibility that nutritional factors might be important in modulating oxidant damage to the infected erythrocytes needs to be explored in greater detail. The significance of deep vascular schizongony in the development of the parasite has not been clarified and is potentially important for the development of novel chemotherapeutic or immunoprophylactic treatments for this disease. Finally, much remains to be learned about the basic mechanisms of host defense and immunoregulation in malaria.

The impact of nutritional factors on the various aspects of the molecular biology of plasmodia is relatively unexplored. Little is known about the metabolic consequences of malaria on the host; careful studies of metabolic balance in these patients have not been performed. Finally, the potential impact of malnutrition on the ability of the host to be immunized against malaria may eventually become of considerable importance. Clearly, then, the interface between nutrition and parasitism in malaria needs further attention.

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Malaria: Nutritional Implications

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Epidemiologic and immunologic factors determine the impact of malaria on the demography and economics of human communities. Where malaria is epidemiologically stable, its effects are most obvious in young children; adults, because of acquired immunity, are much less affected and remain an economically viable workforce. Where the disease is unstable, it affects all age groups and may incapacitate adults enough to impede food production seriously. Three areas are identified in which malaria may adversely affect host nutrition: low birth weight, the development of protein energy malnutrition, and the pathogenesis of anemia. The influence of host nutrition on malarial infections is considered. The view is expressed that, although deficiencies of some dietary factors may potentiate the resistance to malaria conferred by some genetic traits, there is as yet little convincing evidence that malnutritional states in humans materially enhance the severity or lethality of plasmodial infections.

The influence of malaria on human communities is largely determined by the identity of the prevalent plasmodial species and by the epidemiologic form of transmission in the local environment. Of the four plasmodial species that infect humans, two make relatively minor contributions to the sum of human suffering caused by malaria: *Plasmodium malariae* undergoes a prolonged period of development in the mosquito vector that greatly limits its transmissibility, and *Plasmodium ovale* has limited geographic distribution. *Plasmodium falciparum* and *Plasmodium vivax*, on the other hand, are pathogens of great importance. Both are widespread throughout the world and have the ability, given suitable circumstances, to spread rapidly and cause severe, incapacitating illness. Of these two parasites, *P. falciparum* is the more dangerous because untreated infections with this species frequently terminate in death, whereas untreated infections with *P. vivax* are rarely lethal.

Macdonald [1] has described the two epidemiologic extremes in which malaria can exist: one where instability is the dominant feature and where incidence is characterized by marked seasonal swings or by intermittent, sometimes cyclical, epidemics; the other where stability is the keynote and where incidence remains uniform and relatively unchanging for long periods of time. Between these two extremes, intermediate epidemiologic patterns occur. Although many factors—entomologic, climatic, genetic, and sociologic—combine to shape these patterns, one factor, the acquisition of protective host immunity, is of paramount importance. The intensity and duration of infectious challenge are important features in the evolution of such immunity in both the individual and the community. In communities exposed to frequent, repeated inoculation over many years, the resultant high level of communal immunity stabilizes the epidemiologic situation. The best example of stable malaria occurs in the areas of tropical Africa where *P. falciparum* is highly endemic. There the brunt of infection falls on young children, with consequent inflation of morbidity and mortality in early life. In older children, the progressive acquisition of effective immunity profoundly reduces the lethal and clinical consequences of infection until, in adult life, with the possible exception of pregnant women, a host-parasite balance resembling commensalism is attained [2]. In such a situation adults remain, in the face of sustained infectious challenge, economically viable workers, capable of coping with the strenuous physical activities required for successfully raising and harvesting essential food supplies in subsistence agricultural communities [3]. Therefore, wherever stable malaria prevails, measures to control or eliminate it can be expected to improve the health and survival of young children

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and to contribute to increased population growth, but not necessarily to enhance the productive potential of the community.

In contrast, where populations are exposed to infrequent inoculation or to intense inoculation for brief isolated periods, a high, persistent level of communal immunity is not attained, and the epidemiologic pattern of the disease remains unstable. In this situation all age groups of the community are vulnerable, and infection tends to be followed by severe clinical illness, irrespective of age. If the infecting parasite is *P. vivax*, morbidity greatly overshadows mortality; if it is *P. falciparum*, morbidity and mortality are both prominent. With unstable malaria, the full economic impact of the disease becomes obvious. High adult morbidity may seriously interrupt civil administration, disrupt lines of communication, and impede the planting, tending, and harvesting of food crops. Perhaps the best description of unstable malaria and its consequences is that by Christophers [4] concerning the cyclical epidemics of the Punjab in the early years of this century. Other more recent examples are the explosive epidemic that followed the introduction of *Anopheles gambiae* to Brazil in the 1950s [5], the epidemic of *P. falciparum* in the Ethiopian Highlands in 1958 [6], and the resurgence of malaria caused by *P. vivax* in Sri Lanka in 1967–1968 [7]. Unstable malaria is the epidemiologic form most feared by malariologists, particularly when, for any reason, the disease becomes resurgent in a country after many years of effective control by drugs or by insecticidal control of the mosquito vector.

Today, while we recognize that acquired immunity can profoundly modify the consequences of malarial infection in both the individual and the community, we remain relatively ignorant of how protective immunologic responses are assembled and modulated. Two decades ago evidence suggested that antibody-mediated mechanisms formed the basis of protection; this evidence was based on the successful passive transfer to children of immunity by the immunoglobulin G (IgG) fraction of immune adult serum [8]. However, recent animal studies [9] have shown that mice rendered deficient in antibody-producing cells (B cells) remain capable of resolving acute malarial infections; these results indicate that cell-mediated responses may play an important role in protection. Current theory indicates that host responses to malaria are complex, involving close collaboration between macrophages, different subsets of T cells, and B cells [10]. Collaboration appears to be effected through soluble mediators, as yet poorly defined and characterized, which are secreted by participating cells. In the course of the host response, specific antibodies of the classes IgG, IgM, and IgA are synthesized, and complexes of antibody and antigen develop, some of which appear capable of activating complement. Some of these interactions lead to the death of the parasite by mechanisms as yet unknown. Others may have no protective effect, but instead may initiate new disease syndromes such as the glomerulonephritis which sometimes develops in infections with *P. malariae*. Yet other interactions may induce depressed host responsiveness, which enhances plasmodial survival within the host and may inhibit responses to heterologous antigens. This latter phenomenon must be borne in mind during the analysis and interpretation of the results of studies assaying immunologic defects in individuals who are both malnourished and malarious. Lack of knowledge of the various components of malarial immunity, their activation, and their sequential function currently inhibits speculation on how they may be influenced by concomitant malnutrition of the host.

Effects of Malaria on Nutritional Status of the Host

Malaria possesses considerable potential for adversely influencing host nutrition. It can restrict food intake through anorexia and vomiting. In its febrile phase it induces negative nitrogen balance [11]. Through its immunosuppressive effects [12], it may enhance susceptibility to infection with other pathogens, with consequent further nutritional deterioration. In addition, infections with *P. malariae* may on occasion induce a highly lethal nephrosis often characterized by massive proteinuria [13]. Yet, with the possible exception of improvement in hematologic indices, relatively little nutritional benefit to human populations has been observed after successful control of malaria in hyperendemic areas [14, 15].

From studies of hyperendemic malaria with which I have been associated, three major areas in

which the disease may predispose to adverse nutritional changes are discernible. These are the relationship between malaria and low birth weight of infants, the induction of protein energy malnutrition, and the pathogenesis of anemia.

Low birth weight. Wherever *P. falciparum* is highly endemic, exacerbation of malaria occurs in pregnant women, and parasitization of maternal placental blood is frequently demonstrable at parturition [16–18]. Placental malaria correlates with low birth weight; average deficits ranging from 85 to 312 g have been described [19, 20]. Precisely why malaria is reactivated during pregnancy is not known, but placental infection is most common and severe in women pregnant for the first time and diminishes progressively as parity increases. This seems to argue against a hypothesis that the nutritional stress of pregnancy induces attenuation of acquired immunity [21]. Nor is it clear by what mechanism placental malaria leads to low birth weight. In some instances low birth weight may be the result of premature delivery; in others it may be the consequence of placental damage leading to the expulsion of a full-term but undernourished fetus.

Chandra [22] has described how infants who are small for their gestational age, a feature widely accepted as evidence of fetal undernutrition, often have impaired T cell function that can persist through the early months of life and may adversely influence their prospects for survival. To date no studies have determined whether infants of low birth weight resulting from placental malaria show similar immunologic defects.

Protein energy malnutrition. Protein energy malnutrition, as assessed by low body weight for age or height, is a prominent feature of early childhood throughout much of the developing world and often coexists with a high prevalence of communicable disease. Longitudinal studies of the health of children show that episodes of infectious illness frequently precede faltering growth and incipient protein energy malnutrition in a manner suggestive of cause and effect [23–25]. Marsden [26], in a study of Gambian children, found malaria to be the second most common condition associated with failure to gain weight; the most common was diarrhea. Rowland et al. [27], also studying Gambian children, identified malaria and gastroenteritis as the locally prevalent diseases most detrimental to growth at the ages of 0.6–3 years. Comparing children protected by chemotherapy with unprotected children in terms of increase in body weight, McGregor et al. [28] found malaria most detrimental to children 0.5–2 years of age, i.e., after they had lost passive immunity and before they had actively acquired effective resistance to the disease. Such studies, however, indicate only in very general terms that malaria possesses considerable potential for disrupting the growth of young children. They do not furnish any precise assessment of the impact of the disease in those regions of the world where treatment facilities are absent or negligible and where control measures are not practiced.

Anemia. Anemia is an important sequel to infection with *P. falciparum*, but is usually less prominent in infections with *P. vivax*, *P. malariae*, or *P. ovale*. Where *P. falciparum* is highly endemic, malaria-associated anemia is frequent in children less than four years old [29] and in pregnant women, particularly those pregnant for the first time [18]. The pathogenesis of malarial anemia remains obscure. Destruction of erythrocytes by parasitic invasion is undoubtedly important, but immunologic destruction of nonparasitized erythrocytes may also occur [30]. It is not yet clear how common or important this latter component may be. Erythrocytes from malarious subjects sometimes give positive results in Coombs testing [21], and IgG and various complement derivatives have been detected on their surfaces [31]. However, it has not yet been demonstrated that such sensitization leads consistently to erythrocyte destruction and is not merely a relatively harmless sequel to immune complex formation.

Anemia caused by *P. falciparum* has been variously described as normocytic, megalocytic, or microcytic. In West Africa, my experience has been that when anemia follows a single clearly defined episode of infection with *P. falciparum* in an otherwise healthy individual, it is almost invariably normocytic in character. After antimalarial treatment, profuse reticulocytosis rapidly occurs and hemoglobin levels rise swiftly and spontaneously without need for iron or folate therapy. However, in individuals who have recently experienced several acute episodes of parasitemia or who have been chronically infected for lengthy periods without treatment, the anemia is commonly microcytic and bears the morphologic stigmata of iron deficiency. Such individuals often, but not

always, require iron therapy in addition to antimalarial treatment for full recovery.

Precisely how repeated or persistent malaria induces iron deficiency is not clear. It may do so by depressing absorption of iron, by enhancing loss of iron, perhaps over the period of acute illness when serum haptoglobin levels are depressed, or by immobilizing iron for lengthy periods in hemozoin complexes. Which, if any, of these processes is relevant is not known; clearly, the pathogenesis of malarial anemia calls for further research.

Effect of Nutritional Status of the Host on Malaria

Evidence from studies on animals. Scrimshaw et al. [32] have reviewed the results of numerous studies exploring the influence of dietary inadequacies on malarial infections in laboratory animals. Findings relating to specific deficiency states often vary according to the observer and the host-parasite model. Studies of deficiencies of certain nutriments, notably protein, vitamin A, thiamine, and niacin, tend to yield conflicting results; in some experiments such deficiencies are synergistic; in others, antagonistic. In general, fairly consistent antagonistic effects are associated with deficiencies of *p*-aminobenzoic acid, pantothenic acid, and methionine, and synergistic effects with deficiencies of folic acid and biotin. Overall, specific dietary deficiencies seem more frequently to retard than to enhance parasitemia. However, while such studies have the virtue of being made in controlled circumstances, their relevance to humans, in whom deficiency states tend to be complex rather than simple, is debatable.

In a recent study, Targett [33] examined the effects of protein energy malnutrition on malaria in rodents given synthetic diets of precise composition that differed only in protein content. Results indicated an association between the intake of protein and the level of parasitemia. Rats fed on a high-protein diet were highly susceptible to infection; as the protein content of the diet was reduced, levels of parasitemia decreased until, on a protein-free diet, only a transient, patent infection occurred. The link between protein and infection, however, is not simple. Rats fed on a high-protein diet but allowed only half the quantity taken by control animals feeding ad libitum on the same diet showed some retardation of parasite replication, and most survived infection, whereas almost all of the controls died. Since these studies were designed to test the effects of acute nutritional stress on infection, further investigations were made with rats which were chronically undernourished (6.8% protein in the diet) and then exposed to infection. These animals developed only low-grade, resolving parasitemia. If, prior to infection, the chronically undernourished rats were given a high-protein diet, parasitemia increased but not to the level observed in healthy control animals.

Studies of murine malaria have shown that malaria parasites exert oxidant stress on infected erythrocytes [34] and that such stress may be potentiated by a dietary deficiency of antioxidant substances, possibly leading to the premature lysis of the infected cell and to the death of the parasite [35]. Mice receiving diets deficient in vitamin E developed lower levels of parasitemia and survived for much longer periods than did control animals. The oxidant damage affected mature erythrocytes; reticulocytes appeared resistant and remained capable of supporting full parasite maturation. These studies are of considerable interest for, in addition to demonstrating that dietary factors can influence the course of malaria in well-defined circumstances, they also indicate the nature of the mechanism involved. Further relevance is added by observations indicating that erythrocyte sensitivity to oxidant damage may form the basis for the relative protection against *P. falciparum* in humans that the genetic traits glucose-6-phosphate dehydrogenase deficiency and thalassemia are believed to confer [36].

Evidence from studies on humans. A few studies evaluating the effects of diets deficient in *p*-aminobenzoic acid failed to produce consistent and convincing results [37–39]. Apart from these efforts, information linking nutritional status and malaria in humans essentially derives from epidemiologic observation.

Currently, evidence is growing that impairment of human immunologic responsiveness, particularly impairment of T cell function, is associated with protein energy malnutrition [40]. Because T cells are believed to play an important role in the modulation of protective immunity and because in much of the developing world protein energy malnutrition and malaria coexist at a high prevalence, one might expect to find enhancement

of malarial infections a well-documented feature of protein energy malnutrition. Such, however, is not the case. Edington [41] and Brown and Opio [42] found no evidence that African children with protein energy malnutrition were more susceptibile to malaria than were well-nourished children, and Edington (41) and Hendrickse et al. [43] found cerebral malaria more commonly in well-nourished children than in children with marasmus or kwashiorkor.

In The Gambia, McGregor et al. [44] found that children with clinical stigmata of protein energy malnutrition possessed titers of specific malarial antibodies that were little different from those of well-nourished children of the same age. Moore et al. [45] reported that in vitro stimulation with phytohemagglutinen of lymphocytes from children infected with *P. falciparum* produced decreases in blastogenesis more often that it did in lymphocytes from children with acute protein energy malnutrition. Edsall et al. [46] found little difference in the humoral response of well- and poorly nourished Gambian children to tetanus toxoid. In association with malaria, however, responses were substantially depressed.

In summary, at the present time little evidence exists that protein energy malnutrition materially modifies immunologic responsiveness to malaria or, by other mechanisms, enhances the severity of plasmodial infections in humans.

Several recorded instances indicate that hyperferremia following administration of iron may exacerbate malarial infections. Byles and D'Sa [47] noted that infusion of large quantities of iron-dextran into anemic pregnant women increased the frequency of attacks of malaria, and Masawe et al. [48] described how oral or parenteral iron therapy appears to precipitate clinical attacks in patients with latent parasitemia. Murray et al. [49] found that iron repletion of previously iron-deficient, anemic Somali tribesmen was frequently followed by reactivation of preexisting malaria. These latter authors considered that iron may be an essential requirement for parasitic replication and that, consequently, malaria was depressed when their patients were iron-deficient but developed fully after iron repletion.

In the course of field studies in West Africa, I have often treated individuals with iron-deficiency anemia, many of whom exhibited asymptomatic parasitemia, and have not found oral administration of iron to exacerbate malaria. My experience, therefore, varies from that of the Murrays, possibly because the acquired immunity to malaria between the groups concerned is different. In the Somalians, iron deficiency seemed to be primarily dietary in origin and may have been present from early childhood. Is it possible that an iron-deficient diet maintained from early childhood inhibited not only replication of the malarial parasite, but also the acquisition of protective immunity effective against heavy parasitic challenge, so that when iron repletion occurred, parasitic replication easily overcame a weak immunity and became clinically overt?

In Gambians, on the other hand, iron-deficiency anemia is seldom due primarily to dietary deficiency and is almost invariably secondary to infection with either malaria or hookworm. Consequently, iron-deficiency anemia tends to develop in individuals who have had prior extensive infection with malaria and in whom any tendency for iron repletion to initiate large-scale parasitic replication is curtailed by effective immune mechanisms. At any rate, the apparently discrepant consequences of iron repletion in Somalians and Gambians emphasize the need for studies to ascertain whether the sequence in which a host experiences nutritional and parasitic insults is an important determinant of subsequent host-parasite balances.

Conclusion

Evidence currently available does not convincingly support a view that malnutrition significantly enhances the severity of malarial infections in humans. Further factual information is required to relate the severity of parasitemia and clinical illness to carefully characterized nutritional status.

There is also need for further study, under strictly controlled circumstances, of the course and outcome of malarial infections in experimental animals with characterized protein energy malnutrition and other deficiency states. Such studies should seek not only to identify interactions between infection and malnutrition but also to define the mechanisms involved. Attention should be paid to whether differences in the se-

quential presentation of nutritional and infectious insults can modify ensuing host-parasite balances.

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Discussion: Malaria and Malnutrition

Evidence that parasitic infections and malnutrition can occur simultaneously in the same individual is abundant, but the question of whether an interrelationship exists remains unanswered. Little evidence of such interaction can be brought forward in the case of malaria. Dr. Wyler's elegant review of the host-parasite interactions in malaria gives no clue, because none is available, that the infection per se leads to malnutrition. With the specific exception of a few hosts that are genetically endowed with resistance to malaria, anyone exposed is susceptible to the disease. Moreover, intensity of clinical disease is approximately proportional to intensity of infection. The only inference of a possible relationship between the intensity of disease and the nutritional state of the host comes from animal studies demonstrating that folate deficiency of the host correlates with reduced severity of infection.

The effect of clinical malaria on nutrition of the host has not been analyzed critically. It is easy to postulate that a disease as severe as malaria will debilitate the patient; anorexia reduces food intake, and fever increases energy expenditure. Moreover, because of fatigue that follows malaria, those who recover may be unable to compete effectively for food when its availability is limited. Indeed, the whole question of food production by people chronically affected by malaria is wide open and awaits good analysis. Though indirect and secondary, these effects are extremely important and are well addressed in the comments by Dr. Ian McGregor.

Other indirect effects are illustrated by Dr. McGregor. For example, low birth weight caused by malaria has a potential effect on nutrition of the population. The low birth weight of many infants born to mothers who have malaria very likely results from placental insufficiency. But low birth weight may also be due to premature deliveries in clinically ill mothers. In either case, the outcome is quite consequential for the infant's future. Small babies living in poor sanitary conditions have more infections than larger babies, and, since each infection retards growth further, the infant never catches up. Children having inadequate diets who are continuously at the edge of protein calorie malnutrition can easily be pushed over the edge by an episode of malaria. More important, malaria, along with gastroenteritis and respiratory infections, is one of the many causes of intermittent growth retardation in young children.

Lastly, anemia, the classic example of malnutrition, is one of the consequences of malaria. Of course, much of it is a result of hemolysis, which is quickly overcome by the bone marrow response of reticulocytosis; beyond that, however, especially after many episodes of malaria, some individuals become iron deficient. To what extent this iron deficiency anemia is caused by malaria is not known.

Although it is not possible to draw conclusions on available evidence, questions about the relationship between malaria and malnutrition are now well delineated. There are some bits and pieces of relevant information, but systematic research directed toward answering these questions is long overdue.

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Ascariasis: Host-Pathogen Biology

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Ascaris lumbricoides is one of the most common intestinal parasites in humans. Daily global contamination of the soil by *A. lumbricoides* eggs is enormous ($\sim 9 \times 10^{14}$ eggs/day). Physical factors, particularly temperature and moisture, are critical in determining the maturation of eggs to the infective stage and their survival. Transmission of the infection to humans, on the other hand, depends more on various socioeconomic factors. In theory, ascariasis is preventable; it is indeed on the way to disappearing completely in developed societies where there is a high standard of sanitation. Ascariasis remains a problem in developing countries, however, where methods of disposal of human excreta are inadequate. The intensity of invasion is regulated by specific and nonspecific responses of the host to migrating *A. lumbricoides* larvae. Whether or not ascariasis becomes symptomatic depends on the intensity of the infection, the nutritional and immunologic status of the host, and the possible complications that may arise. Host responses to *A. lumbricoides* are brisk during the larval migratory stage in which hypersensitivity reactions may become clinically manifest, whereas people are rather tolerant of intestinal infections with adult worms. The role of ascariasis in the prevalence of allergic asthma still remains unclear. Complications due to migration of adult worms into the biliary duct system and to intestinal obstructions are the major causes of acute morbidity and mortality in ascariasis.

Ascaris lumbricoides is a parasite specific primarily to humans. The physiology and biochemistry of *Ascaris* species have been extensively studied because the parasite is well suited for research in biological laboratories. The host-parasite biology has also been studied in many experimental animal models. Despite the considerable amount of knowledge available on *Ascaris*, several questions concerning the ecologic, epidemiologic, pathological, and clinical aspects of ascariasis in humans remain unanswered.

Ascaris lumbricoides is one of the most common intestinal parasites in the world. There are two conceptually separate populations and reservoirs of *A. lumbricoides*: the adult worms that parasitize humans and the eggs that contaminate the environment. The size of the former population can be estimated at ≥7.8 billion adult worms by multiplying 1.3 billion, the expected number of human hosts infected [1], by six, the expected mean number of parasites in a single host [2]. The factors that regulate the population of *A. lumbricoides* are complex. Among the various ecologic elements, physical factors are most important in regulating the number of invasive eggs in the environment. Transmission to humans is closely related to socioeconomic factors. Various specific and nonspecific host reactions, directed mainly against the migratory larvae, regulate the intensity of invasion.

Ascaris invasion is a sequence of events determined by the parasite trying to complete its life cycle and the host safeguarding the integrity of its own body. The response of the host depends on the stage and intensity of the invasion. The response to *Ascaris* at the larval stage is usually strong, and hypersensitivity frequently occurs. Human hosts are often tolerant of intestinal infection with adult worms. A person can react vigorously to an ascaris allergen if he or she is not desensitized in the course of infection. Complications due to migration of adult worms and to intestinal obstructions are relatively unusual consequences in humans, but they are the most important causes of mortality in ascariasis. Based on descriptions of clinical cases, the complications of ascariasis are easily summarized. However, in terms of public health, morbidity and mortality

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due to the complications of ascariasis have not been well documented and their significance has not been adequately discussed [3]. An analysis of the impact of ascariasis on the nutritional and immune status of the human host is also lacking. The alterations that *A. lumbricoides* produces on the structure, physiology, and biochemistry of the human intestine and the indirect nutritional and immunologic consequences of ascariasis are not yet fully understood. Until these aspects have been adequately studied in laboratories, in clinics, and in the field, any conclusions regarding the global importance of human ascariasis in public health will remain debatable [4].

Specificity of *Ascaris* to the Human Host

Ascaris lumbricoides is a roundworm specific to humans; it has also been found accidentally in other hosts, including orangutan, dog, cat, and sheep. *A. lumbricoides* is most closely related to *Ascaris suum*, the roundworm that infects pigs. These two organisms have minor morphologic distinctions and physiologic differences. They do evidently differ in their capacity to invade their natural and accidental hosts since *A. suum*, which develops fully in the pigs, in man develops to the larval, tissue-migratory stages and rarely reaches the adult intestinal stage [5–7].

Ascaris lumbricoides is the primary cause of human ascariasis. However, in many regions of the world, humans are frequently exposed to the invasive eggs of *A. suum* [8] and *Toxocara* species; the degree to which such exposure to nonspecific but closely related species of *Ascaris* influences the pathology, immunology, and epidemiology of ascariasis remains unknown.

Although infections due to *A. lumbricoides* have been experimentally induced in humans [5, 9, 10], much of our knowledge about human ascariasis derives from infections experimentally induced with *A. suum* in animals. Such infections in pigs provide a good experimental model for studying both invasiveness [11, 12] and intestinal pathology [13] in ascariasis. For immunologic studies, infections with *A. suum* are commonly induced in small laboratory rodents. Monkeys are widely used for observations of the host's response to ascaris allergen. Although such experimental models are excellent in many respects, the limitations are obvious from the interpretation of the results in relation to *A. lumbricoides* infection in humans: the unnatural hosts respond more strongly to the invasion of unusual parasites. Since clinical and epidemiologic observations also have their limitations, many aspects of the human-parasite relationship in ascariasis are not yet understood.

Ascaris lumbricoides Eggs in the Environment

The reproductive potential of the *A. lumbricoides* female worm is extremely high (~240,000 eggs/day) [14] and thus counterbalances the heavy losses in viability and infectivity of the eggs in the environment. The global external environment is contaminated daily by $\sim 9 \times 10^{14}$ eggs. The results of examination of soil for helminth ova provide some information on the extent and intensity of the environmental pollution: in Sawahlunto, West Sumatra, Indonesia, *A. lumbricoides* eggs were found in 45% of 55 samples (2 g each) of soil collected around nine farmhouses [15]; in a study of ascariasis in Poland, 71% of 935 samples (100 g each) of soil had *A. lumbricoides* eggs, and the means for two consecutive years were 1.8 and 2.8 eggs per gram of soil [16]. The infrastructure of the soil and the mechanical action of rain cause a patchy concentration of eggs in the ground [17] and may be responsible for massive infections occurring from time to time rather than limited infections occurring regularly.

Of the various ecologic elements (landscape, weather, and type of soil) that regulate the population of *A. lumbricoides* eggs outside the human host, the most important are the physical factors: temperature, moisture, oxygen pressure, and ultraviolet irradiation. Since the eggshell is permeable to water, desiccation and higher temperatures readily kill the eggs [18, 19]. Depending on the ecologic factors, *A. lumbricoides* eggs can survive for more than six years in a temperate climate [20] but for only a few hours in tropical conditions [21]. In Samarkand, USSR, 0.3% of the eggs in the soil still had mobile larvae and 0.04% were invasive to the guinea pig after 14 years in that climate [22].

Unfavorable climate factors, such as the cold winter in Europe [16] and brief deviations from the normally warm, arid climate in Saudi Arabia [23], are responsible for seasonable breaks in

transmission. In many regions of the world with a warm, moist climate, the transmission of ascariasis occurs throughout the year.

Transmission of Ascariasis to Humans

The magnitude of the natural transmission of ascariasis in endemic areas can be measured by examining the reinfection rate after successful mass chemotherapy. This rate is a function of (*1*) the infection pressure (i.e., the number of possible human exposures in a certain area in a given time) and (*2*) the host responses, mainly immunologic, that regulate the number of adult worms that develop. In some endemic areas the reinfection rate is as high as 30% per month, i.e., 30% of the people start to excrete *A. lumbricoides* eggs within the third month after deworming (this includes a two-month prepatent period) [24]. In areas where there is a high reinfection rate, the effect of a single mass chemotherapeutic action may disappear within six months.

The level of transmission of the infection from soil to humans depends on socioeconomic rather than physical factors. The main elements seem to be a dense human population, its involvement in agricultural production (especially with extensive use of human nightsoil), illiteracy, poor sanitation, and particular cultural habits [25–28].

The results of epidemiologic studies carried out in several countries illustrate the global prevalence of ascariasis. In Colombia, for example, the overall prevalence of *A. lumbricoides* infection is 54%, with schoolchildren comprising the group affected most frequently (66%). There is a direct correlation between low salary and high prevalence, and the rural population is parasitized twice as frequently as is the urban population. The frequency of moderate and intense infections follows a pattern similar to that for the overall prevalence; infections with > 5,000 eggs/g of feces constitute about one-third of all infections [29]. In Kenya, it has been estimated that ~25% of the population is infected with *A. lumbricoides*. The prevalence is highest in children, of whom 20%–80% are infected, and ascariasis is more prevalent in densely populated areas, especially in western Kenya and Nairobi. The assumed mean intensity of infection was seven worms per infected person [30].

In the Republic of South Korea, the prevalence of ascariasis in 1971 was 46.4% in the urban population and 59.6% in the rural population. There was little difference in the infection rate between the two sexes and among the various age groups. The level of education and the standard of living had some influence on the prevalence and intensity of ascariasis: graduates from primary schools had a higher prevalence (63.2%) than did those from colleges (37.8%), and the mean number of *A. lumbricoides* eggs/g of feces for hospitalized patients in the open wards was 5,936, whereas for private patients it was only 1,846 [31].

The prevalence of ascariasis may vary in different localities; however, there are few community profile studies that are helpful in understanding the local means of transmission or that permit generalizations beyond the statement that "the prevalence of ascariasis is very high in some families" [25].

In conclusion, the world distribution of ascariasis follows an endemic pattern. The factors responsible for high (>60% of the human population infected) and low (<20% of the population infected, mostly children) endemicity have not been studied sufficiently. A pattern of low endemicity is characteristic for seasonal types of transmission, e.g., in Europe and in Saudi Arabia. In such areas, a patchy distribution of ascariasis (only in some localities or in some families) is frequently observed, especially in areas where ascariasis is disappearing simultaneously with improved sanitation [32, 33]. However, there have been epidemics of ascariasis, e.g., in 1947–1948 around the vast, irrigated fields at Griesheim in West Germany [34]. The various endemic and epidemic patterns of ascariasis not only depend on the selective pressures in the environment but also are regulated by the immunity of the local human population.

Regulation of the Intensity of Invasion

Ascaris lumbricoides must cross several barriers when invading a human host. For a successful invasion, the mucosa of the small intestine, the hepatic tissue, and the alveolar walls of the lung must be penetrated; passages must be made through the lymphatics, the blood vessels, the upper respiratory tract, and the stomach (twice); and several rapid changes in the quality of the biotope and in the protective mechanisms of the host must be withstood (figure 1). Even after finally settling in

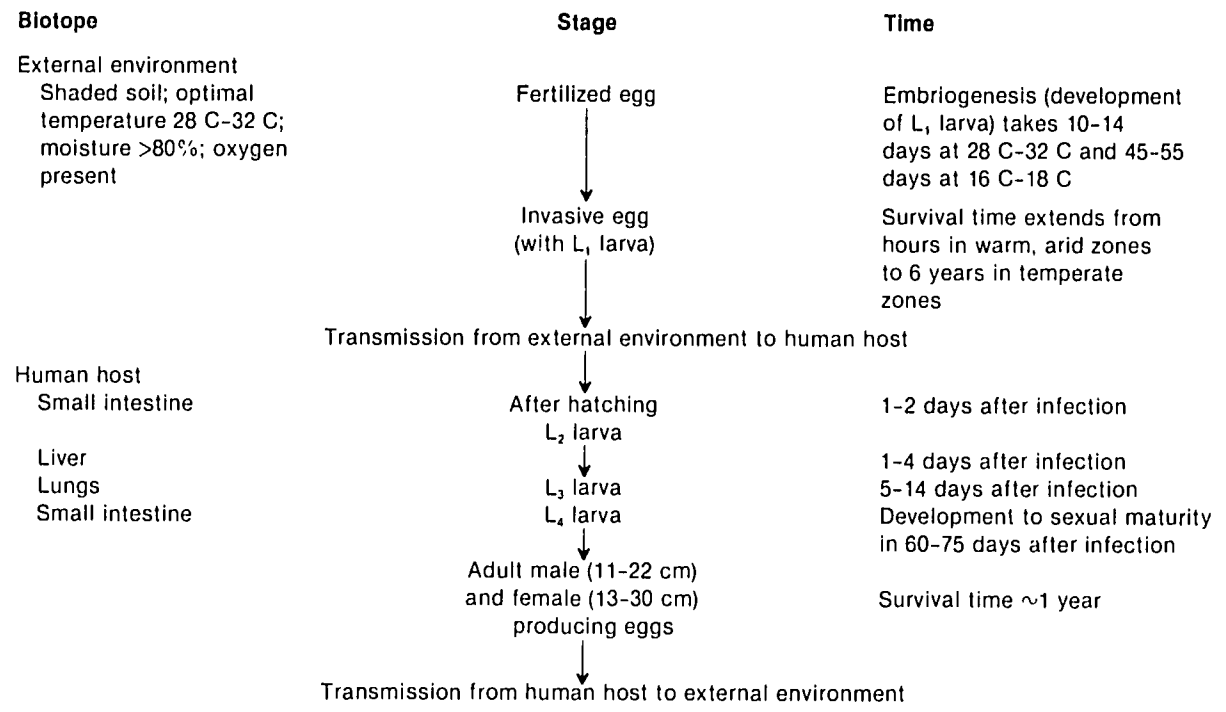

Figure 1. Diagrammatic representation of the life cycle of *Ascaris lumbricoides*.

the small intestine, preadult and adult *A. lumbricoides* cannot always resist the increased body temperature and peristalsis of the human host.

In humans, sterilizing (fully protective) immunity against *A. lumbricoides* infection is rare; as a rule, immunity is incomplete and manifests itself by a reduction in the number of parasites. The mechanisms responsible for partial resistance to infections with *A. suum* in laboratory animals are active during the early intestinal stage, interfering with the process of hatching and with larval penetration of the mucosa of the small intestine [35, 36], and during the tissue stage, immobilizing and destroying the larvae in the lung tissue [37] and acting on the immature worms in the small intestine soon after the third moulting. Recently, an *Ascaris* culture fluid antigen (ACF) was obtained by cultivation in vitro of third-stage *A. suum* to the fourth stage; this antigen induced significant protection in guinea pigs against a challenge infection [38]. Under experimental conditions, a significant level of protective immunity against *A. suum* in pigs is achieved only after feeding them with multiple, large doses of infective eggs [39, 40]. It is unclear whether the low intensity of ascariasis observed in older people in endemic areas is a result of continuous exposure [41] and, if so, which mechanisms are involved.

The immune response in experimentally induced ascariasis follows the general pattern of development of immunity in a mammalian host; there are, however, some differences between the response in nonimmune and immune hosts. In nonimmune hosts, the first antibodies can be detected on the sixth day after inoculation. The level of circulating antibodies reaches its maximum in the third and fourth weeks and then decreases slowly during the second and third months. IgM antibodies appear first, while antibodies of the IgG classes are prevalent later. The antibody levels correlate well with the number of plasma cells in the lymph nodes and spleen [42]. An immune host responds almost immediately to inoculation with *Ascaris*.

Phills and co-workers [6] observed patients infected with *A. suum* and found that high titers of precipitating antibody with IgM mobility correlated with reduction in worm burden.

Reagins, particularly IgE and some of the IgG1 class, form during the migration of ascaris larvae through the lungs and during the intestinal infection, especially in its early phase when the larvae moult for the fourth time and become preadult.

IgE immunoglobulins are mainly produced by plasma cells in the small intestine.

The mechanisms responsible for sensitization or desensitization and susceptibility or resistance to reinfection are still unclear. Analysis of the protein-polysaccharide antigens of *A. suum* indicates the presence of multiple determinants. Some are immunogenic, stimulating production of specific precipitating antibodies; others are allergenic, responsible for reaginic IgE production and local or systemic hypersensitive reactions, such as bronchial asthma, angioneurotic edema, and urticaria.

Since allergic reactions in ascariasis have a distinct clinical expression, they will be discussed separately. However, IgE reaginic antibodies may play an important role in the promotion of a succession of immunologic mechanisms or their interactions and may thus participate in the reduction of the number of invading ascaris larvae.

Cellular immunity plays an important role in reducing the number of migrating larvae, but the effector mechanism remains unclear; this is not solely a T-cell-mediated phenomenon [43]. The more studies performed, the more complex seems the host's responses to the invading ascaris larvae. Whether specific or nonspecific, the response of the host is directed against the surface of the worm or its digestive cells, which are more vulnerable to cytotoxins. The role of nonimmunologic protective mechanisms may be substantial. For example, fluids extracted from the ascaris body cavity contain eosinophil chemotactic factor and neutrophil chemotactic factor, which have physiochemical characteristics differing from those of ascaris antigen [44]. However, the in-vitro adherence test with washed peritoneal exudate cells from mice showed that there are some nonspecific mechanisms for killing *A. suum* larvae that are mediated by carbohydrates or divalent cations and are independent of the presence of antibodies and/or complement [45].

Ascaris Infection and Disease

There are two extremes in the clinical expression of ascariasis: asymptomatic infection and severe ascariasis, which, due to complications, is frequently fatal. Asymptomatic infections are usually mild and occur in well-nourished hosts; however, some fatal complications may occur even in this group. Intensive infections in young, undernourished children whose immunologic abilities are consistently challenged by other infections are usually symptomatic; such infections are not uncommon in most areas where *A. lumbricoides* is endemic. This generalization takes into account two factors: the intensity of infection and the nutritional and immunologic status of the host. In theory, one may also classify ascariasis as asymptomatic without pathological changes, asymptomatic with pathological changes, and symptomatic due to pathological changes. In practice, however, questions of the degree of structural and functional modifications constituting a pathological change and the degree of pathological changes causing evident or measurable symptoms remain unanswered, since these factors vary greatly in different individuals and populations. Studies of the relationship between *A. lumbricoides* and humans may produce conflicting results unless the biologic potentials of the different hosts are comparable. The more known about the host, the better the understanding of the ascariasis in that host. This statement applies to the whole range of problems of polyparasitism and to the relation between nutrition and infection.

In ascariasis the pathology and symptomatology differ widely between the tissue phase of infection caused by the migrating larvae and the intestinal phase caused by preadult and adult worms. The difference is mainly in the type of reaction and/or its intensity. In the tissue phase the inflammatory and immunologic reactions prevail, whereas in the intestinal phase the host's intestinal functions seem to be most affected.

The pathology and clinical aspects of the migratory phase have been widely studied and reviewed [46, 47]. In countries such as Saudi Arabia where *A. lumbricoides* transmission is seasonal, pneumonitis due to *Ascaris* is common and may be an even more serious public health problem than the intestinal infection that follows it [48].

Host Responses to Ascaris Adult Stages

The host usually responds to intestinal infection with adult *Ascaris* with a great deal of tolerance, a response that is typical for infection with most intestinal luminal parasites. Roentgenographic studies of ascariasis in humans show that 87% of the worms are present in the jejunum [49]. The worms remain stationary most of the time; braced

against the intestinal wall, they are not affected by normal intestinal peristaltic action. The spiral forward movement and a tendency to enter small openings (whether it be the ampulla of Vater or a drainage tube) are characteristic of *Ascaris* species.

Observations in pigs infected with *A. suum* showed highly significant hypertrophy of the intestinal muscle layers, a corrugated appearance of the mucosa, a shortening of the crypt depth, and a diminished amount of mucus [13]. These changes correspond to the disordered pattern of the small bowel (most commonly a coarsening of the mucosal folds of the small intestine) observed during roentgenographic examination in the majority of patients with ascariasis [50]. The relationship of these morphologic changes to the symptomatology of ascariasis and to the impaired absorption of nutrients is not clear. Strong inhibitors of the trypsin and chymotrypsin of the host were found in extracts of *A. suum* and in supernatants from culture media in vitro [51, 52]. It is unlikely, however, that ascaris antienzymes greatly disturb the digestive processes of the host.

The metabolism of *Ascaris* has been studied extensively; however, there is still little information on how well the host tolerates ascaris metabolites and whether they interfere with the host metabolism. Some interesting observations have been made on the presence of volatile fatty acids excreted in easily detectable amounts in the urine of the infected host [53], on functional pyridoxine deficiency [54], on substandard levels of vitamins A and C in parasitized children (reviewed by Layrisse and Vargas [55]) and on the antimetabolic activity of some ascaris metabolites [56]. Studies have indicated that ascariasis itself is responsible for decreases in growth, absorption of various nutrients, and lactose tolerance [57]. These pathological effects seem to be closely related to the intensity of the ascaris infection as well as to other factors, including polyparasitism, that affect the nutritional and immune status of the host. The effect of ascariasis on nutritional status is reviewed separately [58].

Local intestinal hypersensitivity reactions have not been adequately studied. Arseculeratne et al. [59] have recently proposed that *Ascaris* may be involved in the pathogenesis of necrotizing enteritis. Ascaris antigen may be responsible for a type I hypersensitivity reaction leading to shedding of the epithelium at the tips of the villi and/or infiltration of eosinophils at the site of an antigen-antibody reaction; *Ascaris* may also act directly by liberating vasoactive amines, which cause the degranulation of intestinal mast cells and all its consequences. If these observations are confirmed, necrotizing enteritis must be included among the serious complications of ascariasis.

Host Responses to the Ascaris Allergen

The ascaris allergen is the most potent allergen of parasitic origin. It is present in all stages of the ascaris life cycle, and its physico chemical and biologic properties are known [60]. An increase in circulating IgE globulins is common in human ascariasis but is not necessarily related to the atopic changes present [6]. Ascaris infection causes a nonspecific potentiation of IgE since only a small percentage of IgE globulins has antibodies specific for *Ascaris* [61]. The ascaris allergen can cause a hypersensitivity reaction in the lungs, skin, conjunctiva, and gastrointestinal tract. Such reactions have been observed in infected individuals and in laboratory workers who were in contact with the ascaris allergen. Coles [62] has described a gastrointestinal allergy to the ascaris allergen in an uninfected laboratory worker who experienced repeated episodes of abdominal pain, heartburn, and diarrhea. Casuistic descriptions of cases of allergy to *Ascaris,* which is sometimes life-threatening, are an important source of information.

However, strongly conflicting conclusions have emerged from studies on the relation between ascariasis and the prevalence of allergic asthma. It has been suggested that high levels of serum IgE caused by a high rate of infection with helminths suppress the prevalence of asthma in children in tropical countries because parasite-specific IgE saturates binding sites on mast cells and prevents IgE specific for common, inhaled allergens from making contact with mast cells in the respiratory tract [63]. More recent studies have shown that parasite-specific IgE on bronchial mast cells did not prevent acute asthmatic episodes after exposure to housedust antigen [64]; on the contrary, an *Ascaris*-induced immune response enhanced IgE-mediated reactivity to common, inhaled allergens in both allergic and clinically nonallergic individuals [65]. The existence of a beta adrenergic blockade, as shown by a negative epinephrine test,

may also explain the increased incidence of eosinophilia and allergic manifestations in children infected with *Ascaris* [66].

An evaluation of the impact of allergy due to *Ascaris* on the health of whole populations is not possible without further well-controlled studies in areas where ascaris infection is endemic.

Serious Complications of Intestinal Ascariasis

The most serious complications of human ascariasis are due to migration of the adult worm and to intestinal obstruction by a bolus of adult worms. The migration of ascaris worms outside their natural biotope is promoted in the host by fever, a diet rich in pepper, anesthesia, and improper treatment; it is probably more frequent in infections with a single worm or worms of the same sex [47]. Such migration may cause (in order of decreasing frequency) the following complications: obstruction of the hepatic duct, appendicitis, intestinal perforation, including penetration of intestinal incisions, and pancreatic duct obstruction [67]. Vomiting of adult ascaris worms occurred in 3.3% of the 580 cases observed by Pawlowski [47]; as a result, *Ascaris* may penetrate the upper respiratory tract and the eustachian tube.

The intestinal obstruction most commonly occurs at the terminal ileum and is caused not only by an aggregation of crowded worms but probably also by an intestinal spasm produced by irritation of some receptors in the mucosa [68]. Intestinal obstruction is more frequent in intensive infections. The rate of intestinal obstructions per year in the southeastern United States is approximately two per 1,000 in children aged 1–5 years infected with *Ascaris* [3]. Intestinal obstruction due to ascariasis and complications due to migration of *Ascaris* constituted 10%–15% of all acute abdominal emergencies in Cape Town, South Africa, and were second in frequency only to acute appendicitis [69]; the peak incidence was observed in children between four and eight years of age. In Acapulco, Mexico, where *Ascaris* is a common parasite, intestinal obstructions and subobstructions rank fifth as a cause of admission to hospital; among 1,461 pediatric admissions in one year, 85 children were admitted because of obstruction due to *Ascaris* [70].

There is still inadequate information about the frequency of life-threatening complications of ascariasis requiring surgery in many endemic areas; thus, evaluation of the approximate rate of mortality from *A. lumbricoides* in the world is difficult. Even if fatality is as low as six deaths per 100,000 [25], several hundred deaths would occur among the millions of people who are infected by this parasite.

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Ascariasis: Nutritional Implications

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Ascaris lumbricoides, the roundworm, is one of the largest parasites of man and probably infects one in four persons in the world. Despite its prevalence, ascariasis is a largely neglected public health problem that has attracted relatively little scientific inquiry. Frequently, a number of biases contribute to the uncritical conclusion that infection with *A. lumbricoides* adversely affects the nutritional status of the host. This situation is exacerbated by a number of studies that have confirmed these biases but have employed questionable methods, such as the use of small samples and indistinct categories, the neglect of the double-blind safeguard, the selection of inadequate controls, and the performance of experiments that are not reproducible in a variety of circumstances. It is interesting to note that studies claiming positive correlation between ascariasis and protein energy malnutrition have not found a significant difference in weight between infected and uninfected children before intervention. Furthermore, several recent studies have shown no significant improvement in nutritional status after intervention. Thus, the causal relationship between ascariasis and protein energy malnutrition is not clearly proved, and it is premature to advocate mass treatment of children in ascariasis-endemic areas as a method to enhance their growth and development.

To believe with certainty we must begin with doubting.
Stanislaus, King of Poland, Maxims No. 61

Ascaris lumbricoides, the roundworm, is one of the largest parasites that infects humans, and it is generally believed to infect one of every four persons in the world [1]. Despite these considerations, this parasite has been the subject of relatively little scientific inquiry, and ascariasis is a neglected public health problem. Although one aspect of ascariasis, the role that the parasite plays in the nutrition of the host, has been the subject of considerable speculation, it too has attracted little scientific inquiry until recently. One should analyze this issue with considerable skepticism because in the place of factual information are many biases that lead uncritically to the conclusion that *A. lumbricoides* adversely affects the nutrition of the human host. These biases are: (*1*) *A. lumbricoides* inhabits the small intestine of the host, where a major share of digestion and absorption of nutrients occurs. One is tempted to conclude that the parasite competes directly with the host for a finite amount of nutrients. (*2*) Other intestinal helminths are well-known causes of malnutrition. *Ancylostoma duodenale* and *Necator americanus* can cause microcytic, hypochromic anemia; hypoalbuminemia; and stunted growth. *Diphyllobothrium latum* can cause hypovitaminosis B_{12} and megaloblastic anemia. In the popular lexicon, infections with *Taenia* are associated with hunger and weight loss. *A. lumbricoides* might, therefore be grouped with other worms as a cause of malnutrition before any association is scientifically proved. (*3*) A wide range of other viral, bacterial, and protozoan pathogens that produce both systemic and enteric infections is well known to be detrimental to the nutrition of the host. (*4*) Some studies have concluded that ascariasis is detrimental to host nutrition. These studies should be critically evaluated, however. The examination of the relationship between infection with *A. lumbricoides* and the nutrition of the host is a complex endeavor requiring the control of many variables. (*5*) Intestinal parasites and malnutrition occur most often in persons of low socioeconomic status. Although these two conditions coexist in the same populations and are each directly related to poverty, they are not necessarily related to each other. These preventable health conditions are occasionally the focus of social and political activity, which, however well intended, often attributes a cause-and-effect relationship to coexisting conditions and thereby concludes that ascariasis is a cause of malnutrition.

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Mechanisms of Action

Sporadic reports in the literature have claimed that infection with *A. lumbricoides* causes malnutrition, stunting, xerophthalmia, vitamin deficiencies, and other nutrition-related conditions. However, few studies have proved these claims and shown the actual mechanisms of action. Furthermore, those who have studied malnourished children infected with *A. lumbricoides* examined absorption before and after treatment instead of using concurrent controls. The mechanisms they have hypothesized are: (*1*) consumption by roundworms of nutrients needed by the host; (*2*) interference with intestinal absorption due to mucosal damage by the parasites; (*3*) loss of nutrients, fluid, and electrolytes through diarrhea and vomiting; and (*4*) production of proteolytic substances by the parasites.

Protein deficiency could be caused either by impairment of digestion and absorption or by loss of protein through the roundworm eggs. One million eggs, which are produced daily by five female *A. lumbricoides*, contain 4.24 mg of nitrogen, an amount that is not critical for the well-nourished host [2]. Jejunal mucosal abnormalities in infected persons were found by Tripathy et al. [3], Lagundoye [4], and Maxwell et al. [5]. Layrisse and Vargas [6] described changes in intestinal microflora, which aid the biosynthesis and digestion of nutrients. Chatterjee hypothesized that trypsin and chymotrypsin are neutralized by "ascarase," an antienzyme polypeptide product of *A. lumbricoides* [7]. The larval stages of *A. lumbricoides* could affect the nutritional status of the host when they migrate through the viscera. The ability of migrating larvae to cause the Loeffler syndrome suggests that they could have other, more subtle effects that impair host nutrition by either specific or general means. This aspect of ascariasis has not been studied.

Clinical Studies

One of the earliest clinical studies of ascariasis and nutrition was performed by Venkatachalam and Patwardhan in 1953 [2]. Studying a small number of hospitalized Indian children with moderate infections (mean, 26 worms), these investigators found a significant reduction in mean fecal nitrogen excretion after deworming. The change in nitrogen excretion was not due to improved hospital diet, the nitrogen content of the eggs, or the drugs used to eliminate the parasites. Tripathy et al. confirmed this work and demonstrated both intestinal loss of 7%–9% of dietary fat and abnormal carbohydrate (D-xylose) absorption in infected subjects [3, 8].

Some studies have found no relationship between ascariasis and the nitrogen or carbohydrate metabolism of children. Bray [9] studied four Nigerian children and found no consistent differences in nitrogen absorption or utilization before or after deworming. Teotia et al. [10] found that only one of five Indian children infected with *A. lumbricoides* exhibited fat malabsorption. Freij et al. [11] found no significant differences in nitrogen, fat, and xylose absorption in a small number of lightly infected children who received either piperazine or a placebo.

Several studies have indicated that *Ascaris* can interfere with absorption of vitamin A and contribute to xerophthalmia. Rodger et al. [12] found a group of infected patients to have a somewhat lower mean serum vitamin A value than uninfected controls, but this study did not include statistical analysis of the difference. Sivakumar and Reddy [13] showed that children infected with *A. lumbricoides* absorbed significantly less of a test dose of orally administered, radioactively labeled vitamin A than did uninfected controls. They suggested that in areas where xerophthalmia is common, vitamin A deficiency could be exacerbated by the presence of *A. lumbricoides*. Mahalanabis et al. [14] found that patients with ascariasis showed poorer absorption of radioactively labeled vitamin A than did uninfected controls.

Morgan et al. compared the infected subjects with the uninfected subjects studied in the Louisiana portion of the Ten State Nutrition Survey [15]. No significant difference between subjects infected with *A. lumbricoides* and controls was found with respect to mean levels of hemoglobin, hematocrit, vitamin A, carotene, vitamin C, or total serum protein. The 31 controls in Morgan's study had slightly higher mean albumin levels than the 31 subjects with ascariasis; the difference was statistically significant. Blumenthal and Schultz [16] compared the nutritional status of 30 children living in rural Louisiana who were infected with *A. lumbricoides* with that of 30 uninfected matched controls. Ascariasis had a statistically

significant adverse effect on levels of albumin in serum and vitamin C in plasma, but no child had inadequate levels of these nutrients. Evidence suggested that the infection adversely affected the ratio of weight to height as well as riboflavin levels, whereas it had no significant effect on seven other laboratory measurements. Dodin also showed a relationship between ascariasis and vitamin C metabolism [17]. All of 38 patients infected with *A. lumbricoides* had abnormally low excretion of vitamin C after a test dose, whereas only three of 13 uninfected controls failed to excrete a normal amount of the vitamin.

Recent Community Studies

Until recently, no published studies have examined the long-term relationship between the elimination of infection with *A. lumbricoides* and protein energy malnutrition in children living in communities where ascariasis is endemic. In the past few years, several independent longitudinal studies have been published on this subject [18-21]. The methods and conclusions of these studies are examined critically here because they could be important determinants of future research and public health policy.

Gupta et al. [18] studied the effect of periodic deworming on the nutritional status of preschool children in Uttar Pradesh, India. The children were undernourished and were receiving supplementary food. Children in two villages were given tetramisole every four months for one year (total, three doses), whereas children in two other villages were control subjects given a placebo. The weight and infection status of each child was determined at each four-month interval. The authors claimed that the prevalence of ascariasis and the severity of protein energy malnutrition were the same for the two groups at the onset of the study, and that nutritional status remained unaltered in the controls but had improved strikingly in the treated children eight and 12 months after the start of the study.

A number of deficiencies in the design of this study and in the presentation of the results cast doubt on these conclusions (table 1). The control subjects were not randomly selected, and they were a separate and distinct group. The authors' claim that the study and control groups were comparable socioeconomically and environmentally may or may not have been true. During the 12 months of the study, one or more external factors could have affected one village more than another. For example, unobserved differences in the distribution of supplemental food or in intercurrent infections could have influenced the final results. The identities of the experimental and control subjects were known to the investigators; that is, the study was not conducted in the traditional double-blind manner to ensure against observer bias. The principal investigator, not a disinterested observer, supervised the measurements. A small percentage difference in the reference weight

Table 1. A comparison of the designs of three studies of the relationship between ascariasis and protein energy malnutrition.

	Reference		
Factor	[18]	[19]	[20]
Location of study	India	Tanzania	Kenya
Number of subjects	Infected: 58 Total: 154	Infected: 78 Total: 273	Infected: 61 Total: 186
Intensity of infection	Unknown	Unknown	Light (average, 7 worms)
Random selection of subjects and controls	No	Yes	No
Double-blind observation	No	Yes	Yes
Control of major variables			
Intercurrent disease observation	No	No	Yes
Equal distribution of supplemental food	No	Not applicable	Not applicable
Drug administration	No	No	Yes
Length of observation period	12 months	12 months	14 weeks
Statistical methods	Change in reference weight-for-age (1% considered significant)	Rate of weight gain	Percentage of expected weight gain and change in skinfold thickness

for age separated the categories designated improved and deteriorated. An accurate judgment of the significance of the nutritional changes would utilize the reference measurements of weight-for-height and would consider the effect of a greater percentage difference between the categories of improved and deteriorated. Most important, the conclusion that a significant change occurred in the nutritional status of infected children given tetramisole is based on an exceedingly small number of subjects. A change in the status of three children would have led to the opposite conclusion: that no statistically significant relationship appeared between ascariasis and nutritional status.

Willett et al. [19] studied 341 Tanzanian preschool children. The subjects were randomly assigned to treatment with levamisole or a placebo given at three-month intervals. Weights and heights were measured at each three-month visit for a period of one year. The authors found that the rate of weight gain was 8% greater for those receiving levamisole than for the placebo-treated controls; however, this difference is not statistically significant ($P = 0.06$). Among 78 children known to be infected with *A. lumbricoides* at the begining of the study, the rate of weight gain was 21% greater for those treated with levamisole than for those receiving the placebo. This difference was statistically significant ($P = 0.03$). The rate of increase in height did not differ for the two groups.

This study by Willett et al. [19] avoided several of the pitfalls of the previous work by Gupta et al. [18]. The subjects were randomly assigned to treatment and control groups, and the study was conducted in a double-blind manner. It should be pointed out that the authors found no statistically significant difference in weight gain between all the children who received levamisole and all the children who received a placebo. The only significant difference involved the children who were infected with *A. lumbricoides* at the beginning of the study. Those who received levamisole gained 21% more weight than those who received a placebo. Several observations can be made about these results. The P value of this part of the study was marginally significant ($P = 0.03$). Since the sample size was small ($n = 78$), a change in the status of only a few children could change the conclusion. Moreover, there is no assurance that the infected children in this group who received levamisole or the placebo were comparable in certain important respects. They were comparable for age, height, and initial weight, but they might not have been comparable in intensity of infection or incidence of intercurrent disease during the one-year study period. Because the sample size was small, a few fast or slow growers could have significantly altered the results. The variability of results in a small study group is illustrated by the observation that among children who were free of infection at the beginning of this study ($n = 68$), those who received levamisole gained 13% more weight than those who received a placebo! One would expect the weight gain to be the same for these two groups.

Stephenson et al. [20, 21] performed a longitudinal study of growth in both infected and uninfected children in Kenya. Anthropometric, clinical, and stool examinations were performed three times at 14-week intervals. All children received levamisole at the second examination. Infected children did not differ from uninfected children in percentage of expected weight gain during the first 14-week observation period. In the 14 weeks after deworming, previously infected children showed a higher percentage of expected weight gain than uninfected children. After deworming, triceps skinfold thickness increased significantly in previously infected children vs. uninfected children. Multiple regression analysis showed that, of the variables studied, infection with *A. lumbricoides* was the most important for explanation of the changes in skinfold thickness.

The studies of Stephenson et al. differ in several respects from other longitudinal studies of ascariasis and the nutritional status of children in communities where the parasite is endemic. Clinical examinations were done throughout the study; an additional measure of nutritional status, skinfold thickness, was included; and the statistical analysis was done in a sophisticated manner. Nevertheless, there is a major fault in the study design. Levamisole was given to all children so that any unknown effects of the drug would occur in both infected and uninfected subjects. As a result, treated, uninfected subjects, rather than untreated or placebo-treated, infected subjects, were used as controls. The latter would constitute a true control group. This fault makes the results difficult to interpret. In addition, the number of infected subjects in the study was relatively small; the weight

gain in treated children, although significantly different than that in untreated children, was relatively small in absolute quantity; and the study period after deworming was relatively short (14 weeks). Whether the weight gain can be sustained during and after periodic treatment is unknown.

Substantial doubt remains about the cause-and-effect relationship between ascariasis and protein energy malnutrition. In none of the above-mentioned studies, where a positive correlation is claimed, was a significant difference in weight found between infected and uninfected children before intervention. Several recent studies [11, 22] also showed no significant improvement in nutritional status after intervention. Until the putative association between ascariasis and protein energy malnutrition is proved in studies that are designed to avoid statistical error and are reproducible under a variety of circumstances, the advocacy or institution of mass treatment programs to enhance the growth and development of children in countries where ascariasis is endemic would be premature.

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Discussion: Ascariasis, Hookworm Disease, and Malnutrition

The influence of *Ascaris lumbricoides* on nutritional status is uncertain. While a few studies suggest an association between ascariasis, protein malnutrition, and xerophthalmia [1], it remains unclear whether this is a fortuitous association or a true cause-and-effect relationship. The mere presence of worms in a child does not necessarily have nutritional significance. Although it is obvious that duration and load of infection, as well as the quality of diet, are of crucial importance to the outcome of infection, these factors have not always been evaluated.

Clinical studies of children infected with *Ascaris* demonstrate malabsorption of various nutrients, including protein, fat, carbohydrate, and vitamin A [2]. Deworming alone improves absorptive function and results in significant increase in serum levels of vitamin A, an observation suggesting that round worms interfere with intestinal absorption [3]. The weight of evidence at this time, though not always consistent, supports the concept that severe ascariasis can lead to malnutrition. However, there have been no convincing epidemiologic studies indicating that ascariasis is a cause of malnutrition in poor communities containing multiple, potentially causative factors. Recent community studies [4-6] deserve critical evaluation since they may be very influential in determining public health policy.

None of the studies show a correlation between severity of infection and malnutrition in children; the available data demonstrate only that deworming may have a beneficial effect on growth of infected children. One study often cited [4] is particularly difficult to interpret since the number of subjects was small. There were no data on severity of infection, and the actual magnitude of weight change was not presented. Two additional studies [5, 6] include a larger number of subjects and report an improvement in growth rate after deworming of infected children; however, there are other problems that confound interpretation. On the basis of such limited observations, periodic deworming is being suggested as an important public health measure for combatting malnutrition in children. While heavily infected individuals may derive some benefit, mass antihelminthic treatment of all children in a community does not guarantee nutritional benefits. Indeed, in areas where infection prevalence is ~30-40%, studies of community treatment fail to demonstrate the desired effect on growth [7].

In similar fashion, there is insufficient evidence to prove that hookworm causes malabsorption or malnutrition. Some patients with hookworm infection experience weight loss, edema, and other signs of malnutrition, including depressed levels of albumin, folic acid, and vitamin B_{12} in serum, but these findings could be due to concomitant dietary inadequacies rather than to malabsorption. In contrast, iron deficiency anemia associated with heavy hookworm infection is well defined and is a serious public health problem. Whether or not a person infected with hookworm develops anemia depends on three factors: the number of worms present, dietary intake of iron, and iron reserves of the individual. The amount of blood lost is proportional to the worm load, but in communities where diets are iron deficient, even mild infection may cause significant anemia. In Mauritius, for example, mild infection is associated with severe anemia because iron intake is only 5-10 mg/day [9]. Dietary supplementation with iron corrects the anemia without the need for deworming. In western Nigeria, where iron intake is high, anemia occurs only with heavy infection [10].

There are, then, two components of therapy: antihelminthic drugs and iron. Individual patients having hookworm disease should be treated with both. However, only the most effective and economic approach is warranted for mass treatment of entire communities. Treatment of anemia due to hookworm infection with antihelminthics alone will work, but will do so slowly. A study in Puerto Rico showed that hemoglobin levels were restored by antiparasitic therapy only after 18-24 months of treatment. But clinical studies [12] demonstrate that therapeutic doses of iron produce a much more rapid response. In community studies, small daily supplements of iron alone maintain normal hemoglobin levels in subjects infected with hookworms [13]. In Venezuela, two communities with the same prevalence of hookworm infection were treated with either 60 mg of iron daily for three months or with placebo [14]. There was a signifi-

cant increase in hemoglobin levels in the group receiving iron supplement, but there was no change in the hemoglobin levels of the control community. Iron supplementation can therefore be supported as the appropriate public health approach to the control of hookworm anemia in endemic areas. The success of such a program would depend on the method selected for supplementation. There are practical problems in distribution of iron tablets, and regular intake cannot be assured unless a dietary staple can be fortified. In the absence of such a vehicle, it may be reasonable to propose that iron therapy be provided for an initial period of time to correct anemia and replete iron stores; this would be followed by periodic deworming for a sustained effect. The feasibility, efficacy, and cost effectiveness of such methods for the control of hookworm anemia need to be thoroughly evaluated in the field.

VINODINI REDDY

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Discussion: Ascariasis, Hookworm Disease, and Malnutrition

Recent field studies, although differing in design and quality, suggest that intestinal infections with *Ascaris lumbricoides* have a small and statistically significant effect on the nutritional status of young children whose diet is marginally adequate. The mechanism by which *A. lumbricoides* adversely affects growth is uncertain. Balance studies indicate that the worms restrict the full utilization of energy, protein, and certain micronutrients (such as vitamin A) by the child [1, 2]. However, it may be that ascariasis also negatively affects appetite and general well-being in addition to causing abdominal pains and that such secondary effects contribute more to poor nutrition than do direct metabolic effects of worms in the gut.

Most studies showing effects on growth involve children with light worm burdens [3]; this may be one reason why observed effects are so small. It would be interesting to know what happens in individuals with heavy infections. If new studies are undertaken, they should be conducted where infections are heavy, and great attention must be given to study design.

There is also a patent lack of accurate data on the incidence of serious complications of ascariasis, notably intestinal obstruction and the migration of worms to aberrant sites such as the common bile duct. Intestinal obstruction due to worms is said to be the most frequent cause of abdominal emergencies requiring surgery in young children in some Brazilian hospitals. The effects of migration of ascarids through the lung and the liver have not been adequately studied in humans. Much more is known about these problems in the pig where pathologic changes in tissues due to larval migration of *Ascaris suum* have been well described [4, 5]. For years pig breeders have been convinced that deworming improves the health and growth of young pigs.

Although exceptions occur, parents in most countries are genuinely concerned about *Ascaris* infections in their children; the presence of worms is not considered either benign or desirable. Experience in both Bangladesh and Kenya suggests that the desire of mothers to have their children dewormed could be used as a means of encouraging attendance at health centers and other medical facilities providing primary health care. There, deworming could be combined with immunizations, treatment of other medical conditions, growth surveillance, and health and nutrition education [6].

The prevalence of ascariasis is not being substantially lowered by present programs of improved sanitation, purified water supplies, personal hygiene, and health education. Until poverty and the crowded, unsanitary conditions that are collateral to it are eliminated, transmission of *Ascaris* will continue at high levels [7]. At the same time, several highly effective drugs are now available; these are extremely safe and relatively inexpensive. Antihelminthics used successfully against ascariasis include piperazine, levamisole, and pyrantel. However, a recent report that use of piperazine leads to the development of clinical malaria in six to 14 days suggests to the authors that suppression of malaria was a nutritional consequence of severe ascariasis [8]. The two concurrent infections apparently represented a desirable "ecologic balance" that contributed to the health of the host. However, this report and a series of similar studies by the same authors are poorly designed and, therefore, do not permit such conclusions to be drawn, although the observations do raise interesting questions [9]. It is very common for children with ascariasis to have severe attacks of malaria, and populations with high prevalence of both diseases are so numerous that it is difficult to understand how infection with *A. lumbricoides* protects against the ravages of malaria.

The time has come to evaluate thoroughly the effectiveness and health benefits of a large-scale treatment program; this should be done in an area where ascariasis is prevalent and parasite loads are high. Acquisition of valid data will require use of the best experimental design; this should include proper randomization and a placebo-treated group. Undoubtedly, reinfection would occur in the drug-treated group, but it should be possible to lower worm burdens and reduce prevalence sufficiently to produce beneficial clinical effects if there are any.

In contrast, the nutritional implications of hookworm disease are better described, and estimates of the relative amounts of blood lost from the intestines due to *Necator americanus* and *Ancylostoma duodenale* are reasonably definitive [10]. There is no doubt that heavy infections with

hookworms are an important cause of anemia, particularly in those whose iron intake, iron status, and iron utilization are all low. It is less clear whether hookworm disease causes intestinal injury and malabsorption or whether such mechanisms contribute to malnutrition in those with heavy worm burdens. The report of a "natural experiment" involving heavy infection in a group of young adults is interesting; nine months after the study there was no villous atrophy and little hypoalbuminemia, and intestinal function was normal in spite of a mean weight loss of 7 kg per person [11]. The explanation offered--that the patients were self-starved because they feared that eating would precipitate abdominal pain--is not well documented. Did the hookworms initially cause an intestinal pathology, which had disappeared by the time the patients were studied? Could these heavy infections have caused marked anorexia by a physiologic rather than psychologic mechanism? The fact that this episode led to such debilitating disease and substantial weight loss suggests that hookworm disease can indeed cause malnutrition as well as anemia.

The relationship of hookworm disease to anemia and, subsequently, to reduced productivity of workers is a subject of much interest [12, 13]. In many tropical countries, iron deficiency anemia is very common and hookworm disease remains an extremely prevalent infection. Furthermore, iron deficiency of any etiology and its relation to infection and immune function is currently attracting attention. There are now effective drugs for the treatment of hookworm infection that include bephenium, pyrantel, and mebendazole. As is the case with ascariasis, collateral efforts to improve environmental hygiene, increase construction and use of latrines, and introduce other appropriate public health measures (such as building concrete floors and increasing the use of shoes) generally do not substantially reduce the prevalence of this disease. As desirable as these efforts are in controlling hookworm infection and other diseases generated by fecal contamination, they are unlikely to have much impact if the conditions that coexist with poverty persist and the infection itself is not specifically treated.

At present, consideration should be given to major deworming programs as an effective means of decreasing worm burdens; in this way, the frequency and/or magnitude of iron deficiency anemia would be reduced, and worker productivity and general well-being would be improved. In some countries these actions might be combined with efforts to fortify foods with either iron or ascorbic acid to reduce the prevalence of iron deficiency anemia. Well-designed and well-conducted community-based programs for control of hookworm infection, including periodic antihelminthic therapy with careful prospective evaluation of effectiveness, are necessary to achieve optimal results.

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Hookworm Disease: Host-Pathogen Biology

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The hallmark of hookworm infection, a common helminthic disease, is iron deficiency anemia. The development of anemia is dependent on the intensity of infection, the species of hookworm, and the ability of the host to resist infection and to maintain adequate stores of iron. When conditions are appropriate, the incidence of anemia caused by hookworm is high and has a significant economic impact since it results in a reduction of worker productivity. Loss of blood is caused by direct ingestion of red cells and by tissue trauma produced by worm attachment and feeding. This focal trauma may involve multiple villi and is characterized by local hemorrhage, tissue cytolysis, and neutrophilic response. Although focal intestinal lesions are apparent, their significance is questionable since diffuse mucosal changes are absent in intestinal biopsies of patients with heavy hookworm infection. Short-range control measures protecting against hookworm infection have not succeeded. Development of a vaccine against hookworm infection in humans is problematic since functional protective immunity in humans has not yet been demonstrated and no suitable animal model of hookworm infection in humans is available. At present, the most effective method of intervention appears to be supplementation of food staples with iron.

Hookworm infection, and its association with anemia, has been recognized since the middle 1800s. Approximately one quarter of the world's population is infected with this helminth. The effects of the disease are not dramatic since mortality is relatively uncommon. Anemia and the resultant decrease in worker productivity are both common and chronic, a situation that leads to a prolonged loss of economic productivity [1]. Evidence of slow learning and apathy in children with significant hookworm infections has also been demonstrated. Because of these chronic effects, hookworm disease may produce substantially more damage to the health of a nation than would a more acute disease with higher mortality rates. Despite these facts, interest in hookworm has been declining, as evidenced by its omission from the World Health Organization's list of the six major tropical diseases of the world. Reflecting this trend, current research into the pathophysiology of hookworm infection in man is limited. At present, there is no suitable animal model of human hookworm infection that can be used to study the pathophysiology and immune reaction of the host. A tentative model of human hookworm infection has been developed in puppies but appears to require steroids for consistent maintenance of the infection [2]. The chimpanzee can be infected, but the scarcity and cost of this resource precludes its use [3].

Three species of hookworm infect humans: *Ancylostoma duodenale*, *Necator americanus*, and *Ancylostoma ceylonicum*. The latter species appears to be of minor importance since it is not highly virulent, rarely constitutes more than 10% of the total hookworm load, and is always found in the presence of other hookworm species [4].

Hookworm infection in humans is limited geographically because the larvae require temperatures >10 C and abundant moisture. *N. americanus* has a wider geographical distribution than *A. duodenale*, but mixed infection is common. There appears to be little competition between the two worms when both are present in the same host.

In a recent review, Hoagland and Schad [5] compared the characteristics of *N. americanus* and *A. duodenale*. The latter worm was the greater opportunist since it had the capacity to infect by both the percutaneous and the oral route. In contrast, *N. americanus* only infected percutaneously. The ability of *A. duodenale* to infect

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via the oral route may explain the greater prevalence of this worm in young children exposed to both species. A comparison of the adult worms reveals that *A. duodenale* has a shorter life span, a greater ability to arrest its development, and a higher production of eggs. However, *N. americanus* causes five to ten times less blood loss and therefore is better adapted to parasitize humans. The infective larvae of *N. americanus* have a larger, more-developed boring spine (useful for penetrating the skin) than do *A. duodenale* larvae. This morphologic difference may be partly responsible for the higher percentage of *N. americanus* that successfully complete the migratory cycle and become adults after infecting via the percutaneous route.

Life Cycle

Major research on the developmental cycle of the hookworm in the environment was done in the 1920s. The ova hatch in one or two days in aerated, moist soil at optimal temperatures of 23 C to 33 C. The rhabditiform larvae feed on bacteria and fecal material.

Studies of *Nippostrongylus brasiliensis*, a nematode parasite of the small intestine of rats, provided useful information on the ultrastructure of this larval stage. The rhabditiform larvae are well suited for energy synthesis and growth. Their intestinal tract has an absorptive structure with a well-developed layer of microvilli, and the intestinal cells contain abundant rough endoplasmic reticulum and ribosomes [6]. When these larvae moult, the old cuticle is retained as a detached sheath over the new, third-stage cuticle. At this time, the larvae, now filariform or L_3, cease feeding and stop growing. Their energy reserves, which come from endogenous stores, are primarily utilized for larval movement. The intestine of the filariform larvae then regresses. Ultrastructural examination of the intestine reveals narrow intestinal cells that have few microvilli and lack synthetic structures. The lumen of the intestine is filled with membranous whorls and lipid droplets. These features represent a lack of synthetic activity that is demonstrated by the failure of the filariform larvae to incorporate significant levels of radioactive uridine into RNA [7]. When the L_3 larvae infect a suitable host, synthetic activity resumes and the intestinal cells contain ribosomes and endoplasmic reticulum. Synthetic activity can also be stimulated in vitro by elevating the temperature from 25 C to 37 C in the presence of as-yet-undefined nutrients [7]. Although these studies were done on *N. brasiliensis*, it is probable that studies on hookworm larvae would reveal similar findings.

Hookworm filariform larvae have severe restrictions in their lateral movement and usually remain close to the area where the stool is deposited [8]. They are attracted by contact (thigmotropism), temperature, oxygen, and CO_2 and move vertically up through the soil to the surface. Under optimal conditions, the larvae may remain infective for several months; however, the death rate is highest in the first 10 days, and, under tropical conditions, 90% of the larvae die in the first three weeks.

Ancylostoma duodenale worms, faced with inclement seasonal conditions, have evolved a protective mechanism whereby the hookworm larvae may remain dormant, a phase indicated by a subsequent decrease in total output of eggs. In Bengal, larvae acquired during the rainy season of one year appear to remain dormant until just before the monsoon of the following year when they resume development and mature [9]. This phenomenon was further corroborated by the unusually prolonged prepatent periods (period from initial infection until commencement of ova production) in volunteers given *A. duodenale* infection [10]. Why *N. americanus* cannot respond to seasonal adversity by arrested development is not known.

Walking with bare feet on ground infected with larvae is the usual method of transmission. The oral route may also produce hookworm infection when *A. duodenale* larvae present on vegetables grown in fecally contaminated areas are ingested. Transmammary infection of hookworm, although well documented in seals and dogs, has not been proved significant in the transmission of hookworm disease in humans [3].

In general, larvae rapidly penetrate the skin, proceed to the lungs where they break through the alveoli, crawl up the trachea, and return to the upper small intestine where they moult and develop into mature worms. In the case of *A. duodenale*, infection not only occurs percutaneously but also by direct oral infection. Orally ingested *A. duo-*

denale worms may develop to maturity in the intestine and do not require migration through the usual pulmonary cycle. The morphology of the adult worms has been well described. Differentiation of the two species by the comparison of the mouth structures (teeth in *A. duodenale* and buccal plates in *N. americanus*) is relatively easy.

The mature worm usually inhabits the upper small intestine. With severe infections, crowding may result, and the worms may be found as low as the ileum. The attachment site of the worm is not fixed and changes every 4-6 hr so that the worm can feed and mate [11]. In the rat, *N. brasiliensis* worms travel up the intestine in response to a bolus of food [12]. The worms are often found in aggregates in the normal rat, but this activity is inhibited in the immune rat [13].

Individual worms may live five or more years, but the majority of the population dies after one or two years. Thus, chronic infection is usually accompanied by frequent episodes of reinfection.

The adult worms secrete an anticoagulant and an acetylcholinesterase [14]; the latter secretion may be useful for attachment of the hookworm to the intestine. It is not clear whether or not cytolytic enzymes are secreted into the tissue.

Studies of the dog hookworm *Ancylostoma caninum* revealed that the worms were able to attach, ingest, and digest a bolus of tissue within 10 min. The worms burrow through the lamina propria of the mucosa and may proceed to the muscularis mucosa over a period of 4-5 hr [11]. The muscularis mucosa provides an effective barrier to further penetration. The worms have a strong sucking action and will ingest a variety of substances including blood, plasma, saline, and even formalin [15]. They appear to ingest a plug of tissue, which then undergoes cytolysis in their intestine. The effect on the mucosa extends well beyond the tissue in apposition to the worm's buccal cavity. In addition, cytolysis is present in the tissue around the buccal cavity. In fact, a lesion that can involve multiple villi may develop. This lesion is characterized by focal hemorrhage, tissue cytolysis, and vigorous neutrophilic response. In chronically infected dogs, eosinophils are also found in the inflammatory exudate that collects around the worm. The above pathological findings are focal in nature; repair of these intestinal lesions proceeds rapidly and without sequelae. The worm appears to cause loss of blood by two mechanisms: direct ingestion of red cells [15] and tissue trauma that results when the worm attaches and feeds [11]. However, the pathology of hookworm infection in humans is less clear because of the inclusion of cases from areas where tropical enteropathy is endemic. In areas where tropical enteropathy is uncommon, intestinal biopsies of individuals with heavy hookworm infection do not reveal significant diffuse mucosal changes [16].

Although hookworm infection commonly occurs in humans, the significance of the disease is dependent on the intensity of the infection, the species of hookworm, and the host's resistance to infection and ability to maintain adequate stores of iron.

Clinical Aspects

In an appropriate host, larvae rapidly penetrate the skin and generally produce mild clinical manifestations (ground itch). The cutaneous reaction of the host has not been well defined immunologically. The bacteria carried by the larvae may be responsible for much of the cutaneous reaction since axenic larvae *N. americanus* produce little reaction when they penetrate the skin [3].

The clinical reaction of the host to migration of the worm through the tissues of the lung appears to be relatively mild. The pathology of these changes has been examined by use of the experimental model of *N. brasiliensis*. In these studies, the injection of living larvae into nonimmune rats incited alveolar hemorrhage and edema. Dead larvae do not produce the same changes. Most likely, these changes are due to the active movement of the larvae through the arterioles of the lung. However, the possibility that these changes are due to secreted toxins cannot be eliminated [17].

Intestinal disease during the early stages of infection may be marked by abdominal pain, intense nausea, weight loss, and moderately severe diarrhea. Initially, volunteers infected multiple times had prominent intestinal symptoms. These symptoms disappeared after the third and fourth episodes of reinfection. It was suggested that the disappearance of symptoms was associated with the concurrent rise in systemic antibody that occurred in these volunteers [14]. Local immunity could possibly limit the intestinal damage produced by

the worms, but no studies that examine this factor have been reported.

The acute changes described above are associated with the direct damage to the host produced by the migration and invasive activity of the worm. In general, however, it is rare that the host suffers any major inconvenience because of these activities.

Far more ominous are the silent bloodletting activities of the hookworm that may eventually produce iron deficiency anemia, the hallmark of this infection. The occurrence and extent of the anemia depend on a complex interplay of host and parasite, and anemia will not develop if stores of iron can be maintained. Depletion of iron stores by hookworm infection will occur faster and at lower worm burdens in growing children who have increased iron requirements and in menstruating women who have increased loss of blood than in adult males [15]. Further exploration of the relationship of folate deficiency, increased demand for iron, and immunosuppression is warranted in pregnant women infected with hookworm. Other contributory factors also influence the level of stored iron. In developing countries, most dietary iron is ingested from vegetables and cereals. Iron taken in this form is not as well absorbed as is iron obtained from animal protein. The availability of the iron for absorption is also affected by hypochlorhydria, chelation of dietary iron by foodstuffs, and the intake of vitamin C [18]. The immunity of the host may also affect the threshold at which a given hookworm infection will cause anemia [3].

It is not known whether or not humans can develop a functional protective immunity to hookworm. Such protection may affect the degree to which a given hookworm infection will cause loss of blood. Immune dogs, for example, can limit the number of hookworms that inhabit the intestine and have less blood loss per individual worm than nonimmune controls [3].

Another mechanism that may contribute to anemia secondary to hookworm infection is the shortened life of the red cell in infected patients. This decreased half-life persists after vermifuge; therefore, it is probably secondary to the anemia or associated with malnutrition [15].

The mechanisms responsible for loss of protein into the lumen of the intestine are similar to those responsible for loss of iron. Plasma directly ingested by the worm and, more important, the breach in epithelial continuity with the resultant leak of plasma from the traumatized tissue result in loss of both protein and iron. Blackman et al., using ^{131}I-labeled albumin, have demonstrated that fecal protein loss correlates with hookworm load. They concluded that there is a daily loss of 0.1 g of albumin per 100 *N. americanus* hookworms [19].

How much of the labeled protein is hydrolyzed, reabsorbed, and again available for further synthesis of albumin is not known. Furthermore, although iron deficiency anemia is a well recognized associate of heavy hookworm infection, malnutrition is not [15]. For example, in the series of patients studied by Blackman et al., there was no correlation between the concentration of serum albumin and the number of worms harbored by the patient. Similarly, field studies in South America [20] did not show any association between hookworm egg counts and levels of serum albumin. The finding is not surprising considering the multiplicity of variables that can affect this parameter. In a study of malnourished children in Bangladesh, hookworm infection was associated with a significant reduction in hematocrit but not in level of protein [21].

When poorly nourished individuals heavily infected with hookworm are nutritionally repleted, neither their worm burden nor their daily loss of blood decreases in quantity [22]. However, good nutrition may protect the individual by limiting the number of worms that complete development. In the dog model for hookworm infection, malnourished animals develop heavier hookworm infections than do normal controls given the same initial infective dose [3].

Hookworm control can be achieved by restructuring the socioeconomic and sanitational milieu of countries where the disease is prevalent. Desirable though this goal may be, its attainment is improbable. Massive programs are costly and impractical. The development of a hookworm larvae vaccine for humans might be possible. Such a vaccine has proven useful in controlling hookworm infection in puppies [3]. In older dogs presumably sensitized previously, vaccination with irradiated larvae was occasionally associated with allergic bronchospasm. At present, limited knowledge of

human immunity to hookworm infection precludes development of such a vaccine.

Immunology

It is not known whether repeated multiple exposures under natural conditions confer protective immunity in humans. However, under experimental conditions, repeated infection (four times) with small inocula of *N. americanus* produced repeated infection with no demonstrated decrease in worm load [14]. Yet, there is a rise in specific IgE antibody and IgG antibody to the secretory products of the worms. Antibody against the hookworm acetylcholinesterase is also found. These antibodies appear to play no protective role because the infection with *N. americanus* could be initiated and the cycle completed in their presence [14]. Since the intestinal secretions were not examined, the presence of local specific IgA antibody is not known. The epidemiologic curve of hookworm infection suggests that some degree of immunity although of short duration, may occur. Worm burdens are higher in children and in the elderly and are generally reduced in young and middle-aged adults [3]. Therefore, both multiple and chronic hookworm infections (as occur in nature) may be necessary for protective immunity in immunocompetent hosts. Functional protective immunity has not been demonstrated in humans under experimental conditions [8], and its role in regulation of hookworm infection in humans is still conjectural.

However, the classic animal model of immunity to nematodes demonstrates that rats infected with *N. brasiliensis* expel the mature worm two to three weeks after infection [23], although rats with iron and protein deficiencies do not efficiently expel the adult worms [24]. Expulsion appears to be a combined effort of antibodies, T-lymphocytes, and an as-yet-undetermined type of B-cell. Expulsion may be avoided or delayed by giving multiple small infections or by infecting young rats [25]. Adult worms that develop in an immune host appear to be "adapted," suggesting the possible occurrence of immune evasion. Compared with normal adult worms, adapted worms are less antigenic, less quickly expelled, stunted, and have a characteristic acetylcholinesterase isoenzyme pattern [23]. Expulsion of worms is accompanied by an increase in numbers of goblet cells, eosinophils, and plasma cells in the lamina propria [26]. Local anaphylaxis is also postulated as one of the contributory mechanisms in expulsion of *N. brasiliensis* [23]. The rodent-nematode model does not closely mirror the human reaction to hookworm. Thus, development of an animal model that closely approximates hookworm disease in humans and allows for studies of immunologic transfer is required.

Treatment

Therapy for hookworm infestation is presently more efficacious and less toxic than treatment in the past. Older, more toxic drugs such as bephenium and tetrachlorethylene are being replaced by broad-spectrum, low-toxicity antihelminthic agents like mebendazole, pyrantel, and levamisole.

Hookworm therapy is efficacious for the individual patient. However, large-scale, periodic programs of hookworm treatment undertaken without accompanying major changes in sanitation are not recommended. Based on experience with other intestinal parasites, it is likely that the treated population will be rapidly reinfected from the contaminated environment. Traditional, short-range measures used to control hookworm infection include education, the use of footwear, and the use of latrines. This approach to hookworm control has not been particularly successful in most rural areas. In India and Bangladesh, the villager will frequently walk barefoot during daily activities in his village in order to protect his shoes (a costly commodity). On reaching an embankment road or the paved roads of the city, he will again put on his shoes. Therefore, although shoes are worn, local habits may still allow for hookworm transmission. Latrines, even when present, often are poorly designed and frequently are not used.

Supplements of iron for infected individuals in endemic hookworm areas have been effective in controlling anemia [1]. Supplementation is currently the most rational and achievable intervention available for counteracting the effects of disease caused by hookworm. It has the advantage of being a cheap and effective method of treating iron deficiency anemia irrespective of its etiology. Supplementation may be provided in available food staples such as sugar or flour, depending on local preferences. A note of caution is, however, appropriate. Oral supplementation of iron in

poorly nourished Somali nomads (members of a milk-dependent culture) was associated with an increased risk of bacterial and protozoal infection [27]. These results are puzzling, since, in the iron-deficient host who is receiving oral supplements, the ingested iron would be avidly bound to transferrin and little free serum iron would then be available for use by bacteria or protozoa. Since it is not yet known whether such supplementation is associated with increased rates of infection in other populations, controlled studies that address this question are appropriate.

Although the above solutions may be effective for a short period of time, they will not effectively reduce the reservoir of hookworm. Successful long-term control demands the development of a satisfactory method of feces disposal that is well adapted to a particular culture and is locally acceptable.

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Hookworm Disease: Nutritional Implications

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Iron-deficiency anemia resulting from intestinal blood loss is the major consequence of hookworm infection. Development of the anemia can be prevented, and it can be treated by administration of iron. Hypoproteinemia, often associated with hookworm infection, may be the result of either protein malnutrition or increased intestinal loss of protein. It is unlikely that the worms cause diffuse morphologic or functional alterations of the intestine. Fortification or supplementation with iron is a practical method to control hookworm disease in endemic areas.

Hookworm infection is widely prevalent, affecting almost a quarter of the world's population [1, 2]. This disease is a frequent cause of iron-deficiency anemia [3] and related poor physical performance [4]. Various nutritional deficiencies coexist in many individuals with hookworm infection, and the relative importance of this infection to nutritional changes associated with it remains ill-defined [5, 6].

The major nutritional consequences of a parasitic infection on the host are the effects on the intake and digestion of food, on absorption of or competition with the host for the nutrients, and on nutrient losses from the gastrointestinal and urinary tracts and the skin, or through increased catabolism [7]. In the case of hookworm infection in humans, many of these parameters have been inadequately studied. It is generally accepted that iron-deficiency anemia resulting from intestinal blood loss is the most important outcome of hookworm infection [3, 6, 8]. To a lesser extent, loss of protein from the gastrointestinal tract may ensue. Although several studies showed the coexistence of morphologic and functional changes in the intestine with hookworm infection, the role of the worms in the causation of these abnormalities is disputed [9]. Little is known about the effect of the host's nutritional status on the outcome of hookworm disease. For this review we have concentrated on the nutritional aspects of infection of humans with *Ancylostoma duodenale* or *Necator americanus*, and, wherever there is paucity of data on human infection, we have referred to work on *Ancylostoma caninum*, *Ancylostoma braziliense*, and *Ancylostoma ceylanicum* infections in dogs and *Nippostrongylus braziliensis* infection in rodents.

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Iron-Deficiency Anemia

The role of hookworms in causing iron-deficiency anemia has been studied extensively by Roche and Layrisse [3] and has been summarized in subsequent reviews [6, 8]. Adult hookworms live in the upper small intestine, usually in the jejunum, where they attach to the epithelium [10]. A portion of the intestinal mucosa of the host is actually sucked into the worm's buccal cavity, thus allowing the worm to ingest tissue fluid and blood [11, 12]. The hookworms frequently move around and reattach themselves to other areas of the intestine, but the initial leakage of blood and tissue fluid may continue [11, 12]. Most of the blood ingested by the worms is later expelled [13], thus becoming available for reabsorption by the host. It is estimated that each *A. duodenale* worm causes the daily loss of ~0.15 ml of blood (range, 0.05–0.30 ml) [6, 14] and each *N. americanus* worm ~0.03 ml of blood (range 0.01–0.04 ml) [3, 6, 15]. Expressed as a function of egg output in feces, the estimated daily blood loss is 4.47 ± 1.16 ml/1,000 eggs per g of feces in the case of *A. duodenale* [14] and 2.14 ± 1.01 ml/1,000 eggs per g of feces in the case of *N. americanus* [15]. The average daily blood loss may thus range from 0.03 to 8.0 ml in a patient with a light infection (i.e.,

<2,000 eggs per g of feces) with *N. americanus* to well above 60-100 ml in a patient with a heavy infection (i.e., >13,000 eggs per gram of feces) with *A. duodenale*. Since the bleeding generally occurs in the upper small intestine, the hemoglobin iron is available for reabsorption: 20%-80% (mean, 36%-40%) of the iron may be reabsorbed and reutilized [3, 16-18]. Thus, in the case of *A. duodenale*, a fecal loss of 0.023 mg of iron per worm or 0.7 mg of iron/1,000 eggs per g of feces occurs in a person with normal hemoglobin values (15 g/dl). However, the iron loss would diminish as the person becomes more anemic [3].

Ecologic factors that control intestinal blood loss have not been well studied in humans. In dogs younger *A. braziliense* worms cause greater loss of blood than do older worms [19]. It is not clear whether the similarity of the results for blood loss in the various studies of humans reflects a "steady state" of worm loss and reinfection. Crowding of worms is found to reduce blood loss per worm; in dogs the blood loss per worm is greater in mild infections with *A. caninum* and *A. braziliense* than in severe infections [20, 21]. This pattern noted in some studies of humans as well [22, 23]. Since crowding also results in reduced egg output per worm [24], it is likely that the blood loss expressed on the basis of egg output per g of feces would remain steady.

Although blood loss in hookworm infection is predictable, the development of anemia is influenced by the status of the host in regard to iron. Thus, in persons with adequate iron stores, anemia may never develop [3]. Roche and Layrisse calculated that it would take an adult Venezuelan farmer who weighed 60 kg, had normal blood hemoglobin (15 g/dl) and iron reserves (900 mg), and was infected with 700 *N. americanus* for 220 days to show a decrease in concentration of blood hemoglobin. Following the slow development of anemia, a new steady state would be reached in an additional 800 days, when iron utilization would again match iron losses [3]. In most areas of the world where anemia due to hookworm infection is prevalent, the dietary iron intake is seldom low [25]; however, the iron is not readily available for absorption [25-27], and intestinal abnormalities that reduce absorption of dietary iron often exist [28]. The anemia can easily be corrected by iron replacement without the removal of the worms (29, 30). Alternatively, removal of the worms would lead to gradual restoration to normal of the hemoglobin values by absorption of available dietary iron [3].

Intestinal Protein Loss

Hypoproteinemia with hypoalbuminemia often accompanies anemia in patients with hookworm infection [9, 30]. The degree of hypoproteinemia correlates with the degree of anemia [9]. The relative contributions of worm-induced intestinal protein loss and diminished dietary protein intake in causing the hypoproteinemia have not been carefully studied. While the worms feed in the intestine, variable amounts of plasma and extracellular fluid along with erythrocytes may be lost into the intestinal lumen [11, 12]. Loss of protein into the intestine has been studied by the measurement of fecal nitrogen excretion [31, 32] and by the use of proteins labelled with ^{131}I [30, 33] and ^{51}Cr [23, 34, 35]. While the fecal nitrogen excretion was not markedly different between patients with mild infection (<200 worms) and those with no infection [31], fecal nitrogen excretion was increased in patients with heavy infection [32]. Studies by Gilles et al. [30] and Blackman et al. [33] with ^{131}I-labeled albumin revealed that the intestinal protein loss was increased with heavy hookworm infection. However, there are methodologic problems in studies with radioiodinated proteins [36]. Using ^{51}Cr-labeled albumin, Gupta et al. [34] found that protein loss in patients with mild infection (<1,340 eggs per g of feces) was not greater than that in controls [34], whereas Areekul et al. [23, 35] showed that there was increased intestinal protein loss that correlated with the worm load. Gilles et al. [30] and Areekul et al. [35] showed that the protein loss exceeded that from blood loss alone, but the truth of this observation has not been adequately determined with the use of multiple, simultaneously labeled plasma proteins.

Although there is increased plasma leakage into the intestinal lumen, it is most probable that proteins can be digested and reabsorbed [5]; in most instances it is unlikely that the protein loss would exceed the capacity of the remaining intestine to digest and reabsorb the protein. It has been suggested than an inadequate protein intake is often responsible for the hypoproteinemia [37], and this view is supported by the increase in serum albumin

that results from institution of an adequate diet, despite continuing worm infection [37, 38].

Intestinal Structure and Function

Several investigators have studied the morphology and absorptive function of the small intestine of patients with hookworm infection [9, 30, 37, 39–45]. Absorption of D-xylose, fat, vitamins A and B_{12}, and folic acid have been determined. In a study of 14 hookworm-infected Puerto Rican patients, Sheehy et al. [39] observed abnormal intestinal histology and impaired absorption of D-xylose and fat; many of these parameters improved following deworming. Tandon et al. [40, 41] and Chuttani et al. [42] have also demonstrated similar intestinal morphologic abnormalities and functional defects in patients in India, but they were unable to correlate these changes with the worm burden or to demonstrate consistent improvement after deworming. Furthermore, these same abnormalities were observed in the control population [41]. It may be noted that in both Puerto Rico and India tropical enteropathy is highly prevalent and is the most likely cause of the intestinal abnormalities observed [28]. This view is supported by workers in other areas of the world where these intestinal abnormalities have not been found in patients infected with hookworm [43–45].

Vitamin B_{12} levels in serum are usually normal in subjects with hookworm infection [36, 39, 43], but Saraya and Tandon [41] found low levels in 43% of their patients as compared with 27% of a control population. Absorption of vitamin B_{12} is also normal in patients infected with hookworm [39, 43, 45]; however, they often have a low level of folate in serum [36, 41, 43, 46, 47], but it is not clear whether this finding is related to the worm, to low dietary intake of folate, to impaired absorption of dietary folate [36, 43], to protein deficiency, [36], or to iron deficiency [46, 47].

Mayoral et al. [37] have suggested that the intestinal abnormalities result from protein malnutrition. In a careful study of a small number of patients, they noted regression of intestinal abnormalities after protein repletion without worm removal. Severe iron deficiency has also been implicated as a cause of intestinal abnormalities in children [48] but not in adults [49].

These studies indicate that, although focal damage of the intestinal mucosa due to feeding activities of the worms is common in patients infected with hookworm [11, 12], it is very unlikely that the hookworms directly cause any diffuse intestinal morphologic or functional abnormalities.

Other Nutritional Consequences for the Host

Both decreased appetite and increased food intake have been described as consequences of a hookworm infection [50], but there have been few systematic reviews of the dietary intake of people with this disease [3]. Studies with rats have shown that infection with *N. braziliensis* leads to diminished intake of food [51].

Little is known about the effect of hookworms on the digestive function of the host. One report claims that tryptic activity is reduced in the duodenum in humans with hookworm disease [52]. Even though there is no study of the quantitative nutritional requirements of the adult hookworm [53], it is generally believed that the worms are unlikely to reduce the host's nutrient supplies significantly. There is little information on the degree to which hookworm disease affects supplies of the micronutrients zinc, copper, and cobalt, although it has been suggested that zinc losses would be considerable [5]. Few studies have been done on the metabolic consequences of hookworm infection in humans [54].

Impact of the Host's Nutritional Status on Worm Infection

There have been few careful studies to determine how the nutrition of a human host affects hookworm infection. A study in Guam indicated that malnourished children developed more serious consequences from acute anemia caused by hookworms [55]. Lunn [56] found that hookworm infection was more often associated with kwashiorkor than with marasmus. The importance of the iron status of the host on the development of hookworm anemia has already been discussed.

Nutritional deficiency has been found to lead to a heavier worm burden in dogs infected with *A. caninum* larvae [57]. Immune-mediated spontaneous expulsion of worms in the course of *N. braziliensis* infection in rats was reduced by the host's diminished intake of dietary protein [58]. This

change is believed to be due to the decreased immune function resulting from protein malnutrition [59]. Because there is no clear evidence of immune-mediated worm expulsion in hookworm infection in humans [6], the relevance of these studies to the clinical situation remains questionable. The repletion of protein or iron in humans infected with hookworm did not lead to spontaneous worm expulsion or reduction in egg output in the stool [37].

Consumption of a chemically defined diet led to an increase in intestinal abnormalities in mice infected with *N. braziliensis* [60]. Inadequate intake of protein and iron has been found to reduce the antihelminthic effect of benzimidazoles in rats infected with *N. braziliensis* [61].

Public Health Measures: Nutrition Programs

Prevention of hookworm infection can be achieved by improvement in sanitation and proper disposal of human excreta [50, 62]. Promotion of the use of footwear and education of the populace have also been recommended as control measures [8, 50]. However, in most communities where hookworm disease is prevalent, these measures may not be economically feasible. Since the major consequence of hookworm infection in humans is iron-deficiency anemia and since its development can be prevented and treated with adequate oral intake of iron, fortification of food with iron is a practical approach in the control of anemia due to hookworm [26]. The particular food to be fortified may have to be determined for each community [26, 63]. Iron supplementation may also be a practical approach [26], as in the case of schoolchildren and factory workers. Iron supplementation for workers on Indonesian rubber plantations led to a decrease in anemia and an improved physical performance [64]. Such programs, of course, cannot control other adverse effects of hookworm disease, such as a reduction in total dietary intake of nutrients.

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Amebiasis: Host-Pathogen Biology

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Invasive amebiasis caused by *Entamoeba histolytica*, and particularly amebic liver abscess, is a major public health problem in Mexico and some other countries because of the high incidence and mortality of this disease. This paper first discusses the pathogenic effect of *E. histolytica* and the defensive response of the host and then reports studies concerning the experimental induction of protective immunity to amebic infection. The pathogenic effect of *E. histolytica* is probably initiated by a lectin-mediated adhesion of trophozoites to target cells; the adhesion is followed by cytopathic activity and phagocytosis by the ameba. The defensive response is characterized by humoral and cellular immune reactions. Humoral immunity manifests itself by specific circulating antibodies useful in the diagnosis and seroepidemiology of amebiasis. Cellular immunity is shown by several characteristic reactions. Experimental induction of immunoprophylaxis with *E. histolytica* antigens represents the first stage in the development of a vaccine against *E. histolytica* for use in humans.

Infection caused by *Entamoeba histolytica* occurs throughout the world. It is not an exclusively tropical parasitosis, for it has been found in all climates, including subpolar regions [1]. It is, rather, an infection that primarily affects undernourished populations that live in poor sanitary conditions and lack adequate education in hygiene; it is, therefore, one of a number of diseases related to poverty and ignorance. Most of the individuals infected with *E. histolytica* are healthy carriers of this protozoan. The ratio of carriers to patients with clinical evidence of invasive amebiasis is difficult to estimate and varies in different populations. We estimate that in Mexico this ratio is one patient with invasive amebiasis for every four or five asymptomatic carriers.

One of the investigations undertaken by our group was that of distinguishing between avirulent and virulent strains of trophozoites isolated from asymptomatic carriers and from patients with active amebiasis, respectively. Light and electron microscopy showed no morphologic differences between strains [2, 3]. However, several biological differences were found. (*1*) Concanavalin A agglutinates trophozoites of pathogenic strains and does not agglutinate carrier strains [4]. (*2*) Trophozoites of pathogenic strains can ingest human red blood cells in greater quantity and more rapidly than those of carrier strains [5]. (*3*) Intrahepatic inoculation of hamsters with trophozoites from carriers does not produce lesions [6], but inoculation with pathogenic strains produces amebic abscesses [7].

Moreover it has been recently found that pathogenic strains of *E. histolytica* have an isoenzyme electrophoretic pattern different from that of nonpathogenic strains [8]. This finding may provide another useful procedure for differentiating between virulent and avirulent strains. Although it is well known that some strains of *E. histolytica* are avirulent and that others have different degrees of virulence, it is also true that the degree of virulence of one cultured strain may vary spontaneously and can be artificially exacerbated. However, we do not know the intrinsic factors that determine the pathogenic activity of the ameba, nor do we know whether a carrier strain can become pathogenic.

Several criteria have been used for assessing the incidence of invasive amebiasis in a given geographic area. One useful index for this purpose is the number of liver abscesses recorded in the area. This index is useful because liver abscesses are identified with relative ease by either clinical data or postmortem studies [9]. Intestinal amebiasis, on the other hand, is not as useful for determining the incidence of invasive amebiasis because of the difficulties involved in diagnosing this infection.

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Another index for evaluating the incidence of amebiasis is seroepidemiologic data, the value of which has been recently demonstrated and will be discussed in this paper.

In Mexico the incidence of amebic liver abscess is very high, and the disease has a poor prognosis [9, 10]. We still have no adequate explanation for these facts. Amebic liver abscess is found in ~ 2% of all adult patients and in 3%–4% of autopsies performed in general hospitals; liver abscesses are more frequent in men than in women by a ratio of 3 : 1 [11]. During the last century when chemotherapy was not yet available, mortality from amebic liver abscess was 80% [12]. Although this rate has declined considerably because of improved diagnosis and treatment, amebic liver abscess is still a significant public health problem in the developing nations of the world. Malnutrition, particularly in children, is one factor that contributes to increased mortality [13].

Intestinal amebiasis can be either benign or severe. The benign forms occur as acute diarrhea and dysentery and are more frequent in children, in whom *E. histolytica* is the etiologic agent for these acute episodes in 2%–14% of cases [14]. The severe forms are fulminating amebic colitis, colon ameboma, and amebic appendicitis; these have a mortality rate that varies from 20% to 54%. These severe forms of colonic amebiasis are seen 10 times less frequently than amebic liver abscesses in Mexico [15].

Pathogenic Activity of *E. histolytica*

The virulence of *E. histolytica* has been studied in vivo and in vitro by several investigators. The cytopathogenic effects of live trophozoites in vitro have been described for chick embryos [16], leukocytes [17], HeLa cells [18], rabbit kidney cells [19], MDCK epithelial cells [20], polymorphonuclear leukocytes, and hamster ovarian cells [21]. In an in vivo model, we have shown that amebic liver abscesses can be produced in hamsters by inoculating them with axenic cultures of *E. histolytica* and thus have demonstrated that this parasite has intrinsic pathogenic activity [22]. Similarly, Diamond et al. also produced amebic abscesses in the cecum of newborn guinea pigs by injection of axenic cultures [23, 24].

The cytopathogenic mechanism of *E. histolytica* is not yet well understood, although considerable progress has been made. The first step in the process of tissue invasion seems to be the adhesion of trophozoites to epithelial cells [25, 26]. Attachment may be mediated by a lectin on the surface of the parasite cell [27]. Immediately after the trophozoites establish contact, severe cytopathic alterations become apparent. Using cinemicrography, we have demonstrated these changes in colonic and hepatic cells and cell fragments of hamsters; using the same method, Ravdin et al. [28] observed the same changes in hamster ovarian cell monolayers. Phagocytosis begins almost simultaneously with the CPE, and destruction of tissue takes place within a few hours [25, 28]. In our experiments, we observed rapid motility of trophozoites, their obvious affinity for epithelial cells, and the resistance of connective tissue to amebic attack. It was also possible to observe the initial phases of tissue invasion and the production of typical lesions in whole hamster cecum and liver incubated in culture medium [25]. These results indicate that two mechanisms have a role in the pathogenic action of *E. histolytica:* first is the cytocidal effect exerted by viable trophozoites adhering to target cells; second is active phagocytosis by the ameba. In addition, these studies indicate the importance of the role that the external membrane of *E. histolytica* plays in the pathogenic action of this parasite.

Extracts of *E. histolytica,* prepared by lysis of trophozoites, exert a CPE on cultured mammalian cells; this effect is manifested by cell-rounding and agglutination of cells by detachment of the monolayer [28–30]. The CPE is neutralized by immune serum [31] and by serum α-globulins [28, 29, 31]; it is reversible and not lethal [28, 31]. Extracts from the most virulent amebic strain show a greater cpe than do extracts from less virulent strains [31]. Certain properties suggest that this amebic "toxin" has a lectin-like activity [30], although this toxin is different from the lectin related to trophozoite adhesiveness [32]. A hemolytic effect on red blood cells by extracts of *E. histolytica* has also been described for different species [33]. The participation of these cytotoxic substances in the pathogenic action of the whole, viable trophozoite must be evaluated by further research.

Host Defense Reactions Against *E. histolytica* Invasion

Several recent studies have shown that humoral and cellular immune reactions participate in the host's defense against invasive amebiasis. Leukocyte and macrophage defense mechanisms, although not yet fully characterized, probably take part also.

Humoral immunity. The humoral immune reaction is identified by the presence of specific circulating antibodies, which are generally detected in patients one week after the onset of symptoms. In experimentally infected hamsters, antibodies are identified one week after inoculation. Most antibodies are found in the IgG fraction [34, 35] and appear to belong to subclass 2 [36]. Although it is probable that circulating amebic antigen is present during some phases of invasive amebiasis [37], circulating antigen-antibody complexes have not been found in patients with amebic liver abscesses [38]. The lack of these complexes is undoubtedly one of the reasons for the absence of immunopathologic lesions from patients with invasive amebiasis.

In addition to characterization of the humoral response, the identification of specific circulating antibodies has two practical applications: the diagnosis of invasive amebiasis and the seroepidemiology of amebic infection. The diagnostic usefulness of antibody detection is based on the fact that such antibodies are found in > 90% of patients suffering from amebic liver abscess or other severe forms of invasive amebiasis. Moreover, our experience shows that antibodies to *E. histolytica* are identified in only a small percentage of population with no clinical evidence of amebiasis (6%) and in the population of asymptomatic carriers of *E. histolytica* (6.6%) [39].

Of the different methods employed for detection of antibody to *E. histolytica* we found that counterimmunoelectrophoresis, which was developed in our laboratory, and indirect hemagglutination are the most sensitive and specific tests [39, 40]. The results of both tests correlate for most cases. Our experience with the enzyme-linked immunosorbent (ELISA) [41] assay is limited, but our impression is that results are similar to those obtained by the other methods.

The usefulness of detection of antibody to *E. histolytica* in the seroepidemiology of amebic infection is based on the fact that antibodies persist in serum after invasive amebiasis is cured [42] and probably also after subclinical amebic infections. Seroepidemiologic surveys carried out by several investigators in different geographic locations have shown the value of this method [43, 44]. A survey of this sort was conducted in the population of Mexico; it showed that the average frequency of antibody to *E. histolytica* among the total population sampled was 5.95% (range, 2.53%–9.95%). The survey took into account economic differences among various parts of the country and included 19,442 individuals living in 48 different localities [45]. This survey demonstrated that amebiasis is highly endemic in Mexico and that antibody to *E. histolytica* occurs in persons of all ages, with a slight predominance in children of school age. It also showed that in areas where the frequency of amebiasis is high, there are apparently healthy individuals with antibody titers similar to those recorded in patients with invasive amebiasis. Finally, it was observed that overcrowding and poor sanitary conditions in some communities and the lack of education in hygiene foster the dissemination of amebiasis. Although we did not determine the nutritional status of the individals in this survey, it is well known that malnutrition is associated with poor sanitary conditions in Mexico.

An important controversial point concerning circulating antibodies to *E. histolytica* is whether or not they have any protective effect, or whether they are only by-products of invasion by *E. histolytica* [46]. Studies by our group have demonstrated the following. (*1*) Immune human serum and γ-globulin obtained from this serum inhibit the growth of *E. histolytica* in vitro [47], and the same serum neutralizes amebic pathogenicity [48]. (*2*) Immune human serum and antiamebic γ-globulin are capable of killing 90% of trophozoites of *E. histolytica* within 60 min [49, 50]. (*3*) Absorption of immune serum, or the Ig fraction with *E. histolytica* trophozoites or antigen obtained from a trophozoite homogenate, suppresses this cytopathogenic effect [51]. (*4*) Immune human serum partially protects hamsters against the effects of intrahepatic inoculation of virulent *E. histolytica* [52].

Another factor that may contribute to localized defense against *E. histolytica* is intestinal secretion of IgA. This immunoglobulin inhibits intestinal

absorption of antigens [53, 54], and its role in local defense against enterobacteria, particularly against *Vibrio cholerae* and enterotoxigenic *Escherichia coli* [55] has been demonstrated. Furthermore, coproantibodies have been found in 79%–80% of patients with intestinal amebiasis [56, 57]. The ratio of IgA to other immunoglobulins in coproantibodies, as well as their protective effect against amebiasis, has not been determined. Lastly, *E. histolytica* is capable of activating the alternate pathway of complement [58], as are other protozoans [59]; through this mechanism, sera lacking antibodies to *E. histolytica* are capable of destroying trophozoites. This mechanism may be important in nonspecific host defense against amebic infection. A recent study supports a substantial role played by complement in the defense mechanism. Hamsters treated with a cobra venom factor for reduction of the amount of circulating complement before inoculation with amebas developed more severe hepatic lesions than did intact control groups [60].

Cellular immunity. Of the different functional assays of cellular immunity, intradermal reactions against amebic antigen and inhibition of macrophage migration were selected for study by our group.

The intradermal reaction to a standardized axenic ameba antigen was generally negative during the initial phases of amebic liver abscess. Tests against other antigens such as streptokinase, streptodornase, and purified protein derivative yielded positive reactions during this phase. Negative results cannot be attributed to a decrease in circulating T lymphocytes, because there was no abnormality in the population of lymphocytes forming E-rosettes. On the other hand, most patients had positive intradermal reactions to amebic antigen during the late stage of the disease and after convalescence [61–63]. Testing for inhibition of migration of macrophages was also negative during the initial stages of amebic liver abscess in both humans and hamsters. The test yielded positive results after the patient was cured. However, antibodies to *E. histolytica* were detected in the sera of patients and hamsters in the early as well as in the late stages of the disease [61, 64]. The absence of cellular immunity early in amebiasis and its appearance during later stages suggests a state of transient anergy, such as that described for other infectious diseases [65].

Finally, a recent study showed that a subcellular antigenic fraction from *E. histolytica,* which we have named lysosomal antigen, induces blastogenic transformation of lymphocytes in patients with amebic liver abscess [66]. This transformation was observed both in the early stage of the disease and in the months after convalescence, an observation indicating that sensitization of lymphocytes by *E. histolytica* antigens may occur in the early clinical stages and that there is some cellular memory of this process in late stages.

The results described here indicate that circulating antibodies, complement, and cell-mediated immunity participate in the specific host-defense against invasion by *E. histolytica*. Events in the sequence of immune reactions suggest that the primary response in the acute stage of the amebic infection depends on humoral immunity and that cellular immunity develops afterwards. This pattern may indicate a role for cell-mediated immunity in resistance to reinfection by *E. histolytica.*

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Amebiasis: Nutritional Implications

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Studies on the role of nutrition in amebiasis in humans and experimental animals are meager. Some reports suggest that malnutrition of the host increases the incidence of infection and potentiates the severity of the disease. Others suggest that malnutrition protects the host against invasion. A few reports indicate that dietary regimens can alleviate symptoms and even eradicate the parasite. Others doubt a correlation between diet and rate of infection or disease manifestations. The problem is complex because the ameba is influenced by its own diet, which in turn depends on the host's diet, the bacterial flora of the gut, and coexisting infections. The host is variously altered by dietary depletions and supplementations, which affect susceptibility and resistance, and by the presence of other disease conditions. Carefully designed and executed studies of infections in humans and experimental animals, combined with studies in vitro of the nutritional requirements and physiology of the parasite, are needed for definition of the influence of host nutrition in amebiasis.

Amebiasis, as defined by a World Health Organization (WHO) Expert Committee [1], denotes the harboring of *Entamoeba histolytica*, with or without clinical manifestations. The Committee, recognizing both that the parasite may sometimes invade tissue without producing symptoms and that infection without tissue invasion is common but indistinguishable from infection with asymptomatic tissue invasion, classifies amebiasis as either asymptomatic or symptomatic. Symptomatic amebiasis is subdivided into two principal categories: intestinal and extraintestinal. Lesions due to *E. histolytica* have been reported in nearly every organ in the body.

The situation is further complicated. At one time, all *Entamoeba* that were isolated from humans and formed four-nucleated cysts in their life cycle were considered one species. Today at least three well-characterized entities that form these cysts are recognized: *Entamoeba histolytica* (large race), the pathogen; *Entamoeba hartmanni* (small race), of doubtful virulence; and *Entamoeba histolytica*-like amebae (low temperature strains), also of doubtful virulence. Many of the earlier reports fail to distinguish among these amebae.

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Some workers differentiate between large and small races but consider both to be potential pathogens. Some investigators today, despite mounting evidence to the contrary, consider *E. hartmanni* and *E. histolytica*-like amebae to be strains of *E. histolytica*. I view them as separate entities.

Animal experimentation is of limited usefulness because, with the possible exception of the new world monkeys, all three states of amebiasis as they occur in humans; commensalism, intestinal tissue invasion, and extra-intestinal invasion cannot be induced in any one species.

Nutritional interactions between the host and the parasite have received relatively little attention from students of amebiasis. Only a handful of reports have appeared on the role of diet in the production of amebic lesions in experimental animals. Many of these were prompted by the need for suitable animal models for chemotherapeutic trials.

As for studies of human nutrition in amebiasis, even fewer reports are available. Brandt and Perez-Tamayo [2], writing on the pathology of human amebiasis, state: "The influence of nutrition in human amebiasis has been accepted more by reiteration than by demonstration. There are only few studies suggesting a role for nutritional factors in both the existence and severity of the disease in man, and they are all epidemiological in nature." The report of the WHO Expert Commit-

tee [1] briefly mentions the possible role of nutrition in altering the pathogenicity of amebae in experimental animals. Not one of the 30 research proposals included in the report deals directly with nutrition.

Let us now consider some of the available information on the nutritional interactions of host and parasite in amebiasis from two aspects: human disease and animal experimentation.

Some of the literature that I discuss here is considered classic and has been quoted repeatedly. In many instances, the quotations appear to have been taken from other than the original publication; after several cycles of this process, the original is somewhat distorted. What follows is my own direct analysis of each of the works cited, and I am responsible for any error or misinterpretation. The publications of Frye [3] and Scrimshaw et al. [4] provide additional reviews and interpretations of the role of nutrition in amebiasis.

Influence of Diet on the Incidence, Nature, and Severity of Amebiasic Disease

Malnutrition compromises the host (synergism). The studies of Elsdon-Dew [5–7] on the role of diet in human amebiasis deal with three populations in Durban, South Africa: Europeans, Indians, and native Zulus. In the European population, dysentery was rare and extraintestinal amebiasis, such as liver abscess, was practically unknown. Among the Indians, dysentery was also rare, but liver abscess was not infrequent. In the Zulu population, acute fulminating amebic dysentery was extremely common, and extraintestinal amebiasis was frequent. The highest incidence of infection and invasive disease was found among the lower- and no-income groups of the Zulus.

Although the three populations intermingled in their daily lives, the Europeans lived apart in areas of good housing and sanitation. In Cato Manor, a notorious slum and an area in which the highest incidence of invasive amebiasis occurred, Zulus and Indians lived in close association, in substandard housing (shacks), without adequate water supplies or sewage disposal. Nevertheless, invasive intestinal amebiasis was extremely common among the Zulu people only; it was rare among the Indians. The concept that diet could account, in part, for these observed differences appeared in the first of Elsdon-Dew's series on amebiasis in Africans [5] and was developed in subsequent reports [6, 7]. The Europeans ate a balanced diet, and the Indians ate curries and rice supplemented with green vegetables. The diet of the Zulus consisted almost exclusively of maize, supplemented in rare instances by meat or vegetables. Milk, part of the diet of their rural kin, was not available to the urban Zulus. Noting the association of maize diets and amebiasis throughout the world, Elsdon-Dew [5] suggested that factors essential for protection of the bowel wall against amebic invasion may be absent from maize. Later [7], he suggested that diet might effect a change in the bacterial flora of the intestine that, in some unknown manner, causes *E. histolytica* to become invasive. In recent years, bread has replaced maize in the diet of the Zulus [7], but this change is of little consequence because the relationship probably involves the eating of high carbohydrate-containing cereals to the exclusion of nearly all other food. In a more recent publication [8], the Durban investigators considered rapid fecal transmission of the parasite from person to person a major factor in the high incidence and severity of amebiasis among the Zulus. They attached less importance to dietary deficiences because the occurrence of disease has not been related to any specific form of malnutrition. However, the authors conceded that changes in the bacterial flora of the gut could play a role.

Several clinical studies mention malnutrition as a factor predisposing to amebic disease and enhancing the severity of clinical symptoms. However, malnutrition observed in patients with amebic colitis may be a result of the disease itself. Individuals, especially those with intermittent diarrhea, may have symptoms for a year or more before seeking medical attention. Information elicited from the patient regarding dietary habits is the only means for determining the individual's nutritional status prior to the onset of symptoms. A few examples of these studies are presented.

Lewis and Antia [9], in a study of 295 cases of amebic colitis in Ibadan, Nigeria, noted that malnutrition was a factor predisposing to infection and leading to increased mortality. They did not note the type of malnutrition. In Mexico City Gutiérrez-Trujillo [10] observed advanced malnutrition in 76% of 439 cases of intestinal amebiasis in children seen at a pediatric hospital. Only 5.5% of the infants received mother's milk. In another study of hepatic amebiasis in children by the same

author [11], all of 181 patients were in a state of malnutrition on admission. Rajasuriya and Nagaratnam [12], in a clinical study of hepatic amebiasis in Ceylon, elicited dietetic histories from 79 patients. Of these, only 23% ate an adequate diet, i.e., three meals per day comprised of rice or flour preparations, two or three vegetables, green leaves, some animal protein daily, and milk, butter, and fruit. The diets of 50% of the patients were deficient in protein, but otherwise adequate. Twenty-seven percent lived on diets poor in protein and generally inadequate. Thus, approximately 77% subsisted on inadequate protein diets. The authors commented that the predominantly carbohydrate nature of Ceylonese diets was probably an additional factor causing luxuriant growth of the parasite in the gut. Alcoholism as a predisposing factor in liver abscess was also discussed. The chronic alcoholic eats sparingly, often missing meals, and his diet is apt to be deficient in protein. The reduced dietary intake plus the hepatotoxic effect of alcohol could make the liver much more susceptible to invasion by amebae.

Dogs have been used extensively in studies of enteric amebiasis. Faust et al. [13] reported that dogs resistant to amebic infection when fed a balanced ration were more readily infected and exhibited more consistent dysenteric symptoms when fed canned salmon exclusively. The observation that some dogs fed only canned salmon developed dysentery in the absence of apparent infection with *E. histolytica* led Artigas and Beaver [14] and Villarejos [15] to examine this phenomenon. They learned that a salmon diet alone could produce a dysenteric syndrome accompanied by histopathologic changes in the colon [14]. Moreover, when present, amebae were not primary tissue invaders, although they may have aided in the causation of symptoms [15].

Taylor et al. [16] showed that guinea pigs and rats fed with a specially formulated guinea pig diet displayed relatively high rates and enhanced severity of infection with *E. histolytica*. In contrast, a specially formulated ratbreeder diet partially suppressed infection in guinea pigs, whereas it enhanced infection in rats. The authors were able to conclude only that diet influences the course of amebic infection in rats and guinea pigs. The conspicuously low fiber content of both diets may have been partly responsible for the general intensification of the infections. Presumably, such diets reduce bowel motility, thereby increasing the length of time required for the passage of bowel contents. In turn, this slowing of function might afford the amebae more time for colonization and tissue invasion.

Lynch [17], seeking an explanation for why guinea pigs fed a synthetic diet are more susceptible to infection with *E. histolytica* than are those fed a commercial guinea pig diet, found that the synthetic diet caused histologic alterations in the cecal mucosa. Lynch postulated that the synthetic diet conditioned the wall of the cecum to permit invasion by the symbiotic (sic) amebae and bacteria. Moreover, Lynch suggested that diet, apart from any deficiences, might cause tissue disturbances in specific organs for which a given parasite has an affinity and that these disturbances could predispose the tissues to infection.

Ross and Knight [18] studied the influence of protein-deficient diets and low-protein, high-carbohydrate diets on infections with *E. histolytica* in weanling rats and reported that: (*1*) protein-deficient rats were more susceptible to infection, and those infected had more cecal ulcerations; (*2*) carbohydrate supplementation, although it enhanced susceptibility, tended to suppress or control tissue invasion, as was evidenced by a reduction in the number of ulcers in infected animals.

Rao and Padma [19] conducted a study on the effects of host nutrition on the susceptibility to infection and on the immune response to amebic antigen in rats. The results of their experiments were similar to those reported by Ross and Knight [18]. Animals fed a low-protein, vitamin-deficient diet showed increased susceptibility, as measured both by the number of animals infected and by the severity and even fatality of disease. By contrast, in rats fed an adequate diet the incidence of infection was half as high, and the lesions that developed were negligible. Immunized but uninfected rats on the deficient diet showed significantly lower indirect hemagglutination titers than animals fed adequate diets. While acknowledging that mechanisms of immunity in amebic infection have not been adequately investigated, one may speculate that a nutritionally compromised host would have difficulty mounting an immunologic defense against the amebae.

In at least two studies, evidence suggests that lack of a specific nutrient affects the level of resistance to amebic attack in animals. Sadun et al.

[20] reported that feeding an ascorbic acid-deficient diet to guinea pigs resulted in higher infectivity and mortality. Levels of ascorbic acid in tissues of infected animals were not significantly altered, but splenomegaly with hyperplasia of reticular tissue was present.

Larsh [21] found that dogs in which blacktongue (analogous to human pellagra) was induced by diet were more susceptible to infection with *E. histolytica*, had more acute symptoms than control dogs fed the same diet but maintained free of blacktongue by the oral administration of nicotinic acid. Thus, nicotinic acid was in some way involved in the mechanism of resistance to amebiasis in dogs.

Malnutrition benefits the host (antagonism). Faust [22] surveyed an economically impoverished lower-class population in Cali, Colombia, and found a high incidence of infection with *E. histolytica*, but relatively little clinical disease. Cysts were the most frequently observed form of the parasite. Noting large quantities of undigested starch in the average fecal sample, and most certainly cognizant that rice starch is the principal source of carbohydrate in ameba-bacteria culture systems, Faust suggested that the abundance of starch might tend to keep *E. histolytica* in the large intestine. Later, Faust and Read [23] showed that the starch of the yucca tuber and plantain, the principal foods of the surveyed population, could satisfactorily substitute for rich starch in cultures of a Colombian and a non-Colombian strain of *E. histolytica*. Considering this finding and the results of other studies of starches, as well as the protein deficiency of the Cali population, Faust and Read proposed an explanation for the near absence of clinical amebiasis in the presence of a high incidence of infection. They suggested that protein malnutrition produces a deficiency of pancreatic and intestinal enzymes, so that ingested starches are inadequately hydrolyzed and intact starch grains are passed out of the body. *E. histolytica*, colonizing in the large bowel, utilizes certain of these starches and maintains itself in the intestinal crypts without resorting to deep invasion of the intestinal wall in search of the required carbohydrate. In these studies, *E. hartmanni* was considered a form of *E. histolytica*.

Meerovitch [24] advanced a somewhat similar hypothesis to explain why the reptilian ameba, *Entamoeba invadens*, lives as a harmless commensal in turtles but as an invasive parasite in carnivorous reptiles. Meerovitch argued that, in the partially herbivorous turtles, the amebae found all the conditions, especially plant polysaccharide, necessary for encystment and completion of its normal life cycle. In carnivorous reptiles, the lack of plant polysaccharide led the amebae to feed on mucus secretions of the intestinal epithelium and to invade the tissue.

The avidity of *E. histolytica* for erythrocytes is well established. Trissl et al. [25] noted a correlation between a strain's virulence and its ablity to phagocytose human red blood cells. Latour and Reeves [26] provided evidence that *E. histolytica* is an organism with above average requirements for iron. Weinbach et al. [27] identified iron-sulfur proteins as major electron carriers. Diamond et al. [28] showed that, when hamsters overloaded with iron administered orally or parenterally were inoculated intrahepatically with axenically cultivated amebae, they suffered more frequent and more severe hepatic lesions than did normal controls. Moreover, the same authors suggested that iron overload in Zulu men, brought on by the excessive intake of iron from native beer, might account in part for the fulminating amebic dysentery seen in these people (synergism). On the other hand, the iron deficiency anemia commonly observed in women between menarche and menopause might protect them against liver abscess, which is less likely to occur in women than in men belonging to this age group (antagonism).

Murray et al. [29] reported that *E. histolytica*, as determined by serologic technique, was relatively uncommon in nomadic Turkana (three of 230) in Kenya who subsisted principally on a diet of milk, as compared with Turkana (39 of 236) who consumed a diet of milk supplemented by fish. Evidence showed the milk-drinking Turkana to be iron deficient. In a controlled prospective study of pastoral Masai, the same authors [30] reported that administration of iron to correct anemia led to increased susceptibility to amebiasis. The data supporting this contention are meager and open to some question. One year after initiation of the study, Group I (untreated controls) included 35 individuals with cysts, and three with sera positive for *E. histolytica*. Group II (treated by oral administration of iron) consisted of 35 patients: 11 with cysts, seven with trophozoites, and 17 free of the ameba (29 of the pa-

tients, including all those that were infected, were serologically positive). Group III, consisting of six persons (treated by im injection of iron), remained free of the parasite and were serologically negative. Evidence is overwhelming that amebic antibodies in humans are produced in response to direct contact of the parasite with host tissues. Patients who pass cysts tend to be serologically negative. One could argue that during the year of the study, the 11 serologically positive patients who passed cysts had suffered tissue invasion and were now in the healed state. Spontaneous selfcure is known in intestinal amebic disease. But none in the study gave evidence or history of abdominal pain or diarrhea. Even the authors noted the curiousness of this absence. The latex agglutination test used in the study has been shown to give unusually high rates of false positive reactions [31], and an argument that many of the positive reactions could reflect past active infection is not consistent with the history of the patients. The present interest in the role of iron in amebic infection warrants additional carefully controlled clinical studies with full parasitologic testing and more dependable serologic tests.

Alleviation of Symptoms and Eradication of the Parasite by Diet

One of the early experimental studies relating diet to amebiasis was reported by Kessel and Huang [32], who examined the effect of diet consisting exclusively of milk on naturally occurring amebic infection of the intestines of monkeys and children. The children were asymptomatic. Three of five monkeys fed exclusively on raw milk for two weeks became negative for *Entamoeba dysenteriae* (*E. histolytica*) and the commensal *Entamoeba coli* and remained free of these parasites during three months of observations. Two of three children fed exclusively on raw milk were rid of the pathogen and remained free. Two children and two monkeys serving as untreated controls remained infected with the amebae. In a later study, Kessel [33] fed diets of milk, lactose or lacto-kepol (emulsion of lactose, agar, and mineral oil) to rats, monkeys, and humans. Eight of 15 rats, one of 11 monkeys, and three of nine patients (given milk or lacto-kepol) were cleared of *E. histolytica*. Kessel related the clearance of the amebae to changes in the intestinal flora accompanying the experimental diets.

Faust and Kagy [34] showed that the feeding of raw liver to infected dogs not only arrested the development of *E. histolytica* in the tissues and bowel lumen and brought about encystment, but also aided the healing process. In some animals, the parasites were completely eradicated. Dessicated liver extract, while it arrested the invasive process, did not eradicate the parasite. In contrast, Ventriculin® (desiccated hog stomach, Parke Davis, Morris Plains, N.J.) failed to check the disease process and increased susceptibility of the host tissue to secondary bacterial invasion. Larsh [21] suggested that in view of the successful use of raw liver or liver extract to cure blacktongue, the findings just described further substantiate the role of nicotinic acid in the mechanism of resistance to *E. histolytica* in dogs.

Doubtful Correlation Between Nutrition and Amebiasis

In a search for factors responsible for differences in the frequency of clinical amebic dysentery in two rural communities in Tennessee, Alexander and Meleney [35] conducted a detailed and painstaking study of the dietary habits of the two populations. One community, situated in hill country, had a high incidence of infection with *E. histolytica*, but a relatively low incidence of dysentery; the other community located in the lowland, had a lower incidence of infection but a number of acute cases of dysentery. Protein consumption was adequate in both communities, carbohydrate intake more than adequate, and fat consumption less than adequate. A strikingly common feature of the diets was the great quantity of cornmeal consumed.

No correlation could be found between inadequacy of diet and the harboring of *E. histolytica* in either community, with or without acute dysentery. No correlation appeared between lack of vitamins and infections with the parasite. In general, infection was more frequent in both communities among families with lower calorie intakes, but, as the authors conceded, this correlation could have been due to factors other than diet, such as better personal hygiene and protection from infection. The authors noted that the lack of evidence implicating dietary factor as a

cause of acute amebic dysentery did not preclude its influence under certain conditions. Clinical evidence in individual cases strongly supported the view that diet can affect amebic infection

Winfield and Chin [36], studying the epidemiology of parasitic amebae in China, attributed the high incidence of infection with *E. histolytica* in northern China and the low incidence in central and southern China to a combination of food habits and handling, not to diet per se. People in northern China consumed large amounts of bread products, usually eaten cold. During the time between preparation and consumption, which could be hours or days, the cold bread was subjected to repeated contamination from family food handlers, flies, and the dirty hands of the consumers themselves. Understandably, the relatively resistant cyst, the transmissible stage of *E. histolytica*, could be readily passed between family members. In central and southern China, rice was commonly eaten and bread rarely taken. Rice was ordinarily eaten hot and, when kept from one meal to another, was usually stored in covered containers, dispensed with a spoon, and eaten with chopsticks.

Carrera et al. [37] found no significant differences in rates of infectivity or severity of disease in guinea pigs fed an adequate diet, a diet quantitatively deficient in protein, or a diet qualitatively deficient in protein.

Consequences of Amebic Infection on the Nutritional Status of the Host

What little is known regarding the consequences of infection is based more on clinical observations than on experimental evidence; and because of the protean nature of amebiasis, these consequences are not readily identifiable. Diarrhea and, at worst, dysentery accompany intestinal amebic disease. Diarrhea may be continuous or intermittent. From two to 20 or more stools may be passed daily. As a consequence, the loss of endogenous nutrients such as proteins, trace metals, and electrolytes is likely in seriously affected patients. Lewis and Antia [9], in describing mild to moderate amebic colitis in 200 patients who passed up to four loose stools daily, noted the absence of constitutional disturbances. Nevertheless, 12.5% of these patients died because of their infections. Martin et al. [38], in a study of the efficacy of amebacides and antibiotics in amebiasis, examined 644 patients with acute amebic dysentery in a United Nations prisoner of war camp in Korea; 97% had blood and mucus in the stool, and 87% of 560 patients examined by sigmoidoscopy exhibited ulceration. The authors state: "The relative appearance of well-being of the amebic patients, even those whose sigmoidoscopic examination revealed extensive enteric lesions, was in marked contrast to that of the acutely ill, toxic, dehydrated patients with shigellosis." Dehydration and loss of electrolytes appear as common features only of severe amebic dysentery [9, 39]. Electrolyte imbalance appears to be a more important feature of the disease in children. Castañeda-Castañeira et al. [40] studied 103 Mexican children, aged 54 days to 16 years, suffering from dysentery, diarrhea with blood and mucus, or protracted diarrhea without blood. Twenty (19.4%) were found to have invasive intestinal amebiasis. Of these, 60% were found to have electrolyte and acid-base imbalance, and 15% an intolerance for carbohydrate. Anemia is uncommon even in acute dysentery, but serum albumin is low [41].

The problem of identifying malnutrition as a predisposing factor or a consequence of amebic disease has been mentioned. Coexisting helminthic infections can add further complications. For example, trichuriasis (whipworm infection) is at times associated with amebiasis in children and has been suggested as a predisposing factor. From a study of aboriginal children in Malayasia, Gilman et al. [42] provided evidence that malnutrition in patients with coexisting infections resulted more from infection with *Trichuris* than from infection with *E. histolytica*. These researchers found no evidence of chemical or clinical deficiency of thiamine or vitamin A in children infected with either parasite. However, serum albumin was significantly depressed in both groups of patients.

Liver abscess, the most frequent extraintestinal form of amebiasis, is acute and severe. Anemia, which is commonly documented in cases of amebiasis [41, 43, 44], is normoblastic and hypochromic [44]. Mayet and Powell [44] and Diamond et al. [28] have reported that serum iron levels, total iron-binding capacity, and percentage saturation are significantly reduced in patients with amebic liver abscess. These responses parallel those found in patients with acute bacterial or fungal infections. Evidence indicates that these and

other changes in status of iron associated with acute infectious diseases play an important role in host defenses. On the other hand, they could represent secondary pathologic consequences of a disease state [45].

In an effort to determine the mechanisms of the anemia associated with liver abscess, Devakul et al. [46] examined the absorption of vitamin B_{12}. Most patients showed remarkably reduced urinary excretion of B_{12}. The researchers attributed this reduction to faulty intestinal absorption, since all patients had normal renal function, and, in those cases in which both urinary and fecal excretion of B_{12} was measured, the results were parallel. This malabsorption was attributed to changes in intestinal function that occur during active disease but are not related directly to the abscess itself.

Concluding remarks

Clearly, the complexities of amebic infection and disease are capable of frustrating even very careful and intuitive workers who study the problems of nutrition and amebiasis.

Some of the reports presented suggest a correlation between malnutrition of the host and higher incidence of infection and/or severity of disease (snyergism). Some suggest that malnutrition operates in defense of the host, protecting it against tissue invasion antagonism). A few reports suggest that dietary regimens can alleviate symptoms and eradicate the parasite. Others doubt a correlation between diet and rate of infection or disease manifestations.

The ameba itself is influenced by its own diet (which depends on the diet of the host), the bacterial flora of the gut, and concomitant pathogenic infections. The host, too, is variously altered by dietary depletions and supplementations, which affect susceptibility and resistance, and by the presence of other disease conditions. The separation of all of these factors in future clinical studies will require careful attention to the selection and study of the pertinent details of the populations or patients under investigation. Information from such studies would be very useful. Studies in vitro of the nutritional requirements and physiology of the ameba may add pertinent information. Experimental studies in animals may further elucidate the problem. The value of these studies will be enhanced if inherent differences in the virulence of different strains of *E. histolytica* are considered. Some of the animal studies reviewed here can be faulted for a lack of clear identification of the invasiveness of the strains employed. The presence of three morphologically similar amebae in humans, i.e., *E. histolytica* (*sensu stricto*), *E. histolytica*-like amebae, and *E. hartmanni*, must be taken into account. Future investigators must rule out the possibility of mixed infections in the material they use to infect their animal models. Various clues about cereal diets, the importance of trace metals, such as iron, the influence of various factors on amebal growth in vitro, and attachment to substrates and invasiveness suggest that future workers will be able to disperse some of the clouds around this problem.

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Giardiasis: Host-Pathogen Biology

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Giardiasis is the most common waterborne diarrheal disease in the United States and is highly prevalent throughout the world. The clinical spectrum of disease ranges from asymptomatic infection to persistent severe malabsorption. The precise interaction between *Giardia* and its human host remains conjectural because of the paucity of published studies that address the details of its pathogenesis. The immune system of the host responds to this protozoan parasite, and the intestinal epithelium is a site of interaction between parasite and host. Possible mechanisms whereby *Giardia* may alter the host's absorption of nutrients at the epithelial level include direct physical interference, toxin secretion, direct physical alteration of the epithelium, competition for nutrients, induction of an inflammatory response, and coincidential infection of the host with a second organism. The host's immune system may play both a protective and a pathogenic role.

While Lambl was the first to recognize human *Giardia* in stool in 1859, he, in all modesty, chose to call it *Cercomonas intestinalis*. Kunstler named the genus *Giardia* 23 years later, but it was a half century more before *Giardia lamblia* finally received its current name [1]. The organism was in fact first observed as soon as von Leuwenhoek looked at his own stool under his microscope in 1681 [2]. In spite of this long history of recognition, *Giardia* was thought for centuries to be a commensal organism. It was considered to have little relevance to disease, and its occurrence in stool was generally thought coincidental with the presence of more-culpable agents in the stool of the unwell patient.

Epidemiology

It was not until the last two decades that the role of *G. lamblia* in waterborne infectious diarrheal diseases became apparent. This was recognized most dramatically in two settings: (*1*) when community water supplies laden with *G. lamblia* passed through inadequate filtration systems and led to dissemination of the organism and (*2*) when travelers from areas where giardiasis is uncommon returned ill from endemic areas [3]. While disease was undoubtedly present prior to the recent rediscovery of this organism as a pathogen, its clinical significance may have been dwarfed by more-dramatic intestinal illnesses, such as amebiasis, or may have been indistinct from more-trivial intermittent intestinal disturbances.

Waterborne giardiasis. Giardiasis spreads among humans via at least two routes: by infected water supplies [4] and directly from person to person [5, 6]. The first dramatic recognition of community-wide water contamination occurred in Aspen, Colorado, in the late 1960s, when sewage lines crossed the purified water supply and infection was disseminated to large portions of the community [7]. Since then, over two dozen community-wide epidemics have been associated with failure of water purification systems in the United States. Generally, failure of filtration systems was the common factor in these outbreaks [3] since the chlorine concentrations used in community water purification are too low to inactivate giardial cysts. The ultimate identification of giardial cysts in suspected water samples strengthened the argument for the association of failures in filtration systems with outbreaks of disease [8].

There is strong suspicion that animal reservoirs of human *Giardia* exist. This hypothesis grows out of the increasingly frequent observation of *Giardia*-infected beavers in waters upstream from filtration plants implicated in community outbreaks [9, 10]. If valid, the concept of animal reservoirs for *G. lamblia* would help explain the development of infection in persons drinking the pristine

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water in areas unoccupied by humans, such as the upper reaches of the Rocky Mountains.

There are many communities where the water supply is chronically infected with *Giardia*. On a worldwide basis, these communities range from those in developing areas of the world, where water supplies are not formally treated and overlap with sewage disposal systems (e.g., local streams) to communities of such apparent sociocultural development as Leningrad, from which 23% of North American travelers return with giardiasis [11].

Person-to-person spread. Observation of the high frequency of giardiasis among children in day care centers [5] and among promiscuous male homosexuals [6] strongly suggests that the disease can be transmitted by direct contact. These observations have implicated poor personal hygiene and/or personal contact as contributing to the milieu where the organism may complete the fecal-oral route and establish infection in the new host.

The Pathogen

The parasite exists in two forms: the motile, flagellated, 9 × 15-mm trophozoite and the somewhat smaller, tough-walled cyst. The trophozoite is pear-shaped, with four pairs of flagellae extending from its lateral and posterior surfaces. The dorsal surface is convex. Its central surface is concave and contains a structure called the sucking disk, which is refined for adherence to surfaces. This term implies greater knowledge of its function than is probably justified. While the sucking disk acts as a kind of foot, its mode of attachment, at least to the microvilli of the small intestine, may involve digging into the field of pliable microvilli without actually establishing an intradisk negative pressure. Transmission electron micrographs show two nuclei, a microtubular network that seems to be circumstantially associated with the attachment disk, and a series of vesicles that line up along the dorsal surface and may be associated with nutrition of the organism [12, 13]. While endosymbionts (parasites within a parasite) have been demonstrated in a murine strain of *Giardia*, their exact role is undefined [13].

Trophozoites reside in the small intestine where they can attach to the epithelial surface, remain in the unstirred layer above the epithelial surface, or move about in a presumably random fashion [12]. There is no evidence that they are propelled for a particular purpose or by tropism, but no substantive data exist in this area. Presumably peristalsis carries them caudally in the host's intestine and, as they pass toward the anus, they encyst.

The tough-walled, oval cyst contains four nuclei, and its wall is resistant to various temperatures and substances. It is excreted in stool into the environment. Ingestion by a host and passage into the acid environment of the stomach lead to excystation to the trophozoite form [14]. The trophozoite passes into the small intestine, and infection is again established.

Little is known of species variations among various *Giardia* strains or of their respective host specificities. For years each *Giardia* strain was named for its host [15]. This nosology, however, should not be interpreted as implying host specificity by these various strains. While minor changes in substructure help differentiate *Giardia muris* from *G. lamblia* [1], there are no similar morphologic or other clues for differentiating among the more than 50 other named species.

Early studies suggested that *Giardia* isolated from human stool would infect rats and mice [16]. These studies ignored the high prevalence of wild strains of *Giardia* in various rodents and are, therefore, probably of questionable value. The most substantive information regarding cross-species infectivity has been obtained by Davies and Hibler in a transmission study done in Colorado [10]. While they have isolated numerous strains of *Giardia* from various wild mammal hosts, the host specificity of these strains remains unclear. Of great interest, however, are their studies of cross-transmission by passage of *Giardia* obtained from human stool into beagle dogs free of specific pathogens. Because of the careful prospective nature of these experiments, it is safe to say that these animals were not hosts to wild strains of *Giardia* prior to infection. These data provide the first substantive evidence that dogs may provide a reservoir for human *Giardia*. Moreover, these authors have reported that *Giardia* isolated from stools of both beavers and dogs have been transmitted into human volunteers. These data show that certain human *Giardia* strains may cross from one species to another (from dog and beaver to humans) and that these, and possibly other nonhuman hosts, may serve as animal reservoirs for human *Giardia*. The role of

these animals in contaminating human water supplies is strongly suspected [4]. Whether they serve as direct sources of infection (e.g., infection transmitted to humans from domesticated dogs by way of fomites) is still conjectural.

Host-Pathogen Interaction

Giardiasis presents a broad clinical spectrum. It varies in severity from asymptomatic, often short-lived and self-limited infection that probably occurs in most infected persons, to persistent severe malabsorption syndromes with chronic diarrhea and weight loss [11]. It is an infection of the small intestine, and the arena for interaction between host and pathogen is localized to that organ. At least two interfaces exist for this interaction. The first is the interaction between *Giardia* and the intestinal epithelial cell for which there is substantive morphologic evidence and considerable physiologic speculation. The second is the interaction between *Giardia* and the immune system; evidence here is more fragmentary, albeit convincing. A clearer understanding of the net host-pathogen interaction may be derived from consideration of each of these areas separately.

Interaction of *Giardia* and Epithelial Cells

Giardia appear to roam over the epithelial surface of the small intestine. For reasons that are still unclear, they will occasionally adhere directly to the epithelial surface. Cross-section electron micrographs show that the disk actually digs into the epithelial microvillus layer, and scanning electron micrographs show circular footprints of formerly adherent trophozoites on the epithelial surface [12, 17].

Morphologic evidence from both light [18–20] and electron microscopic studies [12, 17, 21] argues for a direct interaction between *Giardia* and the epithelial cell. The mechanism for this interaction, however, is less clear than its pictorial representation. Electron microscopic studies show that the epithelial cells of rats contain deformed and blunted microvilli in the cells under adherent *Giardia* [17]. These epithelial microvilli are normally rich in the digestive enzymes of the small intestine.

The invasive trophozoite, moving about in a random fashion, has also been observed between epithelial cells [22]. What pathogenic role, if any, these invaders play is unclear. In view of the millions of intraluminal organisms, invasion must be an infrequent event. Whether invasion reflects the occasional, opportunistic transgression between loosely adherent, randomly senescent, and dying epithelial cells, or is the result of penetrating skills that permit assertive action on the part of the parasite is unclear. Electron microscopic evidence showing degenerating cells adjacent to invading organisms suggests the former conclusion [23].

There is considerable physiologic evidence for malfunction of the epithelium of the small intestine in giardiasis. Temporary disaccharidase deficiency has been well documented [20]. Since disaccharidases are located primarily in the microvilli of the jejunal epithelial cell, such a deficiency represents the functional counterpart to the morphologic alterations described above. Other alterations that have been described include fat and B_{12} malabsorption [20, 24], which indicates that dysfunction extends into the ileum. Clinically, the patient with giardiasis has a malabsorption-type diarrhea consisting of frequent bulky stools of relatively high fat content. Epithelial cell dysfunction is a sufficient explanation of all aspects of malabsorption that are observed in giardiasis.

Possible Mechanisms for Epithelial Damage

There are numerous possibilities whereby infection with *Giardia* may affect epithelial function. Evidence is sparse in support of any of them to the exclusion of the others.

Physical interference. Selected electron micrographs and light photomicrographs raise the suspicion that the absorptive surface area may be mechanically blocked by large numbers of attached trophozoites. There is, however, no quantitative data supporting this theory. Moreover, the large absorptive surface area of the small intestine would seem to compensate readily for such a possibility, and the sporadic absence of detectable cysts and trophozoites in clinically ill patients makes this unlikely. Simply put, there are not enough trophozoites to cover adequately the enormous functional surface of the small intestine.

Soluble toxins. An appealing hypothesis, discussed extensively by Meyer and Radulescu in their exhaustive review [25], suggests the secretion by the trophozoite of a soluble toxin that interacts

with the epithelial cell. However, to date none has been identified. Preliminary evidence suggested that cultured trophozoites exert a toxic effect on tissue culture fibroblasts in vitro. This area remains a tempting one for investigation.

Damage by direct interaction. Morphologic evidence has demonstrated that the microvilli under attached trophozoites may be directly altered by contact with trophozoites [17, 18, 21]. The possibility of interaction between host and overlying trophozoites is plausible only if recovery of the epithelium is delayed, which would allow extensive damage by relatively few trophozoites. Deformation of microvilli under the sucking disk seen in electron micrographs [17] and the above-described interaction between trophozoites and fibroblasts in tissue culture remain the strongest evidence for this hypothesis.

Competition for nutrients. The relatively low numbers of giardia trophozoites (as opposed to the enormous epithelial surface) are the most cogent argument against the hypothesis that trophozoites usurp the host's share of ingested nutrients. While sharing intraluminal nutrients surely must occur, its importance to host illness is undefined. There is no obvious mechanism, however, whereby such passive competition would result in morphologic changes in the epithelium. While competition seems a likely occurrence, it is probably of little pathogenic significance.

Induction of inflammatory response. An inflammatory response involving polymorphonuclear and mononuclear cells in the submucosa of the epithelium occurs in giardiasis [18, 26]. Such cells might conceivably secrete inflammatory mediators such as kinins, which could alter epithelial structure and function. The intensity of the cellular response appears to be proportional to the intensity of the infection and/or the extent of observed epithelial cell change [26]. It is in all respects similar to the inflammatory response seen in other diseases of the small intestine associated with shortening of villi and elongation of crypts (e.g., gluten enteropathy). Whether this inflammatory response is protective, pathogenic, or both is not apparent from available observations.

Coincidental infection. In 1967 Yardley and Bayless [19] suggested a role for altered bacterial flora in the pathogenesis of giardiasis. Tomkins et al. [27] have presented evidence that infection of the small bowel with bacteria normally not inhabiting that organ may contribute to the pathogenesis of superimposed giardial infection. The effect of antibacterial drugs, such as metronidazole, in the treatment of giardiasis may support this argument as well. Others [28] have reported simultaneous giardiasis and overgrowth of the small bowel with bacteria in persons with symptomatic giardiasis, some of whom had an excessive amount of deconjugated bile salts in the jejunum. The latter observation suggests a possible mechanism for steatorrhea in giardiasis. On the other hand, coincidental experimental infection of mice with another intestinal parasite, *Trichinella spiralis*, in addition to *Giardia*, resulted in suppression of the intensity of giardiasis [29]. Further observations of concomitant bacterial infection of the small bowel will be necessary to support the appealing hypothesis that bacterial overgrowth participates in the pathogenesis of giardiasis.

Interaction of *Giardia* and the Host Immune System

The interaction between the parasite and immune system may have two possible outcomes. The first is a putative protective response, for which reasonably strong evidence exists. The second is an immunopathogenic response, for which the evidence is more tentative.

Protective immunity. Several lines of clinical evidence suggest a protective immune response in human giardiasis. In the mid-1950s, Rendtorff and Holt [30, 31] prospectively infected prisoner subjects with giardia cysts. While the number of subjects was small, efforts to reinfect these persons with a second challenge with *Giardia* resulted in fewer infected subjects and suggested a protective effect of the earlier primary infection. Also compelling is the more-frequent development of clinical infection in short-term visitors to endemic areas such as Aspen, Colorado [7, 32], than in long-term residents of those areas [3]. However, repeated giardial infection in the same host may result from an incomplete protective immune response. Other possible explanations for this observation include variations in *Giardia* species or the recurrence of occult or incompletely treated infections.

Evidence that a humoral immune response is an important part of the host protective response derives from the frequent observation of giardiasis in association with common variable immuno-

globulin deficiency syndrome [33–36]. This association has suggested that humoral immunodeficiency may be a generalizable phenomenon that has relevance to persons who do not have recognized immunologic disease. Eighty percent of persons with common variable immunodeficiency and immunodeficient sprue, a *Giardia*-associated illness, improve when treated with anti-*Giardia* drugs [33]. Suffice it to say, however, that evidence for immunodeficiency in otherwise healthy people has been unavailable. There has been no identifiable circulatory immunodeficiency in persons with giardiasis [37]. Moreover, efforts to document secretory immunodeficiency in small bowel secretions have not demonstrated reproducible secretory immunoglobulin deficiencies [38–40]. Studies of possible cellular immunodeficiency have not been reported. While giardial infection is a frequent occurrence in persons with humoral immunodeficiencies, occult immunodeficiency does not appear to be a prerequisite for giardia infection in the otherwise healthy individual.

Laboratory evidence of a humoral immune response was suggested by the preliminary studies of Ridley and Ridley [41]. Vivesvara and colleagues [42], employing axenically cultivated *G. lamblia* trophozoites as indicator cells for an indirect immunofluorescent antibody test, have provided even more substantive evidence of such a response [42]. These observations indicate that circulating antibodies of an undefined class were present in serum at titers of 1:16 or greater in 43 of 44 persons with symptomatic giardiasis, whereas titers of 1:4 or less were detectable in uninfected control subjects. These antibodies persisted for at least two months and probably longer.

Studies in a murine model of giardiasis developed in our laboratory support the protective role of immunity for this infection in the mouse [43–45]. These studies employed a rodent strain of *Giardia* isolated from a golden hamster and studied in CF-1 Swiss albino mice. Maximum levels of trophozoites in the small bowel and cysts in the stool occurred in seven to 14 days after oral inoculation and disappeared after six to eight weeks [43]. Moreover, efforts to reinfect such animals resulted in little or no detectable infection [46]. The clearance of infection and resistance to subsequent reinfection was probably associated with the thymus-dependent immune system; this was demonstrated by studies in inbred, congenitally athymic animals (*Nu/Nu*) [47]. Infection of these T-cell-deficient animals resulted in prolonged infection for up to 20 weeks. Efforts to orally reinoculate these animals resulted in recurrence of high levels of cyst excretion in stool, albeit for a reduced period.

Studies of resistance to infection in suckling offspring of immune and nonimmune mothers have suggested a role for the secretory humoral immune system [48]. Newborn mice suckling on immune mothers (either their own biological mothers or foster wet-nurses) were resistant to oral infection with giardia cysts, while those suckling on mothers who had never been previously infected (that is, nonimmune animals) were susceptible. This protection in the offspring was lost after weaning. Studies using an indirect immunofluorescent test and purified *G. muris* trophozoites suggest that the mediator of this protection was associated with both anti-*Giardia* IgA and IgG [49]. A role for secretory antibody in host immune protection is consistent with the observation of persistent infection in T-cell-deficient animals, since secretory antibody seems to be a thymus-dependent function.

Infection follows the same uniform pattern: peak excretion in one to two weeks with resolution in six to eight weeks in all murine strains tested, except for congenitally athymic mice and C3H mice [50]. Studies of F_1 hybrids of nonresistant C3H and resistant BALB/c strains showed that the hybrid offspring were indeed resistant to infection. This observation suggests that protection is a dominantly inherited trait.

Role of immune reactivity in pathogenesis. Evidence obtained from this murine model suggests that an intact host immune response to *Giardia*, particularly the cellular immune response, may be necessary for clinical disease. Reconstitution of lymphocytes from the spleen of immunologically intact mice injected into congenitally thymus-deficient mice resulted in reduction of the villus : crypt ratio in *Giardia*-infected mice [50].

Immune response to Giardia: summary and conclusions. From the above studies and additional observations, the following scenario describes a hypothetical model of the interaction between *Giardia* and the host immune system.

Giardia trophozoites come into contact with the immune system in at least two possible locations. One potential site is the intraluminal space, where giardial trophozoites have been found in contact

with lymphocytes by scanning electron microscopic studies of the murine model [12]. A second, more conventional possibility is that submucosal macrophages engulf the occasional trophozoite that migrates between senile epithelial cells. Transmission electron microscopic studies of the murine model have demonstrated fragments of trophozoites in macrophages just below the epithelial surface of the small bowel [23]. Once antigen is initially processed by macrophages and/or intraluminal lymphocytes, the protective immune response (which is thymus-dependent) develops and is partially mediated by secretory IgA in the small bowel lumen. Lymphocyte precursors for IgA secretion, destined for other organs of the secretory immune system (such as the mammary gland), move to these sites via the thoracic duct and the circulatory system and may be trapped by the appropriate organ (e.g., the lactating mammary gland) [51].

Whether or not interaction with cellular components of the immune system also results in killing of the trophozoites is unclear. Secretory IgA may prevent adherence and thereby interfere with establishment of new infection [52]. Mechanisms whereby secretory immunoglobulin interacts with the trophozoite, to the latter's detriment, are unclear and await further study. A second oral challenge with *Giardia*, to which the host is primed, results in a heightened response with rapid clearance of intraluminal infection before clinical illness develops. The role for the immune system in the pathogenesis of the infection is suggested by the increased cellularity in the submucosa of the small intestine of heavily infected human hosts [18] and by reconstitution studies in congenitally athymic nude mice [50].

Conclusion

Giardia and the host interact both with epithelium of the small intestine and, in a more complex fashion, with the immune system. The immune system may also interact pathogenically with the epithelium as well as protectively with the parasite. The end result is malabsorption of important nutrients for the host, with consequences varying from asymptomatic, self-limited infection to severe epithelial dysfunction with accompanying important nutritional consequences.

The conclusions of this paper are supported in a most fragile fashion by the available data. There remain emormous areas for further study of the host-parasite interaction in giardiasis, but, on the basis of currently available data, there is great promise that knowledge of the basic biology of this infection and its consequences for the host will be forthcoming [53, 54].

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Giardiasis: Nutritional Implications

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The debate about the pathogenicity of *Giardia lamblia* in man has ended, and the issues regarding the prevalence of clinical and subclinical infections and their nutritional impact have become the foremost considerations. Giardiasis can produce steatorrhea, maldigestion, and malabsorption of carbohydrates and of vitamins A and B_{12}. The mechanisms of the absorptive dysfunction are not clear, but morphological abnormalities of the intestinal mucosa and/or bacterial overgrowth might play a role. Severe clinical giardiasis can cause "failure to thrive" in young children, but the impact, if any, of subclinical giardiasis on growth in general populations is not well defined. Protein-energy malnutrition appears to predispose to giardial infection, perhaps because of the accompanying hypochlorhydria, immunosuppression, and altered gastrointestinal flora. The lack of a sensitive and noninvasive diagnostic test for human giardial infection limits the investigation of the nutritional correlates of giardiasis.

A major obstacle to generalizations about the impact of giardial infection on the human is the greatly variable expression of the disease. The major recent clinical reviews of human giardiasis all emphasize a spectrum of presentations from asymptomatic individuals with cysts or trophozoites found incidentally on routine stool examination to patients with gastrointestinal symptoms and debilitating malabsorption syndrome [1-9].

The Nutritional Impact of Giardiasis on the Host

Not surprisingly, the prevalence of nutritional disturbances in patients with giardiasis varies greatly with the selection of the series, that is, with only asymptomatic cases, only symptomatic cases, or some mixture of the two. Moreover, quantification of protozoal burden is without significant benefit. A prospective study in which prisoners were intentionally infected with varying doses of *Giardia lamblia* cysts showed no correlation between the dose administered, fecal excretion of organisms, and symptomatic response. Most subjects, in fact, remained asymptomatic, and their experimental giardial infections spontaneously cleared in one to seven weeks [10, 11]. On the other hand, a suggestive correlation between antibody titer to giardial cyst antigen and absorptive dysfunction, diagnosed on the basis of fecal excretion of organisms, was observed in a spectrum of patients [12]. However, in patients with marginal protein-energy nutriture, nutritional insults to the intestine rather than the *Giardia* per se could be responsible for malabsorption [13].

Morphological Changes in the Intestinal Mucosa

A murine model for giardiasis has been developed with *Giardia muris* [14]. When inbred strains of mice are infected with *G. muris*, a predictable decrease in the ratio of villus to crypt cells is seen, and the degree of morphologic damage is proportional to the size of the inoculum of protozoa [15]. Experimental infections with *G. muris* also result in consistent infiltration of the villous epithelial layer with intraepithelial lymphocytes [16].

The issue of morphologic change in human giardiasis, however, is not so straightforward. Radiographic studies based on a limited number of cases have reported the reversal of several patterns, in-

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cluding mucosal edema, a "sprue-like" pattern, dilatation of the duodenum and jejunum, and other "motor disorders," following successful treatment of the giardial infection [17, 18]. A picture of the histologic alterations related to *Giardia* in the human intestine emerged with the application of increasingly sophisticated morphologic investigations of material from intestinal biopsies. Histologic changes are found across the spectrum of clinical presentations, from asymptomatic giardiasis, diagnosed on routine stool examination [19, 20], to giardiasis accompanied by gastrointestinal symptoms [21-23]. The frequency and degree of mucosal injury varies from series to series. Tewari and Tandon [24] found mild cellular changes under light microscopy but no evidence of villous atrophy [20-23, 25-29]. Various amounts of inflammatory infiltration also accompany the villous shortening [19, 20, 23, 25]. Restoration of normal villous architecture and reduction of infiltration and inflammation have been observed after eradication of the infection in most patients biopsied serially [21, 23, 27, 29]. That *Giardia* can have a profound morphologic effect on intestinal mucosa is indicated by several reports of total villous atrophy accompanied by dense round-cell infiltration of the lamina propria in association with giardiasis; the mucosal lesion was reversed after eradication of the protozoal infection [30, 31]. Duncombe et al. [22] found a rough correlation between the degree of mucosal injury and the severity of the diarrhea in 17 patients with giardiasis, 15 of whom had symptomatic illness.

Morphologic studies at the subcellular level have also provided insight into the mechanisms of the histologic damage that might be responsible for mucosal dysfunction in giardiasis. Intraepithelial lymphocytes were observed in patients with moderate and severe malabsorption and giardiasis [32] but not in patients with mild absorptive impairment. Early investigators [25, 27, 33] were unable to demonstrate intraepithelial invasion by *Giardia*. Invasion among epithelial cells by trophozoites, however, has subsequently been demonstrated by a number of investigators [20, 34, 35] and seems to be an established finding, although its role in the pathogenesis of mucosal injury is poorly understood. Several studies of human infection suggest that the *Giardia* attach by means of a specialized apparatus to the microvillous borders of the epithelial cells [36, 37]. This process was proposed as the mechanism of brush-border injury in giardiasis; however, current evidence tends to discredit this hypothesis. An identical form of attachment and brush-border destruction has been elaborately and elegantly demonstrated in experimental infections of mice with *G. muris* [38, 39]. Recently, high quality scanning electron micrographs of *G. lamblia* on human mucosa, published by Dr. Robert Owen [40], demonstrated the same phenomenon (figure 1).

Thus, based on the histologic alterations observed in human and animal giardiasis, a number of pathogenetic mechanisms have been proposed as explanations for intestinal dysfunction. These, reviewed by Tandon et al. [41], include the presentation of a mucosal barrier to the passage of nutrients, cellular injury and inflammation reactions due to the presence of the *Giardia*, and mucosal cell invasion by the trophozoites. A reasonable assumption is that any or all of these mechanisms, alone or in combination, may impair intestinal absorption in an individual with giardiasis. However, other mechanisms, not related to the absorptive surface per se probably also contribute to the abnormalities in absorption and digestion in giardiasis.

Alterations in Biliary and Pancreatic Function

It is not widely appreciated that *G. lamblia*, by local extension from the duodenum, can also infect the biliary and pancreatic tracts. This complication of the disease, although rare, must also be examined in terms of potential nutritional implications. Soto and Dreiling [42] and Goldstein et al. [43] have recently brought this condition to attention in case reports involving two patients with symptoms of cholecystitis/cholangitis. In both patients, biliary drainage revealed no biliary calculi or sludge, but rather abundant trophozoites in the aspirated bile. Eradication of the *Giardia* resulted in prompt resolution of the biliary tract symptoms. Goldstein et al. [43], from a review of the international literature, identified at least eight additional publications describing what they termed "hepatobiliary giardia syndrome." Pancreatic function can also be impaired in biliary giardiasis; a reduction in the production of pancreatic enzyme was encountered in children with chronic cholecystocholangitis induced by *Giardia* [44].

Even in individuals whose giardiasis is limited to

Figure 1. Scanning electron micrograph of *Giardia lamblia* trophozoites in a crevice over a human jejunal villus. From [40], reproduced with permission and kindly supplied by Dr. Robert Owen.

the intestine, the evaluation of pancreatic function has led to interesting observations. In 25 Indian children with symptomatic giardiasis, a reduction in output of pancreatic trypsin and lipase, but not of amylase, was demonstrated [45]. The subjects infected with *Giardia* were also less responsive to stimulation with intravenous cholecystokinin, and they exhibited a positive and significant correlation between excretion of lipase and efficiency of fat absorption. In another report [46], tryptic activity following stimulation of the pancreas with a Lundh meal was reduced in patients with intestinal giardiasis; tryptic activity improved in 90% of the subjects after eradication of the parasites.

Bacterial and Fungal Overgrowth of the Upper Small Intestine

An association between giardial infection and abnormal colonization of the upper intestinal tract has been reported. Nair et al. [47] found that a surprisingly high percentage of patients with giardiasis (30%), as compared with controls (0%), harbored *Candida albicans* in the jejunum. Tomkins et al. [48, 49], at the Hospital for Tropical Disease in London, studied 46 adults with persistent giardiasis acquired during overseas travel. Fourteen of these individuals showed malabsorption in two or more tests, including fecal fat excretion, urinary D(-)xylose excretion, and the Schilling test; they were classified as having "severe" malabsorption. Fecal organisms (Enterobacteriaceae and Bacteroides) were cultured in concentrations of up to 10^7/ml of intestinal fluid from nine of these individuals. Treatment of the parasitic infection with metronidazole also eliminated the bacterial overgrowth in most patients. Patients with mild malabsorption (only one abnormal test), on the other hand, had relatively sterile aspirates. Tandon et al. [41], studying 63 cases of giardiasis in India, found 17 individuals with steatorrhea. Bacterial overgrowth, with concentrations of organisms $>10^5$/ml was found in the jejunal aspirates of eight patients with steatorrhea, but in none of five patients without steatorrhea. Free bile acids were encountered in all cases with bacterial overgrowth, and, to a lesser degree, in most other patients with giardiasis and steatorrhea, even those without contamination of the jejunum. Peruvian investigators [50, 51] claim to have eliminated the malabsorption of patients with giardiasis simply by administering oxytetracycline. The confluence of these reports suggests that part of the pathogenesis of impaired absorption in giardiasis might be the associated colonization of the upper bowel with fecal bacteria. The cause-and-effect relationships in the complex, that is, whether *Giardia* predispose to bacterial overgrowth or vice versa, have not been resolved yet.

Chronic Malabsorption Syndrome in Giardiasis

Although the debate about the pathogenicity of *G. lamblia* in humans has raged for decades, the association of *Giardia* with florid, chronic malabsorption syndrome has been amply demonstrated. Veghelyi [52, 53] is generally credited with the first recognition of this association. Both he and Cortner, however, confused the association with celiac sprue [53, 54]. Chauduri [55], in India, also reported a case of severe malabsorption in association with giardiasis. Subsequently, numerous case reports and reviews have confirmed the occurrence of all the classical manifestations of the

malabsorption syndrome, including wasting, hypoalbuminemia, diarrhea, and steatorrhea, in patients with giardiasis [3, 17, 25, 27, 35, 55–59]. In a majority of the survivors, eradication of the infection reversed the malabsorption and facilitated nutritional recovery.

Specific Absorptive Defects and Nutrient Deficiencies Accompanying Giardiasis

A host of observations in human patients with intestinal giardiasis have documented malabsorption and/or deficiencies of several nutrients. These are fat, carbohydrates (D(-)xylose, starch, and lactose), and vitamins (vitamin A, folic acid, and vitamin B_{12}).

Fat. The most commonly reported absorptive defect in giardiasis is steatorrhea. In 1959, Cortner [54] reported impaired absorption of ^{131}I-labeled triolein in a child with giardiasis. Daily fecal fat excretion in the range of 10–60 g is commonly reported in patients with giardiasis [17, 27, 35, 60–62], but in one study of eight adults, only mild fat malabsorption (<10g) was found [59]. Nonetheless, even in the latter study, improvement in the efficiency of fat absorption occurred in some individuals after eradication of the giardial infection. Steatorrhea, however, does not occur in every patient with giardiasis; the frequency of fat malabsorption has ranged from 12% to 64% in a number of published series [19, 23, 24, 32, 36, 40, 63].

Carbohydrates. The urinary excretion of the partially absorbable, nonmetabolizable pentose sugar, D(-)xylose, during the five hours following an oral dose has been used as an index of intestinal capacity for monosaccharide transport. Barbieri et al. [19] found the xylose absorption test to be abnormal in only three of 11 children with giardiasis. All normalized after treatment. Fourteen of 23 children infected with *Giardia* had reversible D(-)xylose malabsorption in another series [64]. The prevalence of abnormal absorption of xylose in human giardiasis has generally been reported in the range of 23% to 55% [18, 23, 24, 32, 63]. In some series, however, malabsorption of xylose has been virtually nonexistent [40, 59, 65]. Unfortunately, not all investigators in these studies employed the same criteria for abnormal D(-)xylose excretion. Moreover, doubts have been raised about the validity of xylose as an indicator of the behavior of nutritionally relevant hexose sugars, such as glucose or galactose. And finally, the association of bacterial overgrowth with giardial infection and the recent demonstration of D(-)xylose fermentation in the upper gut in such cases [66] suggest that some of the reduced excretion of xylose may result from intraluminal metabolism by bacteria rather than from failure of intestinal uptake.

The digestion of disaccharides and more complex carbohydrates can also be altered by giardial infections. Flat curves of plasma glucose were seen after administration of an oral lactose load to patients with giardiasis [67, 68]. Malabsorption of sucrose was also demonstrated in patients with giardiasis [68]. The malabsorption of disaccharides was transient and responded to the eradication of the infection. Reversible depression of disaccharidases, lactase, sucrase, and maltase has been found in patients biopsied serially before and after treatment for giardiasis [21, 27, 61]. In mice experimentally infected with *G. muris*, intraluminal and mucosal-adherent amylase activity was reduced [69].

Vitamins. The increase in the level of vitamin A in the plasma after an oral dose of an oil-based [54, 70] or water-miscible [71] form of vitamin A was less in patients with giardiasis. Normal curves were restored after eradication of the infections. Circulating levels of tocopherol in six patients with giardiasis were equal to those in uninfected controls [72]. Antia et al. [63] found a reduction in the post-absorptive rise of serum folate in six of eight patients with giardial infection. Low circulating levels of folate were encountered in 36% of 28 patients with giardiasis studied by Hartong et al. [23].

Absorption of vitamin B_{12} has been the most extensively studied aspect of vitamin metabolism in giardiasis. A number of investigators [17, 23, 24, 29, 30, 39, 49, 61, 63, 67, 73] have reported a substantial incidence of abnormal results of the Schilling test among patients with giardial infections. Since *Giardia* selectively colonize the duodenum and upper jejunum, a mechanism for the ileal malabsorption of vitamin B_{12} is not readily apparent, and the possibility that associated bacterial overgrowth plays a role in the abnormal results of the Schilling test should not be discarded. The potential nutritional consequences of giardiasis with respect

to vitamin B_{12} should not be discounted either, for two reports of megaloblastic anemia associated with the giardiasis of immunodeficiency syndrome have been published [74, 75].

Fecal Loss of Endogenous Nutrients in Giardiasis

Intestinal infections can compromise the nutritional status of the host by provoking transintestinal loss of endogenous nutrients. In the case of ulcer-forming or blood-feeding parasites, iron loss is prominent. *Giardia* rarely cause detectable loss of iron. Intestinal protein exudation in giardiasis has not been studied but is not likely to be substantial. The turnover of cells, i.e., the cellular nutrient content, is greatly accelerated in the murine model infected with *G. muris*. Ferguson et al. [76] have shown a production rate of cells that is two-fold greater, without any elongation of the villi, in chronically infected mice. Acute infection significantly increased the production rates of crypt cells and cell renewal [76]. The exfoliation of mucosal tissue, then, appears to be accelerated by giardial infections. Overall, however, fecal loss of endogenous nutrients does not appear to be a major problem.

Competition for Host Nutrients by *Giardia*

No evidence of competition by *Giardia* with the host for nutrients has been documented. The classic example of host-parasite competition for nutrients is the competition for vitamin B_{12} by the fish tapeworm (*Diphyllobothrium latum*). The total biomass of the parasite load and the host's daily requirement for a given nutrient are, theoretically, major determinants of whether or not any nutritional impact on the host occurs. Vitamin B_{12} is especially vulnerable because the daily allowance is in the range of 3 μg per day [77]. The next most vulnerable nutrients are trace minerals such as nickel, molybdenum, chromium, and selenium, with requisite intakes on the order of 75–200 μg daily. The absolute biomass of *Giardia* in a heavily infested person is not precisely known, but it is unlikely to exceed a gram of organisms. Thus, once a nutrient is consumed regularly in amounts in the milligram range, the *Giardia* are unlikely to require more than a minute fraction of the dietary intake.

Catabolic Loss and Metabolic Redistribution of Nutrients in Giardiasis

Infection with *Giardia*, limited exclusively to the intestine, is not associated with systemic manifestations. However, extraintestinal extension of the infection, specifically biliary tract invasion by *Giardia* [42, 43], can present with the classic inflammatory features of acute or subacute cholecystitis or cholangitis. The associated febrile response activates a series of catabolic responses, including impaired fat utilization, mobilization of amino acids, and increased urinary loss of nitrogen and zinc [78, 79]. Stimulation of leukocyte endogenous mediator obligates the redistribution of zinc and iron from the circulation to the liver [80]. The reordering of priorities for protein anabolism in the body consequent to the diversion of amino acids into acute phase protein synthesis and leukocyte proliferation may also have nutritional implications for the patient with hepatobiliary giardia syndrome.

The Effect of Giardiasis on Growth and Development

Experimental infections in mice with 100, 1,000, and 10,000 *G. muris* cysts led to significant, dose-dependent reduction in weight gain after 28 days of infection; infected animals gained 1.4–3.2 g less than control animals [15]. Because several types of parasitic infection are often found together in a given individual, however, the contribution of giardiasis per se to growth impairment in man has not been well defined.

Kay et al. [21] in Melbourne, Australia, reviewed a hospital population of 1,147 children who had undergone diagnostic duodenal aspiration and small bowel biopsy in the course of a three-year period. Giardiasis had been diagnosed in 154. The great majority of the *Giardia* were encountered in children aged one to four, and the most common presenting symptom-complex was diarrhea and "failure to thrive." Careful posteradication follow-up observations lasting from two weeks to 10 months and involving 24 children revealed that during the interval of rehabilitation 19 subjects exceeded the expected, ideal, age-adjusted weight gain. This "catch-up" growth, which ranged from 100 g to 3.2 kg, has been interpreted as evidence

that the symptomatic giardiasis had a major negative impact on protein-energy nutriture.

In a recently concluded study in a highland village in Guatemala, workers from the Program of Nutrition and Infection of the Institute of Nutrition of Central America and Panama (INCAP) sought to quantify the possible nutritional benefits to a community from parasite control programs [81]. In this village, the colonization of the intestines of young children with *Giardia* through early life had been documented in a prospective fashion. Mata et al. [82] followed the prevalence and incidence of infection with *G. lamblia* in a cohort of children through the first three years of life (figure 2). Over 22% of the children had giardiasis at 36 months of age. In this recent study [81] 159 children two to five years of age were randomly assigned to one of four bimonthly treatments (placebo, piperazine alone, metronidazole alone, and metronidazole plus piperazine); growth and parasite loads were followed at intervals for a year. Piperazine treatment produced neither a consistent reduction in the burden of *Ascaris* nor a significant growth effect; metronidazole therapy did reduce the prevalence of *Giardia* in the stools. Moreover, in the two groups that received metronidazole, an average gain of 300 g in weight and 1 cm in height in excess of the mean for the two groups that did not receive this chemoprophylaxis was recorded during the year. The difference was statistically significant only for the increment in height. The biological significance of such minimal differences in growth parameters is not immediately evident.

In addition, the predictive inaccuracy of stool examination for the diagnosis of giardiasis may have some bearing on the interpretation of these findings. Several recent studies demonstrated that only 50% of giardial infections confirmed by duodenal intubation procedures could be diagnosed simultaneously by fecal examinations [21, 71, 83]. In severely malnourished, hospitalized children in Costa Rica, only seven of 38 children in whom *Giardia* were found had positive stools. The remaining 22 children were diagnosed only by the passage of a Beal capsule on a string into the small intestine [84]. Thus, the prevalence of giardiasis in this population was probably underrated, and the efficacy of chemoprophylaxis in the study by Gupta was probably overrated [81].

The trophic effect of metronidazole therapy, apart from its antiprotozoal activity, cannot be excluded as the cause of the differential growth. However, the definition of the role of giardiasis in the aggravation of protein-energy malnutrition in a general population merits further investigation of the type initiated at INCAP in Guatemala.

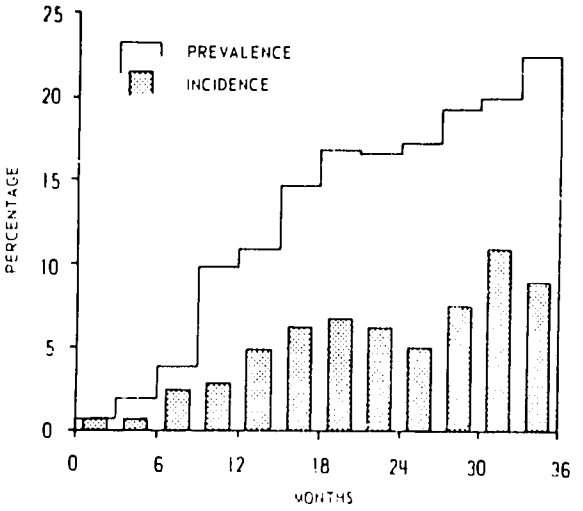

Figure 2. Incidence and prevalence of *Giardia lamblia* infection, determined by weekly examinations, in a cohort of children studied from birth to three years of age in Santa María Cauqué, Guatemala. From [82], reproduced with the permission of the American Medical Association.

The Effect of the Nutritional Status of the Host on Giardiasis

The variable expression of giardiasis suggests that biological factors might condition the degree and persistence of infection. Impaired nutriture can exert both detrimental and protective effects on the host's susceptibility to infection, and, therefore, the nutritional status of the host might constitute one of the biological determinants of the susceptibility to giardiasis in man. Unfortunately, little epidemiologic data is available to help explain the pattern of expression of giardiasis within populations at nutritional risk. Oyerinda et al. [85] in Lagos, Nigeria, described a peak prevalence of excretion of giardial organisms in stools between the ages of one and five; 13.8% of boys and 14.4% of girls excrete *Giardia* in stools. It is intriguing to speculate that the age of highest susceptibility to giardiasis in the Lagos population corresponds to the age of greatest nutritional vulnerability; unfortunately, however, simultaneous data on the nutri-

tional status of the various age strata in the population studied by Oyerinda et al. [85] are not presented.

Synergism

Given the lack of clear epidemiologic associations, we must rely on inferential data and inductive reasoning in determining the influences that the nutritional status of the human host might exercise on the expression of giardial infection. An association between giardial infections and immunodeficiency syndromes has been extensively documented. Immunodeficiency syndromes in humans, primarily those resulting in severe deficiency in the humoral immune system and consequent hypogammaglobulinemia, are associated with intestinal lesions; the histologic picture involves both "nodular hyperplasia" and "sprue-like" (total villous atrophy) lesions, and the alterations can occur simultaneously [67, 86]. The intestinal aspects of this condition have received a host of names, but Ament and Rubin [67] suggest the term "gastrointestinal immunodeficiency syndromes." An important feature of these syndromes, relevant to the present discussion, is the high incidence of coexistent giardial infection. Among a large number of patients with immunodeficiency syndromes, 80% of those with intestinal manifestations had concurrent giardiasis [86]. Extraordinarily high incidences of giardial infections have been reported in many clinical series of immunodeficiency syndromes [86–95]. Whether reduced intestinal levels of immunoglobulins predispose to giardiasis in individuals without frank immunodeficiency syndromes is a matter of controversy. Zinneman and Kaplan [96] found reduced levels of IgA in the intestinal secretions of unselected patients with giardiasis. Jones and Brown [97] have criticized the methodology used in the former study, and, in a subsequent investigation, were unable to confirm the earlier findings. The immune defects prominent in the aforementioned observations are predominantly humoral, specifically involving deficiencies of immunoglobulin antibodies in the IgG and, especially, the IgA class. That cell-mediated immunity is also involved in antigiardial defenses, however, is suggested by studies in an animal model. Athymic nude (*nu/nu*) mice have been found to have more prolonged and more lethal infections with *G. muris* than do immunologically intact mice [98].

Human protein-energy malnutrition is associated with a selective array of defects in host immune defenses [99]. It primarily involves the contribution of cell-mediated immunity [100–102], but, occasionally, deficient levels of IgG and IgA are seen in malnourished children [100, 103], and specific IgA production in response to viral vaccines is attenuated in patients with protein-energy malnutrition [104]. Conceivably, the immune deficiency state induced by such malnutrition provides an intraintestinal milieu conducive to giardial infection in a manner analagous to that of acquired "gastrointestinal immunodeficiency syndrome." The result is a high incidence of giardiasis in conjunction with protein-energy malnutrition.

Decreased secretion of gastric acid and higher intragastric pH are also prominent features of protein-energy malnutrition [105, 106]. Achlorhydria and hypochlorhydria have been associated with increased risk of giardial infection. Over 54% of patients with symptomatic giardiasis have reduced gastric acid secretion [107]. That this reduced secretion is a factor predisposing to rather than resulting from giardiasis is suggested by observations of florid giardial infections following gastric surgery [108, 109] and by the fact that achlorhydric individuals have a higher incidence of giardiasis [108, 110].

Direct observations of this phenomenon in severely malnourished children have been provided by Lopez et al. [84]. The prevalence of *Giardia* rose from 23% in children with a gastric pH of 3 to 60% in children with a gastric pH ≥ 6. The hypochlorhydria of malnutrition, therefore, represents another potential pathophysiologic predisposition to giardiasis.

Protein-energy malnutrition is also associated with bacterial contamination of the normally sterile upper small intestine [111, 112]. In the study by Mata et al. [111], nine of 13 subjects also had giardiasis. It was not clear whether overgrowth favors the pathogenicity of *Giardia* or whether some unidentified common factor predisposes to combined bacterial, fungal, and protozoal infection in the upper gut. If we accept the luxury of certain assumptions about causality, three factors common to human protein-energy malnutrition—immune deficiency, decreased gastric acid

secretion, and bacterial or fungal overgrowth of the intestine--could all promote a more favorable environment for *Giardia* to infect the human host.

Antagonism

Our limited knowledge of the nutritional requirements of *G. lamblia* in vivo limits speculation as to what nutritional deficiency or deficiencies in the human host might be antagonistic to the establishment of giardiasis. Apparently, however, unlike other protozoal endoparasites, *Giardia* are not predominantly intracellular pathogens. Thus, the conventional basis for nutritional protection by malnutrition is not present. As with synergistic interactions, however, more penetrating epidemiologic data on the prevalence of giardiasis in populations with defined nutritional states are essential to the refinement of our concepts and hypotheses regarding possible antagonistic interrelationships of giardiasis and nutrition in man.

Conclusions and Recommendations

Giardiasis is a common protozoal infection, especially in young children. Impairment of nutriture can occur in that minority of giardial infections in which frank malabsorption syndrome or specific malabsorption of one or more nutrients develops. However, with the variability of expression of this disease, the vast majority of individuals with giardiasis have subclinical infections. The public health aspects of the nutritional implications of giardiasis at the population level are of greater importance. Here, however, our information is most limited. Precise data upon which to base any determination of additional nutritional requirements for individuals with subclinical giardiasis are unavailable. The present review indicates that giardiasis might contribute to impaired protein-energy nutriture, as suggested by the Guatemalan study [82]. But the magnitude of the contribution is not major. It is likely, moreover, that the presence of giardiasis in some individuals increases their requirements for total energy, vitamin A, folic acid, and vitamin B_{12}. The ability to utilize fat as a form of dietary energy might be compromised in these same individuals; therefore, complex carbohydrates as the source of additional energy appear to be the prudent recommendation. Information on a number of micronutrients in subjects with clinical or subclinical giardiasis is totally lacking. The lack of a sensitive and noninvasive diagnostic test for accurate assessment of the prevalence of giardiasis in a population of children living in the community limits our ability to perform nutritional and epidemiologic studies to further refine our information.

That the nutriture of an individual retards or promotes the development of infection with *G. lamblia* is not supported by systematic epidemiologic data. Both the anecdotal information available and our own inferences suggest that a synergistic relationship between malnutrition and giardiasis is more likely than an antagonistic one. Prospective studies on malnourished subpopulations of children during rehabilitation from protein-energy malnutrition should be undertaken to provide greater insight into the influence of host nutritional status on susceptibility to giardiasis. The resolution of the issue involving synergism and antagonism is of more than academic interest: it has implications for the determination of cost/benefit analysis and public health strategy to reduce the prevalence and adverse effects of giardiasis in communities. On the one hand, if children with giardiasis can benefit from additional nutrients fed to compensate for the *Giardia*-related increase in requirements, and if, at the same time, their improved nutritional state acts to enhance their resistance to giardial infection, then food supplementation alone represents a comprehensive approach to the control of *Giardia*. On the other hand, if the evidence for either of these mechanisms is uncertain, a definite role for more expensive, chemoprophylactic and/or environmental sanitation measures is suggested. In summary, selective investigation into the nutritional impact of giardiasis aimed at the formulation of the most logical and cost-effective public health strategy is still essential to the resolution of the dilemma.

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Discussion: Amebiasis, Giardiasis, and Malnutrition

Amebiasis, especially with amebic abscess of the liver, is a serious clinical problem in Mexico and some other developing countries. However, in most tropical countries, the clinical disease is not as common, even though the overall prevalence of *Entamoeba histolytica* may be as high as that reported for Mexico. Such observations suggest the existence of strains with special virulence and/or with a particular epidemiologic behavior, since crowding, frequent contamination of food with enteric pathogens, and malnutrition appear common to all populations in which intestinal amebiasis is highly prevalent.

Immunization with antigens of *E. histolytica*, as well as infection with this parasite, may induce suppression of T-cell-mediated immune responses. The clinical significance of this phenomenon is unclear, but the observation complicates interpretation of the depressed immune function so commonly observed among malnourished infants who persistently harbor *E. histolytica* and other parasites. What portion of immunologic abnormalities can be credited to malnutrition and what is the contribution of parasitic infection? Most importantly, what is the consequence for the host and how can the defects be reversed? Unfortunately, previous studies have not taken into consideration the presence of concurrent giardiasis, shigellosis, or other enteric infections prevalent in the same geographic area.

Recent data concerning iron nutriture and infection may be very relevant in amebiasis. Free iron is required in the lumen of the gastrointestinal tract for proliferation of *E. histolytica*. However, iron is not readily available when infants are breast fed. Consistent with this is the fact that babies who are exclusively breast fed are remarkably resistant to colonization and invasion by ameba, other parasites, and bacterial pathogens. Food supplementation programs generally provide iron; however, it is often supplied in forms that have low bioavailability for the host but are readily accessible to the pathogen for its multiplication in the gastrointestinal tract.

Throughout the world, 15%-30% of children in developing countries are infected with *Giardia lamblia* by the age of two years. This may be related to the observation that *G. lamblia* is transmitted by water and also by person-to-person contact. The latter would be an important mechanism of dissemination of infection in crowded households where domestic sanitation is poor and there is little opportunity for personal hygiene. The inoculum may be a factor of major importance in determining severity of the disease in villages. However, the wide spectrum of clinical manifestations of giardiasis and the inadequacy of diagnostic tools make it difficult to clearly establish such relationships in the field. Furthermore, symptoms of chronic giardiasis, such as diarrhea and malabsorption, cannot be separated from those attributed to bacterial overgrowth of the small intestine.

Chronic giardiasis interferes with absorption of fats, carbohydrates, and vitamins; however, there is no evidence of loss of endogenous protein. Although *Giardia muris* has also been shown to impair growth of experimental animals, studies in humans showing an apparent increase in height after prophylactic long-term therapy with metronidazole should be interpreted with caution since this drug is effective against anaerobic bacteria that may be involved in the overgrowth of bacteria in the bowel. It is extremely difficult to assess therapeutic interventions, especially under field conditions where so many variables interact to determine growth and development of children.

Acute malnutrition may affect the outcome of giardiasis by impairing host defenses, lowering gastric acid secretion, altering intestinal motility, or impairing synthesis of secretory IgA. These methods are suggested by studies in experimental animals and clinical observations on the behavior of *G. lamblia* in patients with various immunodeficiency syndromes, in whom massive infection may occur.

The significance of isolated *G. lamblia* or *E. histolytica* infections in the malnourished host remains uncertain. Prospective field studies combined with detailed clinical investigation of preschool children are essential to an understanding of this problem. Because these infections are generally not isolated, other etiologies must be investigated to ensure appropriate patient selection for study so that data can be interpreted and valid conclusions drawn.

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Sociocultural Factors in the Control and Prevention of Parasitic Diseases

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Control and prevention of parasitic disease depends on an adequate knowledge of interactions among factors such as human behavior, the environment, and the life cycles of parasites. Sociocultural factors in large part determine transmission and persistence of parasites. The main determinants are poverty, low educational level, deficiencies in home technologies, high demographic density, and ruralism. Selected interventions designed to improve any of these situations may fail if they are applied in an isolated manner. The holistic implementation of interventions has proved successful in the control and prevention of parasitic infections in several parts of the world. The implementation of several kinds of interventions simultaneously, that is, a holistic approach, combined with an awareness of a society's infrastructure, can produce favorable results. For such an awareness—when it provokes action—can improve the overall quality of life.

The complexity of controlling and preventing parasitic disease stems from the fact that humans and parasites have evolved through millions of years in constant interaction with each other and with the environment. The result is an enormous variety of life cycles and ecological situations, ranging from the simple to the highly complex or even bizarre. Control is then difficult because one must take into consideration not only the nature and natural history of the parasites, but also the biological characteristics and behavior of the humans involved and the environmental circumstances under which they dwell.

As was classically illustrated by Stoll [1], humans live in a wormy world (especially in the tropics and subtropics), whether in relatively undeveloped or in industrialized countries. The list of worms that are pathogenic for humans is still long (table 1) and will get longer as unexpected parasites cross species barriers. Furthermore, new parasitic entities are always being discovered; the relatively recent additions include *Capillaria philippinensis* [2], which causes an enteropathy characterized by protein loss and malabsorption, and *Angiostrongylus costaricensis* [3], which causes eosinophilic granulomas in children.

Regardless of the diversity in natural history of humans and parasites, infection is generally acquired by (*1*) ingestion of food, water, or soil that has been contaminated with feces or urine carrying eggs or cysts of parasites; (*2*) acquisition of cysts or eggs from another person (person-to-person transmission); or (*3*) exposure to vectors carrying infective stages or to larvae of the parasites (e.g., cercariae) released into the environment. This situation explains the multiplicity of infection often seen in poor, underdeveloped regions of the world. For instance, data on rates of infection with intestinal parasites among children of a typical Mayan Indian village of Guatemala (table 2) indicate a very high prevalence and the coexistence of multiple infections [4]. Because the village is in the highlands (elevation, ~6,000 feet), and migration to coastal areas is negligible, neither hookworm nor vector-borne parasitic infections are prevalent. This pattern contrasts with the situation of poor villages in lowland tropical regions, where transmission of arthropod-borne infections is intense, as illustrated by data from Chad (table 3) [5]. The latter situation is more critical because, in addition to the vector-borne infections, villagers in Chad and in similar ecosystems also bear the burden of many intestinal parasites.

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Table 1. Worms important in human infections.

Ascaris lumbricoides	*Trichinella spiralis*
Toxocara canis	*Heterophyes heterophyes*
Lagochilascaris minor	*Metagonimus yokogawai*
Anisakis species	*Gastrodiscoides hominis*
Phocanema species	*Fasciolopsis buski*
Contracaecum species	*Echinostoma revolutum*
Enterobius vermicularis	*Fasciola hepatica, F. gigantica*
Strongyloides stercoralis	*Clonorchis sinensis*
Micronema deletrix	*Opistorchis felineus, O. viverrini*
Trichostrongylus orientalis, T. axei, T. colubriformis, T. vitrinus	*Dicrocoelum dendriticum*
Oesophagostomum species	*Paragonimus westermani, P. africanus, P. skrjabini, P. heterotremus, P. mexicanus, P. uterobilateralis*
Ancylostoma duodenale, A. caninum, A. braziliensis	*Schistosoma mansoni, S. japonicum, S. haematobium, S. intercalatum, S. mattheei, S. bovis, S. spindale, S. rodhaini*
Necator americanus	*Taenia saginata, T. solium*
Angiostrongylus cantonensis, A. costaricensis	*Echinococcus granulosus, E. multilocularis, E. oligarthrus, E. vogelsi*
Wuchereria bancrofti, W. malayi	*Multiceps multiceps, M. serialis, M. brauni*
Brugia malayi	*Hymenolepsis nana, H. diminuta*
Loa loa	*Dipylidium caninum*
Onchocerca volvulus	*Diphyllobothrium latum*
Dipetalonema perstans, D. streptocerca	*Spirometra mansonoides*
Mansonella ozzardi	
Dirofilaria inmitis, D. tenuis	
Dracunculus medinensis	
Gnathostoma spinigerum	
Trichuris trichiura	
Capillaria philippinensis, C. hepatica	

Priorities for Control and Prevention

Each parasite has its particular habitat and, in general, a complex life cycle intimately intertwined with and determined by the biological characteristics and behavior of humans. Even as a desk exercise, the designing of intervention programs for control and prevention of parasitic infections is possible only when much is known about host and parasite. It appears convenient to select those parasites that are most damaging to humans in terms of morbidity, nutrition, mortality, and economic losses. At a global level, the list of important parasites includes about 20 species for which priority can be established (table 4). The problem should be examined in each nation by means of well-established criteria. The parasites listed are important, but skepticism about their overall public-health significance may arise (e.g., Chagas' disease in certain regions of the American continent). Also, the significance of

Table 2. Prevalence of intestinal parasites among three-year-old children in a village of Guatemala.

No. of species per person*	Rate of infection (%)	Cumulative prevalence (%)
0	2.4	
1	30.9	97.6
2	23.8	66.5
3	19.0	42.7
4	9.5	23.7
5	7.1	14.2
≥6	7.1	7.1

NOTE. Data are from [4].

* Values given include all intestinal parasites, four of the most common being *Ascaris lumbricoides* (77.8%), *Giardia lamblia* (19.1%), *Entamoeba histolytica* (10.4%), and *Trichuris trichiura* (3.0%).

such highly prevalent parasites as *Ascaris lumbricoides* and *Entamoeba histolytica* must be judged as a function of geographic location, epidemiologic determinants, and nutritional status. For instance, *E. histolytica* is prevalent and causes serious disease in Mexico [6], but not in Central America. On the other hand, *Ascaris* seems important wherever malnutrition exists since it contributes to wastage [7].

Walsh and Warren [8] established priorities for the control of various global parasitic infections (table 5). Limitations on control are due in great part to sociocultural restraints in the populations involved. Effective control measures apparently exist only for malaria and hookworm, but even with these infections there are problems in certain ecosystems resulting from a particular type of human behavior. Furthermore, human intervention with insecticides and antiparasitic drugs has induced the emergence of and resistance to chemical agents among vectors and parasites.

The priorities in table 5 cannot be generalized to all nations alike. There are well-known areas where control of schistosomiasis and Chagas' disease is a high priority. In other regions, hookworm and cutaneous leishmaniasis are progressively disappearing because of socioeconomic and cultural changes. Furthermore, some parasitic diseases have been controlled to a significant extent in advanced societies (industrial nations)—and, more recently, in countries in transition—as a result of an improvement in the quality of life. For instance, in Costa Rica, the incidence of cutaneous leishmaniasis appears to be decreasing [9],

Table 3. Prevalence of systemic parasites in a village of Chad.

No. of species per person*	Rate of infection (%)	Cumulative prevalence (%)
0	2.6	
1	17.6	97.4
2	47.1	79.8
3	21.0	32.7
4	10.1	11.7
5	0.8	1.6
6	0.8	0.8
7	0	0

NOTE. Data are adapted from [5].

* Values given include all intestinal parasites, with individual rates and sites of infection as follows: *Onchocerca volvulus* (skin), 91.6%; *Plasmodium falciparum* and *Plasmodium malariae* (blood), 43.7%; *Schistosoma mansoni* (stool), 36.1%; *Dipetalonema perstans* (blood), 28.6%; *Loa loa* (blood), 9.2%; *Schistosoma haematobium* (urine), 7.6%; and *Wuchereria bancrofti* (blood), 5.0%.

Table 4. Parasites of high prevalence in humans at a global level.

Plasmodium falciparum, P. vivax
Trypanosoma gambiense, T. rhodesiense
Trypanosoma cruzi
Leishmania donovani, L. tropica, L. brasiliensis, L. mexicana
Entamoeba histolytica
Giardia lamblia
Schistosoma japonicum, S. haematobium, S. mansoni
Dracunculus medinensis
Onchocerca volvulus
Wuchereria bancrofti
Ascaris lumbricoides
Trichuris trichiura
Ancylostoma duodenale, Necator americanus
Strongyloides stercoralis

that of intestinal parasitism and diarrhea has been significantly reduced [10, 11], malaria is largely under control, and Bancroft's filariasis remains circumscribed to its original niche in Puerto Limón on the Atlantic coast [12, 13].

Once priorities are established, the life cycles and transmission mechanisms of the prevalent parasites should be examined to see how human sociocultural characteristics favor infection. Table 6 lists the means of transmission of the main parasitic infections. Transmission to humans may be from an invertebrate (mosquito, reduviid, snail) or a vertebrate animal host or from another human. The parasite undergoes important changes in the vector that lead to development of the infective form. This model demands complex logistics for control: the habitat and behavior of each vector must be known and taken into account as a function of the complex way of life of humans in the various ecosystems. Furthermore, in the control of parasites that have other vertebrate hosts (and may, in fact, represent zoonoses), the complex relationships of these hosts with humans and the environment must be considered.

The other type of transmission is simpler because it involves the passage of the parasite from person to person. Although it may require maturation of infective forms in the outside environ-

Table 5. Priorities for intervention to control parasitic diseases in developing countries, 1980.

Priority, disease	Criterion			
	Prevalence	Morbidity	Mortality	Control
High				
Malaria	High	High	High	Effective
Hookworm	High	High	Low	Effective
Medium				
Schistosomiasis	High	Low	Low	Difficult
Onchocerciasis	Medium	High	Low	Difficult
Low				
African trypanosomiasis	Low	High	High	Difficult
Filariasis	High	Low	Low	Difficult
Visceral leishmaniasis	Low	Low	Low	Difficult
Giardiasis	High	Low	Very low	Difficult
Ascariasis	High	Low	Very low	Difficult
Amebiasis	High	Very low	Very low	Difficult
Chagas' disease	Low	Very low	Very low	Difficult
Cutaneous leishmaniasis	Low	Very low	Very low	Difficult

NOTE. Data are adapted from [8].

Table 6. Transmission of major parasites to humans.

Route of transmission, vector (if any)	Mechanism	Infective form	Parasite
Vertebrate-invertebrate-vertebrate (humans)			
Mosquito	Inoculation	Sporozoites	*Plasmodium*
Mosquito	Inoculation	Promastigotes	*Leishmania**
Black fly	Penetration	Third-stage larvae	*Onchocerca*
Mosquito	Penetration	Third-stage larvae	*Wuchereria*
Tse tse fly	Inoculation	Metacyclic trypomastigotes	*Trypanosoma (African)*
Reduviid	Penetration	Metacyclic trypomastigotes	*Trypanosoma (American)**
Crustacean	Ingestion	Larvae	*Dracunculus**
Snail	Penetration	Cercariae	*Schistosoma**
Human-human	Penetration	Third-stage larvae	Hookworm
	Ingestion	Embryonated eggs	*Ascaris, Trichuris*
	Ingestion	Cysts	*Giardia, Entamoeba*
Vertebrate-human	Ingestion	Cysticerci	*Taenia saginata, T. solium*
	Ingestion	Embryonated eggs	*T. solium*

NOTE. There are other forms of transmission, for instance, man-invertebrate-vertebrate-man, such as in *Diphyllobothrium latum*.

* There could be more than one vertebrate host.

ment, direct person-to-person transmission appears to be important, for instance, with some intestinal protozoa. While parasites with invertebrate hosts may be more difficult to control, the behavior of humans in underdeveloped tropical and subtropical regions favors persistence and interferes with control and prevention of disease caused by parasites that are transmitted from person to person.

Sociocultural Factors and Acquisition of Infection

The fact that incidence of several parasitic infections is decreasing in certain areas that have improved their social and economic situations is a good indication of the relevance of human living standards as a determinant of infection. This relation is well illustrated for malaria, hookworm, and other declining parasitic diseases in Costa Rica, Cuba, and Trinidad-Tobago; a dramatic example involves the control of schistosomiasis in China [14]. Table 7 describes factors favoring establishment of infection with parasites of global significance. Determinants such as poverty, lack of education, and crowding are central to the issue. Religious practices are another variable.

For hookworm infection, ascariasis, amebiasis, and other intestinal parasitic diseases, the determining behavioral factor is defecation on the ground near streams and water reservoirs, which favors contamination of the environment. Indiscriminate squatting results in pollution of home premises, foods, drinking water, and agricultural fields. Infection is usually acquired by ingestion of water and food directly or indirectly contaminated with feces. Transmission from person to person as a result of poor personal hygiene, crowding, and sleeping of several persons in one bed is also important in certain parasitic infections. Behavioral research is needed in order to understand and modify patterns of life that maintain transmission [15].

For schistosomiasis, defecation and urination on the ground near streams and water reservoirs favor contamination of the snail's habitat. Infected snails eventually discharge cercariae into the water, and these larvae infect humans. Ablution favors spread, particularly in the low socioeconomic classes, who must defecate near water sources because of sociocultural traits and prevailing conditions. Squatting at dawn and night also favors exposure to mosquito-borne and hookworm infection.

With guinea worm infection, a serious disabling disease, the larvae emerge from human tissues through broken skin blisters and fall into the water, where they establish themselves inside small crustaceans. Infection is spread to humans who drink water harboring infected *Cyclops* [16]. Evidently, control demands community knowl-

Table 7. Sociocultural determinants of parasitic infection.

Infection	Factors*
Hookworm	Squatting, ablution; agricultural practices; lack of shoes
Giardiasis, amebiasis, ascariasis, trichuriasis	Squatting, ablution; ingestion of contaminated food, water, and soil; living in crowded quarters
Schistosomiasis	Squatting, ablution; agricultural practices; bathing in contaminated water
Guinea worm	Contact with or drinking of contaminated water
Malaria, filariasis	Poor housing; outdoor activities after dark
Chagas' disease	Poor housing; animal reservoirs in or around homes
Sleeping sickness	Working in endemic savanna
Onchocerciasis, leishmaniasis	Dwelling and working near ecologic niches

* The main determinants of parasitic infection that are reflected by these relatively specific factors are poverty, low educational level, deficient home technology, high population density, ruralism, and dispersion.

edge of how disease is acquired; in the absence of this information, preventive measures cannot be taken.

Significant control of malaria has been attained in the past with little regard for sociocultural factors; rather, reliance has been placed mainly on the use of insecticides, treatment, and chemoprophylaxis. However, the development of insecticide resistance in vectors, of drug resistance in *Plasmodium*, and of an increase in extradomiciliary habits of humans has made control more difficult and has set back eradication of malaria in many areas of the world. These complicating factors demand both aggressive research into new approaches to control and greater understanding of the disease among the affected populations [17].

With regard to Chagas' disease, poor housing and crowding are crucial factors because they favor contact between reservoir hosts (domestic animals), humans, and the reduviids harboring *Trypanosoma cruzi* [18]. Similarly, maintenance of Bancroft's filiariasis depends on the availability of individuals with microfilaremia to domiciliary arthropod vectors. Poor housing, unprotected sleeping, and outdoor activities after dark are important elements in transmission.

The relation of humans to cattle in the pasture lands and to water sources determines exposure to tsetse flies. Rates of infection with African trypanosomes vary as a function of distance to these endemic foci [19].

Onchocerciasis is transmitted by black flies dwelling in well-defined ecological niches. Acquisition depends on exposure to bites of *Simulium* in endemic areas and is favored by agricultural practices and ruralism [5].

In cutaneous leishmaniasis, infection is maintained in mammals inhabiting the forest [20]. Humans acquire the disease when they clear the forest land or hunt or when they settle in endemic areas [21]. Special behaviors, such as hunting at night, account for the acquisition of infection only by adult males in certain circumstances [22]. In other instances, dwelling near the habitat of the animal reservoirs (e.g., the hyrax of Ethiopia) is the determining factor for infection of humans [23].

Recent observations by our group revealed that the epidemiology of cutaneous leishmaniasis among Amerinds of Costa Rica, varied according to the degree of clearing of and contact with the virgin forest. The appearance of lesions was more intense and precocious in one locality of the Guaymi (Limoncito), where people live in close contact with relatively virgin forest, than in another (Abrojos), where part of the forest had been cleared. When skin tests (reaction) were performed, 33% of children five to nine years old in Abrojos and 86% in Limoncito reacted to *Leishmania* (author's unpublished observations).

Main Determinants of Parasitic Infection

The main determinants of transmission of parasitic infection are prevailing poverty, deficient education, deficient home technology, high demographic density, and ruralism. These determinants account for the choice of habitats, ways of life, and other important elements that are required for maintenance of infection in humans.

Poverty and low educational level. Poverty and a low educational level coexist with and strongly determine poor housing, deficient personal hygiene, and equivocal attitudes toward

health and disease. Poverty characterizes families with low income or no income at all, deficient maternal (familial) technology, dependence on subsistence agriculture, and lack of sociopolitical development.

Poverty, crowding, and inadequate technology interfere with procurement of the needed amounts of food and exacerbate parasitic infection. The situation may be complicated by seasonality; negative conditions are accentuated during certain seasons of the year in many parts of the world, with an increased risk of infection and malnutrition [24, 25]. Such considerations alone make it difficult to design and effect successful methods for control and prevention. In the correction of these deficiencies, the holistic (integral) approach is certainly the most promising [4].

Maternal (familial) technology. Our observations in a highland Mayan Indian village revealed that certain child-rearing practices and attitudes of mothers (and other members of the family) may be more important in the transmission of disease and the development of malnutrition than socioeconomic class or degree of schooling. Behavior of mothers is often related to training during their own childhood and adolescence. The wealth of maternal information has been called maternal technology [26]. Elements in this technology include (*1*) the handling and storage of water; (*2*) the preparation, handling, and storage of food; (*3*) the care of children during illness; (*4*) alimentation during convalescence; (*5*) attitudes toward primary health care; (*6*) disposal of excreta and waste; (*7*) personal hygiene; (*8*) patterns of eating and sleeping; (*9*) proclivity to improve housing and environmental sanitation; and (*10*) pattern of socializing. A particular mother may store drinking water in a separate earthen jar with a narrow mouth; this simple measure may prevent contamination of the water with pathogenic organisms. Such behavior is not necessarily based upon a concept of causality of disease. Most mothers in the village we studied store water in a large jar, and such all-purpose water becomes contaminated. If a mother habitually boils water, her family may be protected from such contamination.

Inadequate hygiene results in food contamination in the home [27]. In contrast, adequately prepared (well-cooked and well-ground) mixes, purees, and mashes of locally available foods are excellent for children during weaning and for all family members during convalescence from illness. Some mothers limit the intake of food by children during illness and convalescence, while others maintain breast-feeding at these times, thus diminishing deterioration of the child's nutritional status. A deficiency in maternal technology increases the risk of exposure to viruses, bacteria, and parasites and also enhances the negative effects of infection while decreasing the host's capacity to cope with infection.

An important element of maternal technology is a positive attitude toward primary health-care services, which often conflicts with traditional medicine and the local customs and beliefs. Some mothers readily accept the value of primary health care, particularly vaccination, deworming, oral rehydration, and family planning; others fail to do so. Wray and Aguirre [28] advanced the concept of "maternal incompetence:" the failure—unintentional or intentional—to seek medical attention for a child who is suffering from a condition such as acute diarrheal disease, dehydration, or serious infection. Other elements of maternal technology concern habits of eating, sleeping, defecation, ablution, and socializing, all of which are highly relevant to disease transmission [29]. Maternal incompetence and inadequte maternal technology, along with other behavioral factors and social stresses, favor disease transmission and decrease the quality of life.

High population density and ruralism. These two main determinants of infection may have a positive or negative effect, depending on the degree of socioeconomic development. For instance, a high population density in less developed societies favors the spread of parasitic infection, since traditional behavior leads to environmental contamination and to the perpetuation of vector-borne parasites and of carriers and reservoirs of disease. A few individuals harboring parasites easily seed the environment and expose a large number of people to infection in crowded, underdeveloped conditions. This situation accounts in part for the extremely high prevalence of parasitic infections throughout the less developed tropical countries (tables 2 and 3). However, if the level of education rises and personal and environmental hygiene improves, infections can remain circumscribed to a few families within a given community, even if crowding prevails.

Ruralism and population dispersion mean that

isolated families in forest, jungle, or desert have poor access (or no access) to health services, educational facilities, and markets [24]. In socioculturally undeveloped conditions, traditions, beliefs, and taboos persist, as do contamination of the environment and exposure to ecologic niches of parasites. Infections, malnutrition, and other health problems are prevalent and exert their maximal effect under such conditions. However, if significant sociocultural development is attained—as seems to be the case in Trinidad-Tobago, Taiwan, Puerto Rico, and Costa Rica—ruralism and dispersion of the rural population may become an asset. First, communication between families may take considerable time, and this delay curtails the spread of disease. Second, if the family enjoys a high level of maternal (familial) technology, entrenchment of certain parasites, such as hookworm, becomes difficult. In fact, intestinal parasitism in rural Costa Rica now appears to exist only in families with the lowest level of sociocultural development (author's unpublished observations). Furthermore, our observations on the Amerindian Guaymi, who live in marked isolation and dispersion, reveal a lower incidence of intestinal infection than in crowded urban neighborhoods that are more advanced economically. In addition, nutritional wasting and severe forms of malnutrition have not been detected among Guaymi children [30, 31].

The Holistic Approach

A historical appraisal of the results of intervention programs designed to reduce the incidence of infection and malnutrition shows that programs involving food supplementation, installation of latrines, supervision of water supplies, and prenatal care have had very limited impact or have failed to improve the conditions they were supposed to modify [32]. More often than not, the overall cost of the programs precludes implementation among populations who live in areas that are difficult to reach. Cost-benefit analysis indicates that primary health care is probably the most feasible type of intervention for rural developing regions [8].

On the other hand, history teaches a relevant lesson: the incidence of leading infectious diseases declined significantly in Europe and North America before the causes and specific preventive measures were discovered [33]. Furthermore, there is evidence that the orthodox approach to diagnosis and treatment of disease often does not work when underdevelopment prevails and when intervention programs are implemented cross-culturally [4, 34]. Observation clearly indicates that control of seriously debilitating diseases is attained through an improvement of sanitation, housing, and education—that is, the quality of life [35, 36]. Thus, social determinants of disease are the most important factors to identify when planning intervention programs.

The holistic approach (implementation of several types of intervention simultaneously) appears to be the most reasonable means of improving the quality of life. Unfortunately, the cost and effort of such an approach may be staggering in many developing nations. Thus, the holistic approach demands political decisions. These decisions may be catalyzed by the sustained efforts of an outspoken scientific community. However, pressure from the affected population and the eventual politicization of health may be the most important forces in the mobilization of public health programs. The scientific community must offer various alternative solutions to the problems that are identified.

The holistic approach requires an infrastructure for primary health care. The emphasis should be on maternal and child health, with these interrelated goals: (*1*) promotion of optimal nutrition through breast-feeding for several months and adequate food supplementation during the first two to three years of life; (*2*) control of diarrheal disease by oral rehydration and proper alimentation during illness and convalescence; (*3*) prevention of diarrheal disease and parasitic infection by improvement of personal and home hygiene; (*4*) immunization against the common communicable diseases of childhood; (*5*) community organization for improvement of the environment (water supply, latrines, waste disposal) and surveillance of health; (*6*) chemotherapy and chemoprophylaxis where malaria and other drug-susceptible parasitic diseases are prevalent; and (*7*) family planning.

Research on the environmental, sociocultural, and behavioral factors relevant to parasitic infection is needed. A research model different from the purely biomedical one is in order [37]; emphasis should be placed on health services and the transfer of technologies to the organized commun-

ity. The collaboration of researchers in biomedicine, social sciences, and planning presumably will yield better results than have been obtained so far. A next step is the definition of priorities for intervention in each nation and in the various ecosystems within each country. Finally, research should focus on ethnic, cultural, and behavioral factors that determine infection, malnutrition, and underdevelopment in the community. The assessment of priorities for research must be an ongoing exercise, while attempts at control and prevention through the application of existing knowledge should continue. Also, efforts should take into account cost-benefit analyses for improvement of health-care delivery services.

An understanding of the complexity of the determinants of parasitic infection should stimulate governments to undertake the application of the holistic approach. The importance of considering several interrelated measures instead of isolated steps has been pointed out in many investigations and is clear from day-to-day experience. The decision to tackle the holistic approach should be backed by political commitment, a situation that is incompatible with government policy (or lack of policy) in many less-developed countries. No efforts to implement the holistic approach should be neglected by politicans and scientists since the alternatives will lead only to more disease, malnutrition, and suffering, as was predicted and observed in Central America [4].

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Biological Implications of Polyparasitism

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Polyparasitism appears to be the rule, rather than the exception, both in populations and in individuals in the developing countries of the world. Thus, polyparasitism represents coendemicity in the epidemiologic sense and simultaneous infections in individual patients in the clinical sense. The effects of polyparasitism are often clinically inapparent. In some situations, however, combined infections may exacerbate clinical manifestations. Coexistent infections may also, under some circumstances, suppress disease symptoms. The possibility of either synergistic or antagonistic effects must therefore be considered in planning public-health intervention programs, and the priorities or strategies selected may need to be altered accordingly. There are few available data at present that are suitable for evaluation of the real consequences of polyparasitism, in part because of the many confounding variables involved and the lack of prospective studies. Therefore, future intervention programs should be accompanied by an epidemiologic research component designed to detect clinical or laboratory changes in parasitic and other infections or in host responses.

An axiom of modern medicine in the industrialized nations is that patients, especially the young, have one disease or infection at a time. The major common exception to the concept of single agent infection is the polymicrobial, mixed anaerobic-aerobic bacterial process resulting from lesions on mucosal surfaces bearing the normal bacterial flora, e.g., intraabdominal sepsis following perforation of the bowel. In contrast, the appropriate axiom for the developing nations of the world is that multiple, simultaneous infections are the rule, rather than the rare exception. Recently, Buck et al. [1-4] analyzed the epidemiologic and clinical implications of the coexistence of multiple parasitic diseases in a population or individual patient. Polyparasitism represents coendemicity in the epidemiologic sense; in the clinical sense, it signifies simultaneous infections in single patients (including infections with more than one species of the same organism, as in multiple malarias or filarias).

Effects of Polyparasitism

While the majority of the populations of developing nations may have multiple parasitic infections, with an especially high prevalence in rural areas, the actual extent of polyparasitism is unknown. Therefore, its pathologic consequences are unassessed. This lack of information is particularly marked for infections that do not present dramatic or pathognomonic signs or that are clinically inapparent, such as a number of intestinal helminthic infections.

The data collected by Buck et al. in Chad, Peru, and Afghanistan suggest that the distribution of multiple infections in a population and the identity of the organisms involved are not parts of a random process, but are variables governed by unknown selective host factors and ecologic considerations, including the biological interactions of the organisms within the host [2]. These interactions may result in a worsening of clinical manifestations, as in the increased hepatosplenomegaly in combined malaria-*Schistosoma m[illegible]i* infection [4]. The prognostic significance of [illegible] situation is unknown.

It has also been suggested that the interaction between parasites may be antagonistic and thus may actually protect the multiply infected host. This is the thesis of a recent paper by Murray et al. [15] in which the authors propose that "suppression of one infection by another . . . may represent an ecological balance for optimum co-survival of the host and the two pathogenic organisms." In this study 112 children (aged 2-14 years) living in

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two neighboring villages on the island of Anjouan in the Comoro archipelago were divided into four groups on the basis of *Ascaris lumbricoides* egg counts in stool and type of therapy. Groups I and II had a heavy infection (>50,000 eggs/g of feces), and groups III and IV had a light infection (<5,000 eggs/g of feces). Groups I and III were treated with piperazine, while groups II and IV received placebo. All subjects were serially examined for 20 days after treatment (table 1), and the effectiveness of piperazine was documented by weighing of the total quantity of worms expelled.

Blood smears of all subjects were negative for *Plasmodium* at the outset, although malaria was prevalent on the island. A 51% attack rate of malaria was documented in group I within two weeks after piperazine treatment, whereas there were no cases in the placebo-treated group II subjects. Only three episodes of malaria occurred in the 40 subjects who had light ascaris infection (groups III and IV). The extraordinarily high malarial attack rate in group I is unlikely to have been due to newly acquired infection because such a short period was involved. Rather, it is most consistent with an exacerbation of preexisting malaria related in some way to the piperazine therapy and/or the expulsion of many ascarids. Murray et al. suggest that heavy loads of *Ascaris* suppress malarial parasitemia and disease manifestations. The low incidence of malaria in the lightly infected groups further suggests that *Ascaris* does not directly impede the growth of *Plasmodium*, for otherwise these patients would have had more frequent attacks of malaria. The reason for the dramatic increase in the incidence of clinical malaria in group I is thus obscure. Murray et al. suggest that the effect may be indirect; e.g., *A. lumbricoides* may deprive *Plasmodium* of an essential growth nutrient that is made available by the expulsion of the roundworm. This hypothesis is unproved. Furthermore, because the comparability of the four groups with respect to nutritional status, immune function, and incidence of subclinical malarial infection at the outset is difficult to assess, it is impossible to draw firm conclusions from the data presented. Nevertheless, the observations are provocative and, if correct and if related to the presence and treatment of infections with *Ascaris*, would raise additional concerns about implementation of vertical control programs, such as periodic deworming, in areas where malaria is endemic.

Effects on Growth

It has been difficult to prove that intestinal helminths affect human nutrition, because definitive symptoms or signs are difficult to detect. Some published data have been interpreted to indicate a cumulative effect of multiple parasitic infections on the growth of children. In a representative study, in rural Egypt, Abd-el-Aal et al. [6] studied 440 schoolchildren between the ages of 6 and 12 years. About half were found to be infected with one or more helminths, including *S. mansoni*, or *Schistosoma haematobium* (92%), *A. lumbricoides* (41%), *Ancylostoma duodenale* (31%), and other worms. Of the 218 children with diagnosed infection, only 8% were infected with a single type of worm; nearly 46% had double infections, 40% triple infections, and 6% quadruple infections. Table 2 shows the weight, height, and hemoglobin value of the 9- to 10-year-old cohort in relation to the number of diagnosed infections. The data indicate a correlation between the number of agents found per patient and the mean growth deficit recorded. They do not, however, reveal whether polyparasitism is a cause or an effect of growth retardation or anemia.

Longitudinal studies dealing with this point are unavailable, although the studies of Mata [7] on the acquisition of infections and the growth of rural Guatemalan children followed prospectively from birth through five years of age indicate the pres-

Table 1. Impact of anthelminthic therapy for *Ascaris lumbricoides* infection on the incidence of malarial attacks.

Group (*n*)	Level of ascaris infection	Therapy	Mean weight of worms expelled (g)	Malarial attack rate (%)
I (37)	Heavy	Piperazine	274	51.3
II (35)	Heavy	Placebo	9	0
III (23)	Light	Piperazine	20	4.3
IV (17)	Light	Placebo	0	11.8

NOTE. Data are adapted from [5].

Table 2. Anthropometry and hemoglobin values in polyparasitized Egyptian children 9-10 years of age.

No. of parasitic infections diagnosed (number of children)	Measurement (mean value)		
	Weight (kg)	Height (cm)	Hemoglobin (% standard)
0 (12)	29.2	133.3	74.0
1 (5)	28.2	132.4	59.3
2 (27)	26.8	129.0	51.7
3 (27)	25.7	125.3	53.2
4 (1)	24.0	126.0	45.0

NOTE. Data are adapted from [6].

ence of an impressive and heavy pathogenic burden beginning almost immediately after birth. This infection is largely asymptomatic at first; growth then falters at around four to six months of age. Thereafter, growth decrements are associated in general with symptomatic infections and are largely due to anorexia and decreased food intake [8].

Systemic Effects

Blom et al. [9] have recently reported on the relation between multiple infections (involving *A. duodenale*, *A. lumbricoides*, and *Trichuris trichiura*) and the level of acute-phase protein reactants in serum. Increases in α-1-acid glycoprotein, α-1-antitrypsin, and ceruloplasmin were found in multiply infected individuals; these increases suggested an associated inflammatory reaction in the polyparasitized host. The functional significance and metabolic cost of these changes in serum proteins in the multiply infected host are unknown.

Future Studies

Polyparasitism is common in developing countries. The consequences of this reality must be considered in the future in an ecologic sense, for the possible synergistic or antagonistic interactions of various parasites may affect decisions about public-health intervention programs. Detection of these interactions at the clinical or subclinical level is a major task because of the large number of confounding variables to be assessed. There is a great need for prospective studies to address these issues. Relevant data may emerge from future vertical-intervention programs, such as mass treatment of helminthic infections, but this will happen only if such programs are accompanied by an epidemiologic research component designed to detect clinical and laboratory changes in other parasitic agents or in host responses. As these relations may be important conditioning events in the host with regard to susceptibility or resistance to superimposed bacterial, viral, or other infections, this interest is not simply academic. Rather, it is a necessary prerequisite to ensure that, in our attempts to improve health, we do no harm.

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Interactions of Parasitic Diseases and Nutrition: Some Policy Implications

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The scientist's concern for precision in the use of information contrasts sharply with the policymaker's need to make decisions based on limited knowledge. Researchers should assist in the adaptation and presentation of their findings to meet policy requirements. Understanding of the policy process should reduce frustration about how information is used. Examples from the interaction of parasitic diseases and nutrition illustrate the limited but critical role of research findings in the determination of policies and related recommendations for action.

An exploration of the policy implications of the relationships between parasitic diseases and nutrition, including those for both choosing appropriate action and directing applied research, indicates a need for a shift in approach by research scientists. Policymakers operate with incomplete information and imperfect knowledge. They may assess the "weight of the evidence," but frequently they act on the basis of conclusions that fall far short of the validity expected of good science. Many scientists resist the generalizations accepted by advocates of alternative policies or by those who decide among them. The policymaker seeks "what we know," interpreted broadly, while the researcher too often emphasizes "what we don't yet know."

The way policymakers use scientific knowledge requires that scientists wishing to influence policy present and disseminate their conclusions in language and form that is understandable to policymakers. Short, clear presentations in lay language, with fewer qualifications than are customary in scientific publications, influence action far more than do the undiluted contents of scientific journals. The research scientist may choose not to prepare such presentations or may be incapable of doing so, but sympathetic collaboration with those who do is essential if research is to affect policy decisions.

The use of research information to influence policy also requires an awareness of policy constraints. Remedies that appear obvious to the researcher may be irrelevant to decision-makers for political reasons, for lack of technical or administrative feasibility, because of resource limitations or cultural barriers, or because of other considerations. Medically oriented researchers, accustomed to a treatment approach, often have difficulty adapting to considerations of cost vs. benefits that are essential in the selection of public health interventions. When interventions of little scientific validity, with poor benefit to cost ratios, win support for what seem to be irrelevant reasons, the scientists' frustration with policymakers increases further.

Scientists also must recognize that continued recommendations for further study often delay actions that could reasonably be taken with present knowledge. Because the determinants of parasitic infection are so varied and often deeply embedded in cultural patterns, policy recommendations too easily become prescriptions for doing everything. Useful recommendations should provide a basis for the identification and selection of specific policies and priority actions.

The political and economic constraints affecting public health decisions make the identification of appropriate actions involving the interrelationships of parasitic diseases and nutrition an uncertain amalgam. Possible choices are influenced by political decisions regarding preferred goals, by incomplete information about costs and probable results of alternative actions, and by inevitable political pressures. Scientific information forms a part, often quite a small part, of a process very different from the more orderly paradigms that govern science.

Some modest conclusions emerge from review of the interactions between parasitic diseases and nutrition. But the failure of researchers, in collaboration with policy analysts, to identify those conclusions of sufficient validity and importance to affect decisions makes initial generalizations

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broad and tentative. Such generalizations provide only a framework for future research and a structure for the array of research findings in ways that are most useful as a guide to policy decisions.

It is clear, for example, that among mildly infected populations, modest cultural modifications and some strengthening of host resistance through increased nutrient intake, accompanied by early treatment and replenishment of nutrient losses, often make typical parasite loads compatible with adequate nutritional status. The relatively minor influence of certain parasites on nutrition, when infestation is low, has important consequences for the allocation of resources among vector control, curative services, and the strengthening of host resistance.

While the relationships between parasitic diseases and nutrition may support a policy of tolerance to parasite loads in some contexts, they also aid in the identification of environments where the success of nutritional interventions depends on action to control parasites. A high incidence of severe malarial disease, for example, forces attention to the parasite and its consequences, for nutritional as well as other health reasons. The impact of parasitic diseases on nutritional status often reinforces policy recommendations for antiparasitic interventions.

The current emphasis on integrated primary health care requires identification of the most efficient methods of detection, treatment, and nutrient replenishment for different parasite prevalences. Tradeoffs between clinical control and preventive action are derived from applied research on costs and benefits which, in turn, is based on knowledge of the behavior and impact of each parasite species.

The epidemiologic pattern and biological properties of the causative agents in schistosomiasis, for example, favor increased emphasis on treatment. The epidemiologic characteristics of hookworm produce a pattern of infection that is age-specific and, therefore, of minor consequence for the improvement of infant malnutrition, though often critical for improved nutrition in older groups. The presentation of research data and conclusions in ways that facilitate these and other policy conclusions magnify their use and impact. Increased collaboration between scientists and policy analysts can improve the linking of research findings and policy concerns, without infringing on research autonomy.

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The Treatment and Control of Parasitic Diseases

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In many parts of the world, transmission of malaria due to *Plasmodium falciparum* can no longer be controlled by insecticides. Furthermore, this species has developed an amazing capacity for resistance to polyvalent drugs. The advent of new drugs and the possibility of developing a vaccine offer some hope for control of falciparum malaria. The fact that the spread of many parasitic diseases is promoted by contaminated water supplies resulting from inadequate waste disposal raises important questions about the relevance of current research. The control of some endemic infections, like Chagas' disease, would be better served by delivery of available technology than by improved science education. Discovery of means to promote self-help programs in rural communities will be an important aspect of research in disease control in the future.

Many methods for treatment and control of parasitic disease have been developed by members of a captive scientific community working for commercial organizations. One such member is Nobel prize winner P. H. Müller, who is noted for synthesizing chlorophenothane (DDT) and discovering its insecticidal properties. Implementation of new, adequately tested control measures is a task that should be undertaken by ministries of health, not by university professors. Underlying the academic's difficult position is his obligation to provide sufficient evidence, based on scientific investigation, to influence political decisions that pharmaceutical companies and governments make.

This overview will focus on control and treatment of parasitic disease in endemic areas. In nonendemic areas it is usually simply a question of treatment of the individual patient. Physicians in nonendemic areas who are interested in parasitic disease always have difficulty finding patients and often do their research in animal models. No account will be taken of the uneven global distribution of drugs, although there are many examples of drug scarcity in both temperate and tropical countries. Events such as the thalidomide disaster had both negative and positive results in this respect.

Malaria is given special prominence in this paper since it is, and indeed always has been, the principal urgent problem in parasitic disease research.

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Many journals in tropical medicine started as journals of malariology. In retrospect, it is a great pity that more support was not given to research on malaria in the 1970s, but it is easy to be wise with hindsight.

Malaria

The spectacular initial success of many spraying programs that used the residual insecticide DDT has been partly reversed [1] as a result of (*1*) a growing number of vectors genetically resistant to commonly used insecticides (e.g., *Anopheles albimanus* in Central America); (*2*) exophilic and exophagic behavioral changes in vectors (e.g., *Anopheles hyracus* in Afghanistan); (*3*) a lapse of vigilance in control measures (e.g., in parts of India); and (*4*) geographic inaccessibility of transmission sites (e.g., Amazon jungle).

One factor hindering the development of the countries of equatorial Africa is that this zone remains the most persistently intense focus of malaria transmission in the world. This is due mainly to the efficiency of the *Anopheles gambiae* complex of anophelines as vectors and to their capacity for development of resistance to residual insecticides. It must be firmly stated that in some areas of the tropics the "silent spring" philosophy in relation to the use of residual insecticides that contain chlorinated hydrocarbons is unacceptable. The benefits that accrue from spraying with these compounds far outweigh the risk of environmental pollution. Many countries can afford no insecticides other than the organochlorines, in spite of their persistence in the environment. In contrast to *A. gam-*

biae in Africa, no DDT resistance has been observed in *Anopheles darlingi*, a species responsible for >80% of the transmission of malaria in Brazil. Why this is so after >20 years of liberal use of DDT is a question worthy of investigation.

Resurgence of falciparum malaria in the Orient and South America is complicated by a high incidence of resistance to chloroquine. Evidence of similar resistance is beginning to appear in the literature from Africa. I have attended patients with acute malaria for many years, and I have yet to see anyone die of acute infection due to *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae;* however, I am still watching people die of falciparum malaria.

The drugs available for treatment of acute falciparum malaria due to chloroquine-resistant organisms are sulfonamide-pyremethamine formulations, quinine, and mefloquine [2]. Good evidence for resistance of *Plasmodium falciparum* in human infections to the first two of these drugs already exists, and resistance to mefloquine is suspected. After all, it is but another quinoline. Qinghao (*Artemisia annua*), a Chinese herb, has been used for 1,000 years in China for treatment of malaria. Its active ingredient, Qinghaosu, is highly effective against resistant *P. falciparum*. It is an entirely new compound and therefore could hold great promise [3]. Pharmaceutical companies must be screening any new compound for the treatment of protozoal disease for antimalarial activity, since any new type of drug effective against *P. falciparum* is likely to have a bright future.

The pessimistic approach to vaccine development is to start with the people who need it—let us say the three surviving children of a rural subsistence farmer in central equatorial Africa. If such a vaccine existed, the cultural, political, and financial factors influencing delivery would be enormous and lie outside the scope of these remarks. Suffice it to say that it might be many years before the vaccine was available to all who needed it.

Nevertheless, in view of the threat of uncontrollable epidemics of falciparum malaria, research on the development of vaccines has a high priority. Identification of specific protective proteins in the sporozoite coat is an encouraging step forward [4]. There exists the possibility of synthesizing such proteins by use of gene cloning and recombinant DNA techniques. Whether the same protective proteins occur constantly in *P. falciparum* isolates from different parts of the world will have to be defined. The duration of protection of such a vaccine, especially in an environment of naturally high transmission, will need to be measured. While spectacular progress has been made in this field in the space of a few years, it is still too early to say if such a vaccine will ever reach the stage of trials in humans [5]. Still, it is heartening to clinicians to see the forces being assembled once again for the fight against what Shortt once described as "man's ancient enemy."

Parasitic Diseases Other than Malaria

The transmission of schistosomiasis, hookworm, ascaris, amebiasis, and giardiasis depends on fecal contamination of the environment, principally by humans. Early man had similar defecation behavior and shared similar (but not identical) intestinal parasites with many other animals. The basic problem in control of these parasitic diseases is how to make a bore-hole latrine such an attractive proposition to people that they use it habitually. Somehow it has to enter the list of priorities of work, water, food, shelter, pleasure, education, etc. Much sociologic research is needed on this point, but the level of understanding in relation to the transmission of these parasitic diseases is fundamental.

Schistosomiasis

The direct link to irrigation and agricultural development and the vague calculation of the hundreds of millions of people with schistosomiasis served to provide research funding for this problem in the 1970s. Although the number of infected people is large, the number with disease (that is, with demonstrable pathology) is relatively small. Even in the latter group, schistosomiasis as a cause of death is insignificant in comparison to malaria or trypanosomiasis. Nor has it proved easy to measure morbidity, although in a recent study the diminished productivity of sugarcane cutters with hepatosplenic *Schistosoma mansoni* has been clearly demonstrated [6]. However, children with advanced portal hypertension due to *S. mansoni* are seen in our ward in Brazil, and this complication is more common in areas where *Schistosoma japonicum* is endemic. Probably *Schistosoma haematobium* causes more morbidity and mortality in

Africa because of the unfortunate and unexplained location of adult worm pairs in the venous plexus behind the trigone of the bladder. The preferential locations of adult worms and their movements in the portal sytem need investigation.

An enormous amount of information about the immunology of schistosomiasis is now available [7], but, unlike in the study of malaria, no real direction can be discerned at the moment. It is debatable whether activity in this field will continue at the same rate. The problem seems to be one of precise definition of aims. The nature and value to the patient of the immunity that undoubtedly develops in an endemic area requires clarification.

Ironically, as was previously mentioned, drug companies have provided the major advance in terms of specific therapy. Luck was important in the development of the lucanthone-hycanthone-oxamniquine sequence. Today effective drug therapy is available for all three types of human schistosomiasis; single-dose oral therapy is often used. Fortunately, trivalent antimonial treatment (always a great worry to any clinician) is becoming history. Why, for example, metrifonate is effective only against *S. haematobium* and oxamniquine cures *S. mansoni* infection is not clear nor is the precise mechanism of action known. Praziquantel is the first single-dose treatment effective against all three species of schistosome [8]. One hopes that this drug can be manufactured cheaply, as oxamniquine was costing Brazil four dollars per dose at one time.

The control of schistosomiasis has been recently reviewed [9]. The failure of molluscacides to permanently eradicate snails is notable, and research on destruction of snails deserves to be stepped up. The policy for the control of schistosomiasis will vary with the species involved and with local conditions, but drug therapy will be important. It has been shown that great reduction of *S. mansoni* disease can be achieved in a community by administration of four or fewer doses of oxamniquine to each patient, but even up to eight separate treatments given patients demonstrating persistent infection fail to reduce the prevalence to <3.2% [8]. In *S. mansoni* infections the concept of targeted mass treatment is attractive. That is, in an affected community (and in many Brazilian communities the infection affects nearly 100% of the population), persons from age groups in which worm burdens are heavy must be treated. If left untreated, the infection could lead to hepatosplenic disease. Surveillance and distribution could be controlled by the local government if the drug is sufficiently safe. Snail control by the use of molluscacide in areas where *S. mansoni* is endemic is expensive and only temporarily effective. Apparently there is no way of stopping the spread of schistosomiasis in central Brazil, and cases of this parasitic disease have now been recorded in the Federal District.

Metrifonate has proved effective in the large-scale chemotherapy of *S. haematobium* infections. Here, more of a case can be made for mass treatment, since the target pathology in the trigone is more localized and less dependant on worm load. Also, there exists a possibility, in some situations at least, of snail control. Bulinus snails frequently establish transmission in small bodies of water that can be adequately treated.

Views on control of *S. japonicum* still rely heavily on incomplete information from mainland China [10]. Elimination of animal reservoirs (e.g., dogs) is logical, and the amphibious nature of the snail apparently allows it to be killed by burial if a sufficient work force can be mobilized. However, I suspect that targeted chemotherapy may have an important role in controlling this disease.

Hookworm

Effective broad-spectrum anthelmintic agents have recently become available for intestinal nematode infections. Hookworm is the most important of these. Indeed, it can be argued that this infection is a more significant cause of mortality and morbidity than schistosomiasis. Severe anemia due to hookworm is still a common reason for hospital admission in many parts of the tropics. Since the hemoglobin level falls gradually, the patient often walks into the consulting room with an impressive hemodynamic picture, circulating 2–3g per liter of hemoglobin as rapidly as possible. Such an anemia is the result of an interplay of three factors: worm load, duration of infection, and body iron reserves [11]. Hypoalbuminemia is another feature of hookworm disease [12]. It is likely that, in areas of stable transmission, immunity accounts for the low worm burdens present in most adults, but more information is necessary.

The story of the control of hookworm in the southern United States in the absence of effective

drugs shows how much can be achieved by improving sanitation facilities and by the wearing of shoes. The cheap plastic sandal has probably had a great effect on decreasing hookworm transmission. Fixed defecation sites in secluded areas of intense transmission is a factor that produces heavy worm loads.

The focus of research on control measures in endemic areas should be the patient with significant anemia due to hookworm. If such a patient is given oral iron and an effective vermifuge and his defecation site is periodically changed, what are the chances of his returning with an equivalent degree of anemia within, for example, two years? This seems to be a question worth answering, particularly for subsistence farmers who frequently fall into this category. It is noteworthy that in certain areas of rural Brazil two types of rum are available: clear pinga and a rum that turns red when the earth at the bottom of the bottle, which contains iron, is agitated. This second drink is said to function as a tonic, but why that is so is often not understood.

Ascariasis

In the absence of effective sanitation, control of transmission of ascariasis seems impossible because infective eggs can exist in the environment for long periods. More research on the persistence of infective forms of intestinal parasites may produce practical results. Children ten years old and younger grow unsteadily because of heavy worm loads. Due to the size of the worms, they run the risk of obstruction of the intestine or of the bile ducts. Research into control should concentrate on this high-risk age group. Mass treatment in schools with one of the several effective drugs available only temporarily reduces infection in an environment polluted by embryonated eggs [13].

Stool examinations, while simple, are expensive, and I agree with Latham [14] that a rapid method is needed to detect heavy worm burdens in children. An abdominal distension index might be feasible, but factors of lumbar lordosis, endemic malaria, high-residue diets, etc., need to be carefully assessed. A history of passing worms in the stool is unreliable since the benefits of a vermifuge and the psychological satisfaction of passing such a worm are factors that interfere with accurate reporting. Nevertheless, regular vermifuges together with health education appear to be the short-term hopes for controlling morbidity and mortality in children. Research projects will need to define carefully the reinfection risk and to establish the most effective economic way to use the new anthelmintic agents.

Amebiasis and Giardiasis

Amebiasis and giardiasis are waterborne infections, although infective cysts can be ingested in raw foods. Where piped water exists, it must be protected from fecal contamination. Treatment of such water is a subject of current research in giardiasis [15]. Prophylaxis of both diseases depends on this approach.

Why invasive amebiasis is such a problem in countries such as Mexico, parts of Africa (including South Africa), India, and Thailand is still not clear. While it could depend on parasite virulence alone, in some situations the explanation is likely to be complex and involves factors such as host immunity and nutrition. Why only a fraction of *Giardia lamblia* infections are symptomatic is also a puzzle. After all, what governs population dynamics of *G. lamblia* in the small intestine? Why is it often the first protozoan to appear in the feces of weanling children [16]?

The discovery of metronidazole has revolutionized the treatment of symptomatic disease caused by microaerophilic pathogenic intestinal protozoa, and mortality in severe invasive amebiasis has diminished as a result. Under grave conditions such as amebic lung abscess, pericarditis, or peritonitis, the joint action of metronidazole with the standard emetine-chloroquine combination has saved lives that would otherwise have been lost.

In situations where infection rates are low and sanitation good, asymptomatic persons who pass cysts should be treated. The best drug for the treatment of amebiasis where infection rates are low and sanitation good is diloxanide furoate, which, 20 years after my investigations in Nigeria [17], has just been licensed in the United States. In endemic areas where 10%–30% of people have asymptomatic infections, individual treatment of cyst passers seems fruitless, because reinfection is inevitable in the absence of sanitation. A physician has more important things to do in such communities. The concept of commensalism for

Entamoeba histolytica is not proved and requires further work. Also, the significance of an entire family becoming infected and the effect of this factor on the outcome of treatment of the individual index case requires clarification.

Strongyloidiasis

While realizing that not all parasitic diseases of humans can be discussed, it is worthwhile to mention a few infections of importance other than those discussed at this meeting.

Strongyloides stercoralis is a rarer intestinal nematode than hookworm, although it is transmitted similarly. Also, it shares with *Trichuris trichiura* an unexplained focal distribution in many endemic areas. It deserves mention because, in our ward in Brasilia for instance, it is a common cause of adult malnutrition complicated by hypoalbuminemia due to a protein-losing enteropathy [18]. Many interesting problems could be investigated by return to the experimental models developed by Faust in the 1930s. For instance, what is responsible for the buildup of infection to produce the hyperinfection syndrome? Why is this syndrome not associated with eosinophilia? Why are stool examinations negative in some heavy infections? Is Brazilian strongyloidiasis really more resistant to thiabendazole, and, if so, what does this mean? Is the ineffectiveness of mebendazole based on its poor absorption, or is there another explanation?

Trypanosomiasis, Leishmaniasis, and Filariasis

This discussion started with a consideration of two of the parasitic diseases rightly selected by the World Health Organization for attention in a special program. The other three, namely trypanosomiasis, leishmaniasis, and filariasis, therefore merit discussion.

The role of trypanosomes transmitted by tsetse in limiting efforts to raise cattle and reducing the availability of milk and meat in Africa needs no emphasis [19]. Every day at least one plane leaves São Paulo, Brazil, for Lagos, Nigeria, with a cargo of fresh meat. Control of flies is expensive, and a vaccine for cattle might be possible. A breakdown in the vigilance for human infections results in epidemics such as those that have recently occurred in Ethiopia and the Congo basin. New, less-toxic drugs for the treatment of human African trypanosomiasis are urgently needed.

Chagas' disease presents the most pressing problem for public action of any the diseases discussed here [20]. Control of domestic populations of reduviid bugs assumes a new urgency with the development of resistance to previously effective residual insecticides. Unfortunately, spraying is very expensive, and severely affected communities are often remote. However, it may be cheaper in the long run to act now, for children infected this year will place a great burden on hospital services decades from now. Megaesophagus in Chagas' disease is frequently associated with marked malnutrition and parotid gland enlargement (the so-called cat face).

Human leishmaniasis has an impressive geographic distribution; it is spread over the face of the globe in the tropics and subtropics. No clinical protozoologist has experience of all its forms. It usually has the characteristics of an endemic sporadic disease, although epidemics have been reported. More effective and less toxic drugs are the first research priority. Nutritional implications are relatively minor but of great interest. Does the differential wasting described in old accounts of Kala-azar exist? Does malnutrition influence the development of clinical disease to any extent? Why do patients who have contracted leishmaniasis get so thin? Is it that vast parasite loads couple with chronic anemia? Is there any way of measuring such effects? I have recently seen many patients with malnutrition due to restricted food intake that resulted from severe oropharyngeal damage caused by chronic *Leishmania brasiliensis* infection.

A major factor determining pathogenicity in the seven filarial infections of humans is the location of the adult parasites. This must explain the lack of pathology in infections with *Dipetalonema perstans* and *Mansonella ozzardi*. The public health importance of onchocerciasis is better defined than that of Bancroftian filariasis. Severe chyluria must have nutritional repercussions. When should the clinician intervene to stop the leak?

Conclusion

Looking at endemic parasitic disease from the point of view expressed here demands that the

clinical worker not cling to bedside medicine but that he understand the human problem of a parasitic infection in an affected area. This is the philosophy adopted by many institutions including the Núcleo de Medicina Tropical of the University of Brasília. Experience in such a unit inevitably leads to the pragmatic approach to treatment and control expressed here. The research priority should be the cure of human disease (not necessarily infection) in the individual and the community by the most feasible means. Eradication is a word rarely used today when discussing human parasitic infections.

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Nutritional Requirements in Parasitic Diseases

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"Nutritional requirements" means different things in different contexts. Generally, the term refers to national or international standards or allowances of nutrients. Concern here involves the potential need for a change of standards where conditions of disease prevail, because disease increases the nutritional requirements of most individuals. "Nutritional requirements" may also be viewed in terms of food supplies. Analysis of a number of studies indicates that the average growth deficit due to endemic infectious diseases in early life is ≤20 kcal per day (calculated as 5 kcal/g of tissue). Increased weight gain following treatment of intestinal parasites such as *Ascaris lumbricoides* or *Giardia lamblia* provides similar estimates, as does measurement of energy and protein absorption. These values are within normal variance estimates. Sick children do not eat well and apparently do not eat enough on healthy days to correct for the accrued food deficit. Research on nutritional requirements of children needs to focus on management of food resources in entire families.

The term "nutritional requirements" means different things in different contexts. Sometimes we speak of the nutritional requirements of an individual, but these, in fact, are never known. Generally, "nutritional requirements" refers to national or international standards or allowances of nutrients specified for groups of people by expert committees. There exists a potential need to change nutritional requirements because of disease conditions in a given setting, i.e, a need to increase the amounts of nutrients recommended because the prevalent conditions increase the nutritional requirements of most individuals. "Nutritional requirements" may also be viewed in terms of the food supplies necessary to meet the nutrient needs of a community or other group under prevailing distribution patterns.

I have attempted to establish the energy cost of parasitic disease based on the data presented to us here and the concepts emerging from our deliberations. If there is a quantifiable energy cost, then the total need for food is increased, and probably the need for protein and the nutrients involved in metabolism and tissue restoration is likewise increased. The requirement for a single micronutrient is rarely affected by infectious diseases to a greater extent than that for other nutrients. The exception occurs where blood loss is the dominant feature and iron sufficiency is seriously affected, as in hookworm.

In this discussion, the estimations of energy cost are based on assumptions of the energy value of body tissue, normal energy requirements, and body weights [1]. The first, the energy value of tissue lost or gained, is taken to be 5 kcal (21 kJ)/g. The energy requirement during the first year of life is accepted as 112 kcal/kg per day, and during the second year, 103 kcal/kg per day. Standard body weights used are 3.3 kg at birth, 7 kg at six months, 11 kg at 18 months, and 14 kg at three years.

In the report of his longitudinal study of Gambian children, Marsden [2] presented the weight curve of one representative child who had suffered five attacks of clinically significant malaria during the period from birth to 20 months of age (figure 1). The child gained weight during 47 weeks, lost weight during 16 weeks, and maintained essentially constant weight during 25 weeks. Average weight loss, read from the graph, was ~11–13 g per day during periods of weight loss. This loss of tissue is equivalent to about 60 kcal per day or 6,720 kcal over the 16 weeks of loss. The restoration of this deficit would have required only an additional 90–100 kcal per week for the remaining 72 weeks, or about 15 kcal/day, which is less than 2% of the expected normal energy requirement. This figure is of no practical value in setting standards because the coefficient of variation in energy requirements is ~15% [1].

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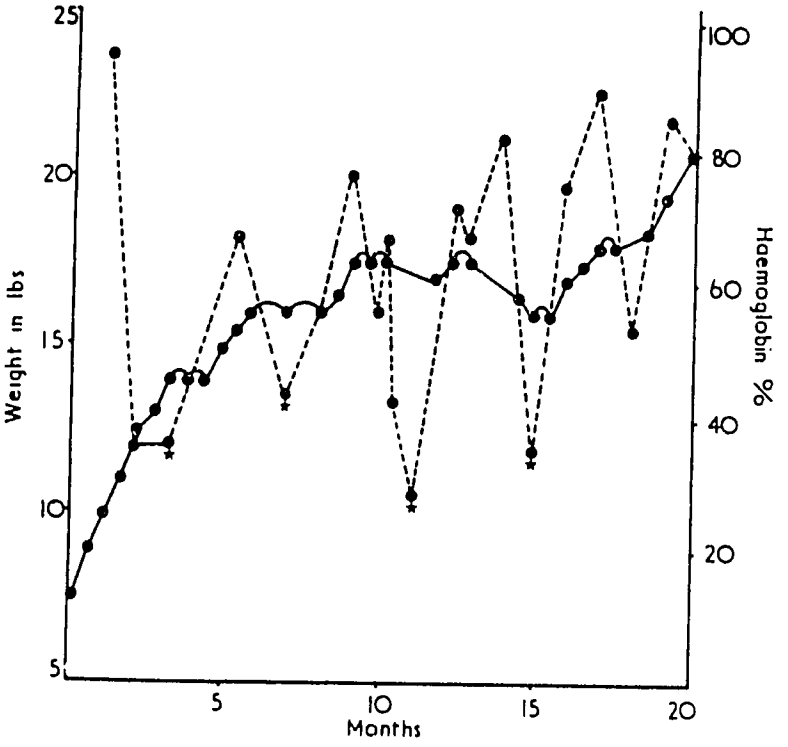

Figure 1. The effect of repeated attacks of clinical malaria on a child's weight and hemoglobin during the first 18 months of life. (- - -) = hemoglobin level; (———) = weight level; and (★) = antimalarial given during clinical attack. Reprinted with permission from [2].

Other studies yielded similar estimates. Cole and Parkin [3] reported the prevalence of malaria in two ways: in The Gambia, malaria was present 1.0% of the time, or nine days in 30 months; in Uganda, children experienced an average of 5.8 malarial attacks in 30 months. Mackey's representative Gambian patient (figure 1) had five episodes in 88 weeks. Since the usual event lasts about four days, malaria might be causing nutritional drain among African children during ~20 days between the ages of six months and three years. The effect of malaria on weight gain was calculated to be −779 g per month in The Gambia [3]; accordingly, 20 days of malaria would diminish weight gain by 522 g. The energy value of the deficit, 2,610 kcal, is 130 kcal per day during the attack, but only 3 kcal per day across the 39 months. This deficit is <½% of the expected requirement.

Comparing a control group of children infected with *Ascaris lumbricoides* with a group of dewormed children, Stephenson et al. [4] reported a difference in weight gain of 200 g over 14 weeks. The difference of 2 g per day amounts to 10 kcal per day, or <1% of a child's normal requirements. In another study of children infected with *A. lumbricoides* [5], treatment with levamisole (L-(−)-2,3,5,6-tetrahydro-6-phenylimidazo[2, 1-b]thiazole), increased weight gain by 400 g per year as compared to treatment with placebo; the effect of treatment in children without infection was 240 g per year. The total effect of treatment in the infected group was worth ~5–6 kcal per day, of which ~2–3 kcal per day could be ascribed to suppression of the parasite per se.

Brown et al. [6] measured the absorption of nutrients by five- to seven-year-old Bangladeshi children before and after treatment for ascariasis. The mean weight of eight heavily infected children was 14.34 kg. I calculated their mean intake, a diet of rice and vegetables to be 1,434 kcal with 20.2 g of protein per day. These figures and the reported percentages of nutrient absorption indicate that the net saving due to treatment was 17 kcal per day, of which 7 kcal was protein (1.76 g) and 8 kcal was fat (0.9 g). Significantly improved absorption could not be demonstrated in the lightly infected children, but the measured difference in absorption was about 7 kcal per day. These figures are consistent with the observed small weight gains due to treatment, which are cited above [4, 5].

Another point emerges from examination of the data of Brown et al. [6]. The diet derived 5.6% of energy from protein, but the fecal saving was disproportionately high in protein, accounting for

41% of the energy saved. There was also improved retention of protein with the treatment of the heavily infected group. Operative net protein utilization increased from 0.101 to 0.163. If both protein retention and energy absorption figures are correct, 1.25 g protein was deposited in about 3.4 g of body tissue. This tissue would then be about twice as high in protein content as is usual lean body tissue [1].

We have two papers with quantitative findings relating to giardiasis. During episodes of infection with *Giardia lamblia* in Gambia [3], decrement in weight gain was 171 g per month. However, because of relatively low prevalence, the mean monthly deficit was 7 g. The energy cost is 1-2 kcal per day over 30 months. Kay et al. [7] present only weight gain after treatment of the 24 most seriously affected children. Actual gains are compared with gains expected according to the child's previous growth projection. For 15 children below three years of age, the observed gain exceeded that expected by an average of 8 g per day over an average period of 3½ months. These are perhaps the least secure values we have here, but they do suggest the possibility of a higher cost, some 40 kcal/day, resulting from severe giardiasis.

Our papers on schistosomiasis include only one that is relevant to this discussion. DeWitt et al. [8] tested the effects of two treatments on the growth and health of infected, malnourished, young men in Puerto Rico. One group of 26 subjects received an enriched diet for the entire 15-month period of study; the other, a group of nine convicts, did not. Chemotherapy for schistosomiasis was instituted for both groups during the last six months. Before the study began, the first group was about 3 cm taller and 2 kg heavier than the second, and while biochemical indicators of nutrition were unacceptable in a large proportion of each group, the convicts were in a noticeably poorer nutritional state. The food supplement was prodigious; energy intake was raised from 2,000 to 4,000 kcal per day, protein intake from 67 g to 178 g, and micronutrient intakes were generous. Anthropometric responses are summarized in table 1. Body weight was affected more by diet than by drug therapy. The difference in weight gain due to the correction of schistosomiasis is equivalent to 19 kcal per day for group one and 22 kcal per day for group two. The data on height are interesting. Even though all the men were in their 20s, those in both groups grew taller. The linear growth effect due to drug therapy appears to be the same order of magnitude as that due to diet.

Recurrent diarrhea, irrespective of cause, is usually cited as the disease factor most likely to affect nutrient requirements under prevailing world conditions. In a final attempt to quantify the energy cost of disease to children's nutrition, I consulted three authorities. Dr. Vinodini Reddy indicates that young children have one or two episodes of diarrhea per year, each lasting two to three days. Dr. Leonardo Mata gave a figure of nine episodes in 24 months, lasting about a week each time. Cole and Parkin [3] reported 2.55 episodes per 30 months in Uganda, whereas in The Gambia prevalence was 0.13, with children affected 3.93 days per month. Evidently, either disease experience or the definition of diarrhea is quite different in various geographic locales.

The range cited provides average estimates of 15-141 days of diarrhea between six months and three years of age. The cost of gastroenteritis to weight gain in The Gambia was 773 g per 30 days and in Uganda was 161 g per 30 days. In 30 months, the average net cost would range from a low of 80 g to a high of 3,633 g. The extreme case represents 18,000 kcal over 900 days or, again, 20 kcal per day. This amount is probably not measurable in light of the average expected requirement of some 1,000 kcal per day.

We must conclude that the uncorrected energy deficit is, in all cases, small in terms of requirement figures. The cumulative impact on achieved

Table 1. Anthropometric responses (mean values) to dietary supplementation and/or drug therapy of schistosomiasis.*

	No drug		Plus drug	
Monthly increase	Supplemented diet	Control	Supplemented diet	Control
Weight (kg)	0.42	0.12	0.54	0.25
Height (cm)	0.15	0.08	0.21	0.17

* These data are adapted from [8].

body size is, on the other hand, very large. This size difference does have an effect on requirements—requirements are lower where disease prevails and full catch-up growth does not occur.

Again let us take as examples the situations in The Gambia and Uganda [3]. The mean gain was expected to be 220 g per month; the observed gain was 98 g and 185 g in the two respective locations. At the age of three years, average body weights would have been about 9.94 kg and 12.5 kg; these figures are 71% and 90% of expected weight. Energy requirements to sustain the normal growth rate for age are expressed on the basis of body weight. Thus, food needs would be reduced by 29% and 10%, on the average, by the age of three years in these two locations. For children growing at two standard deviations below the mean, the situation would be even rosier; they would become better adapted to food shortage with time—or so the "adaptationists" would suggest.

The uncorrected energy deficit is, as we have seen, very small. The question is why children don't catch up in these environments. One reason must surely be that children are sick a large part of the time, and that when they are sick, they don't eat adequately. Food may also be withheld as part of informal therapy.

Prevalence of all disease categories recorded in The Gambia [3] was 0.456. This means that children were affected, on the average, 13–14 days each month. In Uganda [3] there were 1.709 disease episodes per month.

Assuming that food intake was, on the average, half of normal during the days of illness, then, in The Gambia, intake on well days would have to be ($[0.456 \times 0.5] + 0.544x = 1.0$) or 1.42 times the normal requirement, to reach a normal average intake. Mata said that intake was reduced by 19% in his study. Utilizing the same calculation, the intake of Mata's subjects appears to have been 1.07 times normal on days when the child was well, not enough to avoid growth retardation. Martorell et al. [9] have reported intake deficits of the order of 20% during miscellaneous childhood illnesses over the first five years of life. The Gambian disease prevalence and Martorell's observed intake indicate that intake would have to be increased only 16% (plus the 20 kcal or so to cover absorptive losses) on healthy days to meet normal average intakes. This is well within the normal variation in intakes [9]. Why doesn't it happen?

One possibility is frequently cited. Perhaps children cannot physically consume more of the food that is typically available. Traditionally diets of the poor are usually low in fat, high in bulk and water-binding capacity. Unless oil or sugar, or some digestible energy-rich food (such as eggs, whole milk, or meat) is available to raise the caloric density of these diets, it is unlikely that young children would be able to eat enough to meet and exceed normal requirement levels.

There is a second, usually unrecognized explanation. Let us consider what happens to the food that sick children do not eat. If it were breast milk, we could assume it is still part of the mother, but breast milk is not what sick children generally reject. They reduce consumption of foods taken from the family table. Would that food still be available to sick infants when they recover? Children that are malnourished rarely are found in households where the food supply to anyone is truly generous, so it seems unlikely that the rejected food would be wasted. It is far more likely that someone else would eat the food the sick child did not eat. Some other member of the household would benefit, and that extra small amount of food may be making the difference for the maintenance of observed growth of siblings or for the work capacity of parents. There might not be any extra food available in a household where the resources are limited two or three days later when the child is well and able to eat.

I believe that research on nutrient and food requirements now needs to focus on entire families. We need to know what transactions occur within families managing food and other resources in the face of illness and recurrent scarcity. We need also to have answers to critical questions such as the ones raised by Dr. McGregor: Does growth begin to fail before, or only after, the first serious disease episode? Are the poorest consumers affected first, or only most severely?

I do not believe that efforts to prevent and cure parasitic and other endemic diseases need to be based upon a postulate of altered nutrient requirements (see, for example, the study of Beaton and Swiss [10]). The benefits of disease reduction in terms of reduction of human misery should be sufficient to offset the cost of treatment. Neither should we allow the case for the provision of more and better food to rest on an argument that requirements must be increased because of disease.

(see, for example, [11, 12]). Food intake of those most at risk due to disease are not even meeting normal nutritional standards, and continued emphasis on "requirements" detracts from the efforts needed to identify and correct the underlying causes of malnutrition.

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Needed Research on the Interactions of Certain Parasitic Diseases and Nutrition in Humans

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For the purpose of assigning priorities for research, each of the following parasitic diseases is examined in regard to its affect on the nutritional status of the host: schistosomiasis, malaria, amebiasis, giardiasis, ascariasis, and hookworm. The epidemiology, diagnosis, immune response to, and available therapies for these diseases are discussed. It is suggested that highest priority be given to three diseases: hookworm, ascariasis, and schistosomiasis, because they can be treated successfully, diagnosed easily, and have a high prevalence.

The workshop dealt with only certain parasitic diseases of humans: schistosomiasis, malaria, amebiasis, giardiasis, ascariasis, and hookworm disease. These are dealt with in the same order here as in the discussions.

Medical and public health reasons make the treatment and control of most of these infections important for the individual and for the community. The priority for control depends on several factors, including the prevalence and intensity of infection, the extent of the resulting morbidity and mortality, and the social and economic significance of the disease; these factors vary from country to country and also within countries. The ease and cost of control with presently available methods merits consideration.

The purpose of the workshop was to examine the interactions of parasitic diseases and nutrition in humans. The following questions were addressed. (*1*) What effect does each parasitic infection have on the intake, utilization, or loss of nutrients, and what are the functional consequences that may relate to nutrition? (*2*) How does the nutritional status of the host affect the morbidity, the duration of infection, and the immune system or reaction in each parasitic infection? (*3*) What can be said about the effects of parasitic disease on nutrient requirements.

I have kept these questions in mind when examining priorities for research. In general, the concern is to identify the nutritional reasons that add to the many other reasons for the control or limitation of parasitic infections.

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We should remember that helminths do not themselves multiply in the human host. Increased levels or intensities of infection in an individual always result from infections with new organisms from outside the host; they are not due to propagation of the helminths within the body. In all research projects, the use of quantitative rather than purely qualitative methodology is important. This information usually involves egg counts. For many helminthic infections, relatively simple quantitative techniques suitable for field testing exist; examples are egg counts in feces and counting of *Schistosoma haematobium* eggs by means of the Nuclepore® filter (Nuclepore Corp., Pleasanton, Calif.) technique.

General Research

Certain general research areas that are related to several parasitic diseases were identified in the workshop. These include: (*1*) Research on the effect of parasitic infections on appetite. Is anorexia a problem, and if so, to what extent and by what mechanism does it affect nutritional status at different ages and in different segments of society? (*2*) Studies of the effects on certain functions of parasitic infections and the parasite-nutrition interaction. Issues involved include the functional consequences in terms of response to disease, physical activity or work output, cognitive function, reproductive competence, and social and behavioral function. (*3*) Improved research on immune function in severe and moderate protein energy malnutrition and in other nutrient deficiencies, especially in relation to parasitic infections. (*4*) Detailed longitudinal community investiga-

tions that are interdisciplinary, including parasitologists, nutritionists, health professionals, and others. Certain questions concerning the interrelationship of parasitic diseases and nutrition can probably be answered only by long-term, ecologically intense studies. (*5*) Intervention studies in the presence and absence of parasites for the more accurate determination of the effect of the control of parasitic disease (or the reduction of parasite burdens) on the growth of children and on nutritional status; the effect on parasitic infections of nutritional interventions, including supplementary feeding or provision of individual nutrients such as iron; and the evaluation of broad or holistic interventions and their effects on health, nutritional status, and related matters.

Research on Schistosomiasis

Clearly, in schistosomiasis a distinction must always be made between those persons with light infections and those with moderate or heavy infections. In all studies, egg counts are necessary for a prediction of the parasite burden. Light infections, believed to produce low morbidity, are unlikely to have any measurable effect on nutritional status.

Important areas for research on the interactions of schistosomiasis with nutrition are as follows. (*1*) A high priority should be given to longitudinal studies with proper design. Such inquiries should include whether moderate and heavy infections with *Schistosoma mansoni*, *S. haematobium*, or *Schistosoma japonicum* significantly affect the growth of children (and whether they contribute to protein energy malnutrition); anemia and iron nutritional status through blood loss (especially, perhaps, in *S. haematobium* infections); appetite and food intake; and, indirectly, function, including physical activity and fitness, work output, and social functioning. Studies concerning these questions should, for ethical and other reasons, usually use treatment as the intervention, and examinations can be conducted before and after treatment in the same individuals. (*2*) Human and animal studies are needed to determine more precisely how the nutritional status of the host affects the intensity of infection, morbidity from the disease, and immune response. (*3*) For *S. haematobium* infections, studies are needed to determine more precisely how much blood, and therefore iron, is lost in the urine with different intensities of infection.

Research on schistosomiasis should be influenced by the great improvement in recent years in the drugs used for this disease and by the techniques now available for the quantification of eggs in urine and stools, which can be performed rapidly and cheaply in the field.

Research on Malaria

Malaria is by far the most significant parasitic disease in humans, both in terms of prevalence and as a cause of morbidity and mortality. Its treatment and control is of great importance whether or not the disease interacts with nutrition. The type of malaria (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, or *Plasmodium ovale*), its degree of stability in a given community, the ages of those patients being considered, and several other factors need to be kept in mind in research on the interrelationships between malaria and nutrition.

Research is needed on the following aspects. (*1*) Well-designed, longitudinal studies should investigate how malaria affects food intake (e.g., what is fed to the child, how appetite is affected), utilization of nutrients, nitrogen losses in the urine, and physical function. (*2*) It would be useful to have better data on how malaria affects the productivity, physical activity, and social functioning of adults and on how these factors affect agricultural productivity, food availability, etc., especially in areas where malaria is unstable or where epidemic outbreaks occur. (*3*) The role of malaria in gastrointestinal function and as a cause of diarrhea and of nutrient losses from the bowel needs examination. (*4*) The different effects of malaria on immune function should be explored in well-nourished, moderately malnourished, and severely malnourished individuals, especially children. (*5*) In pregnancy, the relationship between malaria (with placental involvement) and premature births or small full-term births is unclear. What is the significance of this relationship? (*6*) The mechanisms involved in the exacerbation of malaria during pregnancy in immune populations need description. Is this phenomenon related to the nutritional status of the pregnant woman?

Why is it seen mainly in the primipara? (*7*) The effect of the nutritional status of the host on the morbidity, duration of disease, and mortality in those with malaria warrants study. Are the responses in patients with kwashiorkor different from those in patients with marasmus; and if so, why? (*8*) In those with subclinical malaria and with signs of undernutrition, we need to know whether supplementary foods, refeeding, or the provision of certain nutrients, e.g., iron, exacerbate the malaria? This problem may require investigation in persons with different types of malaria, in a variety of ecologies, in people with different degrees of immunity and with a variety of diets. The studies need much more careful design, control, and interpretation than similar studies in the past. (*9*) Whether the anemia seen in malaria, which is known to be hemolytic, also affects iron status and the utilization of other hemopoietic nutrients is unclear. Is iron that is laid down in the pigmentation in the liver and other organs in malaria reutilized? What is the true relationship of malaria to folate nutrition in humans?

Research on Amebiasis

Amebiasis remains a common disease in many parts of the world, and in many developing countries its incidence may be increasing. This increase is in part due to the fact that specific control measures are not available.

Relatively little research has been conducted on the interaction of amebiasis and nutrition. Research should address the following questions. (*1*) What effect does severe, invasive amebiasis have on nutritional status, on the utilization of nutrients in the diet, and on loss of micronutrients, such as iron? (*2*) How does diet affect the disease? Do particular diet patterns affect the pattern of intestinal microflora, and how does the pattern of microflora relate to the pathogenicity of the amebae in the gut? Does the provision of certain nutrients, such as iron, influence the amebae to become invasive? (*3*) How does malnutrition of the host affect the parasite and its tendency to be invasive or noninvasive?

Research on Giardiasis

Infections with *Giardia lamblia* are common in both tropical and nontropical countries. One of the problems in field and community research is the difficulty of a definitive diagnosis, especially with asymptomatic cases or light infections. The failure to find evidence of the parasites in stool examinations does not rule out the presence of an infection, but usually cysts can be detected in those whose infections are heavy. Duodenal aspiration is not a procedure that can be recommended for field studies.

Research is needed in the following areas: (*1*) Well-designed field studies should determine the effect, if any, of the parasitic infection on growth and other parameters of nutritional status. In the absence of better definitive diagnostic tests, these studies may have to be limited to before-and-after measurements in patients with proved infections who are treated. (*2*) The effects of giardiasis on the utilization of certain micronutrients, especially vitamin B_{12}, folate, and vitamin A, need investigation. (*3*) Prospective studies involving children with protein energy malnutrition should determine the role of the nutritional status of the host in susceptibility to giardiasis. Studies including feeding or nutritional rehabilitation should ascertain the effects of dietary intervention on giardial infections.

Research on Ascariasis

In recent years several studies have investigated the effects of ascaris infection on the growth of children. These are reviewed elsewhere. Most of the better studies indicate that even moderate infections do apparently retard growth and therefore contribute to protein energy malnutrition. These field studies are consistent with evidence from research involving pigs and from metabolic studies involving humans. However, none of these field studies have been conducted with heavily infected children. Ascariasis can also lead to certain serious complications, such as intestinal obstruction (with heavy infections) or worms that cause problems during ectopic migration to sites such as the common bile duct. The incidence of these

complications is not well defined, but in certain hospitals ascariasis is the major cause of abdominal emergencies requiring surgery in childhood. Relatively little research involving humans has examined the effects of the parasites as they travel through the liver and lungs to reach the intestines. However, reasonably good data on pathological changes in the liver and lungs are available from studies on pigs.

The following areas for additional research were identified. (*1*) A need exists for well-designed, longitudinal field studies in more than one country in which the effect of treatment or other control efforts is measured in children heavily infected with *Ascaris* and in groups where malnutrition is prevalent. (*2*) Studies should determine the extent of morbidity and the relation to nutrition of the stage of infection when *Ascaris* worms are migrating through the lungs. (*3*) Autopsy studies should determine the pathology in the gut and other organs of children infected with *Ascaris* who die of accidents or causes unrelated to gastrointestinal disease. (*4*) Metabolic studies should determine the role of heavy infections with *Ascaris* on the utilization of protein, vitamin A, and other nutrients. (*5*) Studies using hospital statistics should evaluate the importance of complications of ascaris infections (for example, intestinal obstruction, ectopic location of the worm). (*6*) Programs for the control of ascariasis in the community by means of anthelminthics need evaluation. The effectiveness; the rates of reinfection; the delivery systems, either alone or in combination with other health or nutritional interventions; and the economic aspects of such programs need study.

Research on Hookworm Disease

The role of hookworm infections in iron-deficiency anemia has been well studied. There is general agreement that heavy infection with hookworms is an important cause of iron-deficiency anemia in many parts of the world, and that the mechanisms for this relationship have been determined. Therefore, hookworm disease is a clear case in which a parasitic infection results in a nutrient-deficiency disease. The careful work in both animals and in humans has not been adequately extended into field studies or control programs. In all research, quantitative techniques, such as egg counts in feces, are necessary.

The following were identified as research needs. (*1*) Evaluation is needed of programs to control hookworms by means of anthelminthics administered to groups of individuals in the community; the effects of the disease on anemia, iron nutritional status, physical fitness, and work productivity should be determined. (*2*) The effect of hookworm infections on the loss of nutrients other than iron needs investigation. (*3*) Studies should determine the effects of hookworm disease, especially heavy infections, on appetite, function of the gut, and the growth of children.

Conclusions

The workshop suggested that highest priority be given to research on hookworm disease, ascariasis, and schistosomiasis. The reasons for the choice of these three parasitic diseases are discussed below. In addition, malaria is such a serious and important disease that its treatment and control deserve very high priority irrespective of the relationship of the disease to nutrition. Amebiasis and giardiasis are common infections and are frequently important diseases. However, before nutritional studies are undertaken at the community level, some basic problems related to these diseases need investigation. These include the pathogenicity of different strains of *Entamoeba histolytica*, factors influencing the pathogenicity of *G. lamblia*, and the diagnostic techniques (both stool examinations and seroepidemiologic studies) for amebiasis and giardiasis.

Funding agencies might, therefore, give greater priority to research and programs relating to hookworm disease, ascariasis, and schistosomiasis. For all three diseases, currently available drugs can markedly lower the parasite loads without danger of serious complications. All three conditions can be easily diagnosed. Above all, these three parasitic infections have high prevalence; estimates suggest that *Ascaris* infects about 1.2 billion people, hookworm around 700 million, and schistosomiasis perhaps 200 million.

With ascariasis and hookworm disease, the nutritional consequences of the diseases may be their most important effect on human well-being. Therefore, programs of control as well as practical studies to further our knowledge of the relationship between infection with these parasites and nutrition are important. In the case of schistosomiasis, there are good reasons for controlling the disease, especially in those with heavy infections. But the need is clear for studies to determine how schistosomiasis relates to nutrition. Several avenues for study suggest an evaluation of the effects of treatment on nutritional parameters, including iron nutritional status.

Although it was recommended that research priority be given to the nutritional implications of hookworm disease, ascariasis, and schistosomiasis, studies are also needed on malaria, amebiasis, and giardiasis, and on some intestinal parasitic infections not discussed during the workshop but of considerable regional importance. I have outlined above the types of research needed.

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Summary and Recommendations

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Dr. Doris Howes Calloway opened the meeting by defining nutritional status in a functional context. The impetus for arriving at such a definition has been the difficulties inherent in measuring food intake in individuals in the field, in the problem of setting criteria for intake or tissue levels of many nutrients that are predictive of disease symptoms due to incipient deficiencies, the uncertainties of food requirements during periods of stress, and the multiplicity of factors other than nutrition that affect growth and anthropometric measures. Functional indicators with sufficient sensitivity, precision, and reproducibility are not yet sufficiently validated. The relationships between nutritional status and cognitive abilities, social and behavioral attributes, work capacity, reproductive function, and immunologic capacity are currently being evaluated. However, functional adaptations do occur in response to restricted food intake, and there is a need to distinguish between physiologic adaptation and pathologic maladaptation.

Dr. William R. Beisel discussed the concepts of synergism and antagonism of nutrition and infection; these are the situations in which malnutrition either augments severity of infection or affords protection from clinical illness. Previous studies lending support to these constructs are largely descriptive and cannot establish a cause-and-effect relationship. It is unlikely that this relationship can be readily demonstrated for humans, given the large number of uncontrollable variables. For example, parasitic infections are usually multiple, infecting doses are unknown, exposure can be recurrent or continuous, and infections are chronic. Furthermore, determinants of the apparent synergy or antagonism include the species and virulence of the parasite, its own nutritional requirements, the nature and severity of the host's malnutrition, and the functional capacity of immune mechanisms and other host factors.

Drs. Gerald T. Keusch and R. K. Chandra reviewed the immune response to parasites. A number of pathogenic protozoa are endowed with the capacity to invade and multiply within microbicidal cells, such as macrophages, by as-yet-undetermined mechanisms. Helminths do not generally multiply within the mammalian host; this fact dramatically alters the conditions for an immunologic response. Thus, the success of both protozoan and metazoan parasites as pathogens appears to depend on their ability to evade normal host defenses and to escape clearance and elimination. Nevertheless, diverse immune responses can be elicited including T-lymphocyte-mediated recruitment of specific effector cells, granuloma formation, and activation of antibody- and/or complement-dependent mechanisms, macrophages, or other cellular or nonspecific humoral responses.

Drs. Irwin H. Rosenberg and Barbara B. Bowman considered the possible effects of parasitic infection on intestinal physiology as a major determinant of nutritional impact. Various infections can influence alimentation, digestion, or absorption at virtually any point. This may relate to the ability of some parasites to induce fever and systemic metabolic alterations, to release bioactive or toxic substances in the intestinal lumen, to compete for specific nutrients, to cause structural or functional damage to the mucosa, or to alter gut motility. It was suggested that, in the development of malnutrition, anorexia may be the most important consequence of parasitic infection, but both the magnitude of this effect and the mechanism by which it occurs urgently require investigation.

Dr. Michael Katz recounted the remarkable advances in development of antihelminthic drugs that are both effective and safe. Agents that might be chosen for periodic mass chemotherapy against intestinal nematodes are unlikely to cause any harm or exert any adverse influence on the host's nutrition or metabolism.

In subsequent papers, Drs. Kenneth S. Warren, David J. Wyler, Bernardo Sepúlveda, David P. Stevens, Zbigniew Pawlowski, and Robert H. Gilman reviewed the host-pathogen biology of six important infectious agents: three helminths

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(*Ascaris lumbricoides*, the hookworms, and *Schistosoma mansoni*) and three protozoa (*Plasmodium* species, *Giardia lamblia*, *Entamoeba histolytica*). Because of their epidemiology, however, only malaria, giardiasis, and amebiasis were deemed potentially significant problems for the nutritionally vulnerable preschool child. This is not to say that infections with hookworm, *Ascaris*, or *Schistosoma* do not occur in the young. Rather, because these worms do not multiply in the human host and because clinical disease is generally a consequence of heavy infection, it takes time to acquire the worm burden likely to cause symptoms. The distinction to be made here is between infection and illness. In fact, the vast majority of infections with these helminths are subclinical and are unlikely to cause symptoms. When clinical illness does occur, however, it is likely to be chronic, severe, and sometimes fatal.

These distinctions have important nutritional implications. The evidence reviewed by Drs. C. Amechi Akpom, Ian A. McGregor, Louis S. Diamond, Noel W. Solomons, Myron G. Schultz, and Easwaran P. Variyam and John G. Banwell indicates that parasitic infections that are too light to produce symptomatic illness are generally also too light to significantly affect nutritional status. The chronic loss of iron associated with mild-to-moderate hookworm infection is the major exception to the rule, as chronic anemia can develop when dietary intake of iron is limited or is in a form having limited bioavailability. The accelerated metabolism and loss of body nutrient stores, which typify acute febrile bacterial or viral diseases, are also seen during symptomatic systemic parasitic diseases. The papers in this workshop and the subsequent discussion show that parasite-induced malnutrition is generally seen in only a small fraction of patients who harbor parasites.

The final group of papers explored issues concerning strategies for intervention. Dr. Calloway estimated that the growth inhibition resulting from infection is $\leq$20 kcal/day for children; this figure is an average based on studies reported for a variety of diseases. It is extremely small in terms of a child's normal requirement of $\sim$1,000 kcal/day and is probably not directly measurable. If the uncorrected energy deficit is so small, why is it that these children do not catch up in growth during convalescence? Dr. Calloway calculated that, on the basis of reported prevalence and duration of infectious illness and an average 20% decrease in food intake due to anorexia during infection, convalescent food needs must be increased by $\sim$16% to meet normal average intake. Two reasons were offered: low caloric density of available foods limits physical consumption of extra food, and there might not be additional food available in a household of limited resources. Therefore, solutions to this problem may depend on general social and economic advancement.

Dr. Leonardo J. Mata continued this theme by describing the sociocultural factors that contribute to both the high prevalence of infection and the limited effectiveness of interventions. These include prevailing poverty, deficient education, maintenance of practices such as indiscriminate defecation, and high demographic density and ruralism. He pointed out that child-rearing practices and attitudes within families, termed "maternal" or "familiar" technology, differed from household to household and might explain differences between families in the same ecosystem with regard to the incidence of infection and malnutrition. He concludes that a holistic approach is essential for effecting changes in these various social determinants and should include promotion of breast feeding, oral rehydration for diarrhea, education on weaning practices and convalescent feeding, improvement in personal and domestic hygiene, immunization, community planning for environmental improvement, family planning, and chemotherapy and prophylaxis for prevalent infections caused by parasites that are susceptible to drugs.

Mr. James M. Pines discussed the process for setting governmental policies and the use of scientific data by civil planners in establishing such policies and priorities. He stressed that the usual language of scientific communication, which emphasizes the limits of data and qualifies the conclusions drawn, is a barrier to the planner who must formulate decisions based on evidence that often falls short of scientific validity. These decisions are also usually influenced by political, technical, administrative, or resource constraints. Increased collaboration between scientists and policymakers is necessary to improve the link between research findings and policy interests.

Dr. Keusch and Dr. Panata Migasena described polyparasitism, a common phenomenon in populations of developing nations, and pointed out

that combined infection is not a random process but is due to selective host factors and ecologic considerations. The unknown interactions among these infections and the possibility of antagonism between infection and malnutrition raise concern about implementation of vertical control programs (programs directed at a single disease). They suggest the need for prospective epidemiologic research to address the importance of such issues and to consider interventions in a broader ecologic context.

Dr. Philip Davis Marsden presented an overview of current treatment and control of endemic parasitic infections. The transition from consideration of individual patients to that of entire populations requires a change in thinking for the inclusion of a broad range of measures, such as the possibility of mass chemotherapy, simple environmental or behavioral modifications, and vector control. These measures may be used singly or in combination. A pragmatic approach to treatment and control must be based on an understanding of the problems and infections in each endemic area.

Finally, Dr. Michael C. Latham summarized the needs and priorities for research in answer to the many questions raised during the workshop.

Specific Comments

With the information presented in the workshop it is possible to assess the feasibility of, and assign priorities to, various intervention measures. Table 1 provides a framework for the ordering of priorities for dealing with the six infectious agents discussed. These judgments may depend on personal bias, and arguments to the contrary can be made; they are presented as a means of stimulating consideration of the issues raised.

Malaria. This highly prevalent disease in much of the developing world produces significant morbidity and mortality. Acute, febrile disease is accompanied by metabolically inefficient responses, and specific antimalarial therapy should,

Table 1. Assessment of intervention strategies for control of some parasitic infections.

Infection	World prevalence*	Overall morbidity†	Impact on nutrition	Impact of malnutrition	Interventions for disease control: Measure	Feasibility	Priority
Malaria	Very high	High	Yes	Possible clinical antagonism	Vector control	Low to moderate	High
					Mass chemoprophylaxis	Low	Low
					Vaccine	Unavailable	Research needed
Giardiasis	High (?)	Low	Probable	Unknown	Mass chemoprophylaxis	Low	Low
					Water and sanitation	Moderate‡	Moderate
					Education	High	High
Amebiasis	High	Low	Yes†	Unknown	Mass chemoprophylaxis	Low	Low
					Water and sanitation	Moderate‡	Moderate
					Education	High	High
Hookworm disease	High	Moderate	Yes	Unknown	Mass chemoprophylaxis	Moderate	Low
					Iron supplementation	High	High
					Sanitation/education	Moderate	Moderate
Ascariasis	Very high	Low	Probable	Unknown	Mass chemotherapy	Low	Low
					Targeted chemotherapy‖	Moderate	Low to moderate§
					Sanitation/education	Low#	Moderate
Schistosomiasis mansoni	Moderately high	Low	Yes†	Possible clinical antagonism	Vector control	Low	Research needed
					Mass chemoprophylaxis	Low	Low
					Targeted chemotherapy	Moderately high	Moderate to high

* On a population, not individual-patient, basis.
† With symptomatic clinical disease.
‡ Must be combined with continuous education and surveillance.
§ Depends on prevalence of heavy infection and its impact on growth of infants and children.
‖ Delivery to the age group most at risk of heavy infection.
\# Probably must be combined with mass chemotherapy.

therefore, be followed by nutritional rehabilitation for repletion of losses. The nutritional consequences for persons with the chronic form of malaria are far more difficult to assess and manage, for such individuals are also subject to many other stresses, both infectious and noninfectious, that affect nutritional status.

At the same time, there are observations suggesting antagonism between malaria and malnutrition. This evidence includes clinical observations of the rarity of cerebral malaria in the overtly malnourished, as well as the exacerbation of parasitemia in malnourished subjects by refeeding or by administering parenteral iron. The general relevance of these situations is unclear, and, in any event, the mechanisms are unknown. It is possible that the nutritional and temporal requirements for the life cycle of the parasite are involved. For example, if the life span of erythrocytes is shortened, maturation of the organism may be compromised and parasitemia will be suppressed. However, producing severe malnutrition is hardly the way to control malaria.

Current prospects for the development of a vaccine are encouraging. It is difficult to be equally confident about vector control measures. Resistance to insecticides, potential environmental damage, and the cost of continuous intensive efforts are not easily dismissed. Nonetheless, vector control programs can have an impact; however, they should not be initiated unless there is a commitment to maintain the program indefinitely and to install a suitable surveillance system. Such an infrastructure would also permit rapid and effective deployment of a vaccine, should one become available. Chemoprophylaxis is of proven value for short-term visitors to an endemic area. However, widespread mass chemoprophylaxis seems to be unreasonable because of logistics, expense, and the potential for increased drug resistance by *Plasmodium falciparum*.

Giardiasis. *Giardia lamblia* has a worldwide distribution and is currently recognized as an important cause of acute diarrhea and, in a minority of infected patients, of chronic malabsorption. Giardiasis in infants and children has been associated with "failure to thrive," and treatment can produce rapid, incremental, catch-up growth. Experimental models are providing basic new information about both the interaction of the parasite with the epithelium of the small intestine and the immune mechanisms in the host response.

Limited epidemiologic field studies suggest that initial infections in young children are associated with acute diarrhea and, therefore, affect growth and nutritional state. Periodic treatment with metronidazole is said to improve individual growth in such populations. The available data are insufficient to draw conclusions, and further field work is necessary to establish the importance of giardiasis on a population-wide basis. While research thus is a priority, chemotherapeutic interventions are not. Periodic mass treatment is not justified until benefits are more certain, better drugs are available, and risks are assessed.

Because water may be the most important route of transmission of *G. lamblia*, projects for provision of pure water may benefit the population. The feasibility of this action is uncertain; waterborne transmission still occurs in some urban settings in industrialized nations. Until chemical means of destroying infective cysts are available, water purification will rely upon effective filtration for removal of the cysts. With potential reservoirs in wild and domestic animals (beavers and dogs, for example) and the likelihood of spread via person-to-person contact, the problem is even more intractable. Thus, it is difficult to advance support for water purification projects for giardiasis alone. In reality this justification is unnecessary because improvment of water purity and availability is an issue under active consideration by major international health organizations. Such projects, if successful, would have a beneficial impact on many infectious diseases that are waterborne or water washed.

Amebiasis. This infection is even more difficult to assess than is giardiasis. Most individuals who harbor the parasite are healthy carriers; only a few have acute illness. Whether or not first infections are usually symptomatic is not known, and how often acute diarrhea in children is due to intestinal amebiasis cannot be determined. In some countries (e.g., Mexico) amebiasis is an important, severe, systemic disease producing considerable morbidity and mortality.

Models exist for the study of invasiveness and cytotoxic properties of pathogenic amebae but not for intestinal disease. Nutritional considerations have been largely neglected, except for the observed

high iron requirement of the parasite and the apparent increase in severity of disease in iron-overloaded individuals such as the Bantu population of South Africa.

The magnitude of the contribution, if any, of chronic cyst passage to malnutrition in asymptomatic infections is unknown. In any event, simple, safe, and inexpensive prophylaxis is not available, and, therefore, control must presently rest on water and sanitation projects. While amebiasis is hardly a reason to initiate such investments in most situations, it is a potential added benefit of uncertain magnitude to such programs.

Hookworms. This is without doubt an important infection and one that is relatively simple to deal with. The single, most obvious, associated nutritional problem is iron deficiency and secondary anemia. It is rapidly corrected by iron supplementation, even more quickly than by antihelminthic therapy alone. Hookworm is just one of the causes of iron deficiency, which may have many morbid consequences other than anemia. For these reasons, iron supplementation should have the highest priority of the possible interventions. Chemotherapy could safely be reserved for those individuals with heavy infection and severe anemia, but this would necessitate identification of such patients. They are often young adults in the work force, and thus the debility due to anemia may affect productivity and income, with secondary nutritional repercussions for the entire household.

Public health and environmental sanitation measures such as latrines, concrete floors in the home, and the use of shoes can be effective but are often disappointing in reducing the intensity or prevalence of hookworm disease. An investment must be made in both facilities and education if success is to be achieved. This is not an easy task, but, because the benefits extend far beyond hookworm per se, these efforts have some priority. Nevertheless, the greatest benefit for the largest number of people, at the least cost and in the shortest time, will accrue from an effective iron supplementation program.

Ascariasis. Although this is a highly prevalent infection, solid data are lacking on the nutritional impact of these worms in the human. Malnutrition due to many other causes generally coexists in the same population, with no obvious cause-and-effect relationship. The frequency and importance of secondary malabsorption, morbidity accompanying larval migration, or intestinal or ductal obstruction is uncertain, and the nature of host immunity is unknown. Similar remarks would also apply to *Trichuris trichiura*, which is so frequently found with ascaris infection.

The studies showing an impact of antihelminthic treatment on growth of children demonstrate a small positive effect. The effect is too minor to provide a basis for a recommendation of periodic mass deworming programs; the benefit is likely to be small, with little reduction in transmission or reinfection. Whether greater benefits are demonstrable in people with heavy infections is uncertain, and, no matter how likely, the importance of these benefits from the public-health perspective is uncertain. Diligent, long-term, periodic mass chemotherapy may reduce the worm burden per individual and, in conjunction with environmental sanitation, could ultimately reduce transmission and prevalence. This is an enormously ambitious goal and has been advocated for decades with little obvious result because poverty remains endemic. Therefore, the higher priority should be the development of primary health care delivery programs, which might include judicious use of antihelminthics in heavily infected patients. If the basic health program can be initiated, treatment of ascariasis would not significantly increase cost.

Schistosomiasis. Considerable progress has been made in understanding the host-parasite interaction and the immunopathogenesis of schistosomiasis. In experimental *S. mansoni* infections, nutritional deprivation of protein, energy, or certain vitamins inhibits the formation of the egg granuloma and reduces the severity of clinical manifestions of hepatosplenic disease. In the human infection there may be blood loss, and, rarely, malabsorption of vitamins or fat. However, even in the presence of severe hepatic fibrosis and varicosities in the portal venous system, hepatocellular function remains intact, and there are generally no major deleterious nutritional effects. The present data also do not suggest that improving nutrition in malnourished, infected individuals will adversely affect the severity of disease manifestations. Therefore nutritional interventions can be planned, regardless of the presence of schistosomiasis.

Schistosomiasis is a severe, sometimes fatal disease in certain individuals, and this fact must be considered independently of nutritional concerns. The concept of targeted mass chemotherapy aimed at treatment of the age group with the heaviest infections, which is most likely to develop disease, has great intellectual and epidemiologic appeal. Therapy is employed to reduce the intensity of infection in the target population, not necessarily to achieve cure; thus, maximum benefit for the greatest number with minimum toxicity and expense is ensured.

Recommendations

As a general principle, correcting nutritional deficiences in patients with clinically overt infections should be addressed as an essential adjunct to specific antiparasitic therapy on a patient-by-patient basis. Corrective measures must include dietary supplementation during convalescence until deficits are eliminated. Nutritional support may also be needed by patients with asymptomatic infection due to the many other causes of malnutrition. The refeeding of such patients may be followed by an acute exacerbation of the parasitic infection. While this is probably not a common phenomenon, recent observations indicate that it should be anticipated in populations with a high prevalence of malaria.

With the exception of iron supplementation in hookworm disease, nutritional therapy is not an effective way to control parasitic diseases. At the same time, however, reduction in the incidence of clinical malaria, giardiasis, and probably amebiasis may well contribute to an improvement in nutritional state. It remains to be proved whether reduction in intensity of round worm infection will have similar benefits.

Based on the analysis in table 1, priorities for interventions are listed below.

Malaria control. There is an accompanying caveat suggesting that commitment be long term, that a surveillance system be developed to monitor the situation, and that the effort not be diluted by other tasks. The benefits may be limited, but the severity of the problem dictates the priority and supports the vertical intervention.

Iron supplementation for hookworm disease. The vehicle, the form, and the quantity may vary from place to place but the goal is clear: to treat the major manifestation of hookworm disease, i.e., iron deficiency. In the presence of severe protein energy malnutrition with very depressed transferrin levels, iron supplementation (especially by the parenteral route) may contribute to infection morbidity by providing free iron necessary for the growth of the pathogen. This outcome is unlikely to result from continuous, low-level, therapeutic intervention by supplementation or fortification of a dietary staple.

Water and sanitation projects. These should be part of the general effort to improve the living conditions and the health status of a population. Effective implementation will reduce the burden of each pathogen considered here, except malaria, and of many others not discussed. Both technology and education are critical to success. Furthermore, a long-term commitment of financial support and an infrastructure conducive to monitoring and ensuring appropriate use and maintenance of the resources are essential. Without these measures, the technology may become a conduit for the mass spread of infection.

Periodic antihelminthic therapy. Safe effective drugs are presently available and are widely used by individuals for treatment of infection due to *Ascaris lumbricoides* and the hookworms. The organized, community use of antihelminthics is another issue. In temporary campaigns these drugs are unlikely to have a noticeable impact; in continuing programs, combined with environmental sanitation and health education efforts, there is the likelihood of important health benefits. Presently available drugs will not significantly reduce the prevalence of infections due to *Trichuris trichiura* or *Strongyloides stercoralis*, however, and these parasites will have to be dealt with in individual cases where more intensive therapy can be effective. Without the total program to reduce transmission and prevalence of infection, periodic mass treatment campaigns are not likely to have any long-term effect, and the funding required can be better used elsewhere.

Targeted mass chemotherapy against schistosomiasis is an entirely separate issue and is recommended wherever the disease is prevalent. This requires a health sector capable of epidemiologic surveillance so that the population at risk can be reached, the heavily infected target group iden-

tified and treatment directed to them, and follow-up evaluation provided.

The last three recommendations can, and should, be incorporated into primary health care schemes in which nutrition surveillance and education, promotion of breast feeding and appropriate weaning practices, oral rehydration for acute diarrhea, and immunization for the preventable childhood communicable diseases are promoted. In this context, and with the proper involvement of the community in planning and implementation, even the third goal becomes achievable. Integration thus becomes not only the combination of programs or interventions, but the joining of the health professionals and the community to carry out the tasks.

CLASSICS IN INFECTIOUS DISEASES

A Newly Discovered Parasite in the Blood of Patients Suffering from Malaria. Parasitic Etiology of Attacks of Malaria.

Charles Louis Alphonse Laveran
(1845-1922)

Constantine, Algeria

[These excerpts are reprinted from the translation in *Tropical Medicine and Parasitology, Classic Investigations, Volume I*, edited by B. H. Kean, M. D., Kenneth E. Mott, M. D., and Adair J. Russell, pages 23-26. Copyright© 1978 by Cornell University. Used by permission of the publishers, Cornell University Press.]

[Editor's note: like many other notables in the history of tropical medicine, Laveran first became acquainted with the problems he was to study throughout his life during his career as a military surgeon. He was born in Paris, the son and the grandson of physicians, and was awarded his degree in medicine by the University of Strasbourg in 1867. After several military assignments in France, he was transferred in 1878 to Algeria, where he became deeply interested in malaria, the cause of which was then being widely discussed. During a series of microscopic blood examinations of malaria patients in Constantine, he discovered spherical pigmented bodies with ameboid movement which he had until then confused with pigmented leukocytes. This was the third time that microorganisms had been found in human blood, the first two being the causative agents of relapsing fever and anthrax. When Laveran's discovery was confirmed, the Academy of Sciences in Paris elected him to honorary membership. In 1904, Laveran retired from military service and joined the Pasteur Institute, where he devoted himself entirely to bacteriologic and parasitologic research. He published more than 600 scientific papers dealing with malaria and many other tropical diseases. In 1907, he received the Nobel Prize as "initiator and pioneer of the pathology of protozoa."

Many others had seen various objects in the peripheral blood of malaria patients—Meckel (1847), Virchs (1858), Planer (1854), Delafield (1872), and Jones (1876)—yet none developed their observations in a systematic manner. Laveran's first communication appeared in the *Bulletin de l'Academie de Médecine*, 19:1235-1236, 1880. The brevity of the original article did not do justice to this monumental discovery. We have reproduced the following article, in full, with its single plate.]

On 20 October of this year, while I was examining microscopically the blood of a patient suffering from malaria, I noticed, among the red corpuscles, elements that seemed to me to be parasites. Since then, I have examined the blood of 44 malaria patients; in 26 cases, these same elements were present. This convinced me of their parasitic nature. These elements were not found in the blood of patients who were not ill with malaria. I will describe these elements as No. 1, No. 2, and No. 3. Eventually, it will become evident that this nomenclature is useful as it makes no assumptions as to the nature of the parasites.

Please address requests for reprints to The Editor, *Reviews of Infectious Diseases*, Channing Laboratory, 180 Longwood Avenue, Boston, Massachusetts 02115.

Description of Parasitic Elements Found in the Blood

No. 1. These are elongated bodies, with ends more or less tapered, often crescent-shaped (see Plate 5, Figs. 3 and 4), but sometimes ovoid (Fig. 5). In length, they measure from 8 to 9 microns and in breadth, they average 3 microns. A very fine line indicates the contour while the body itself is transparent and colorless at the periphery; toward the central part, there is a dark stain due to a series of rounded granulations that are probably pigment granules. Exceptionally, this stain is situated at the periphery. The granulations are often symmetrically disposed, in a crownlike arrangement, similar to the one I shall describe for No. 2. On the concave side of the crescent-shaped bodies, a curved pale line often seems to connect both ends of the crescent. This line is shown on Fig. 4. No. 1 bodies seem motionless; when their outline changes, it does so very slowly.

No. 2. These bodies present different shapes that vary with their being in states of rest or motion. In states of rest, the body is generally round and transparent, finely contoured, measuring 6 microns in diameter. Inside the body (Fig. 6), round pigmented granules of equal size are usually quite regularly arranged in a ring; one might say they look like a necklace of black pearls.

In motion, one sees very transparent filaments that are rapidly moving in all directions. These

movements may be compared to those of nematodes that would have one end attached to the inside of the spherical part. These filaments set the neighboring red blood corpuscles into motion, and this is easily observed. The length of the filaments or mobile appendices is approximately three or four times the diameter of the red corpuscle. I had the impression that three or four of these filaments surround every so-called No. 2 body, but there may be more of them, since only perfectly focused mobile filaments are perceived. These mobile filaments are sometimes regularly spread out on all sides (Fig. 7) or all are sometimes clustered on one side (Fig. 8). The free ends of the moving filaments are swollen, as is indicated on Fig. 7.

While these filaments or motile appendices move around freely, the spherical body on which they seem to be inserted oscillates more or less rapidly and even seems, at times, to move about so that all its parts follow the same direction. The pigmented granules move around freely inside the body and assume various configurations.

No. 2 bodies very often alter their shapes while one observes them. They become longer, flatten out, and become spherical again. In this last instance, the movements recall those of amoebae. Several times, it happened that while I was observing the motion of No. 2 bodies one of the mobile filaments would leave the round body and continue to move around the red corpuscles. Fig. 9 shows one of these filaments that has become free.

In several instances I have also observed in the slides of malaria patients, apart from the elements heretofore described, rounded bodies larger than the No. 2 bodies and usually even larger than leukocytes, which had inside them moving pigmented granulations. These bodies contained no mobile filaments and their motion was Brownian-like (Fig 10).

No. 3. These bodies are round, larger in diameter (8 to 10 microns and sometimes greater), than No. 2 bodies, slightly granular, motionless, without any apparent peripheral filaments. Inside the bodies one sees pigmented granules sometimes arranged like those in No. 2 (Fig. 11) but more often disposed haphazaradly and in variable numbers. These bodies alter in shape increasingly and so tend to become very different from the type I just described (Fig. 12 and Fig. 13).

In addition to No. 1, 2, and 3 bodies, one nearly always finds small, rounded, mobile, and bright bodies and crimson red or light blue pigment granules. These pigmented granules are free or are included in No. 3 bodies or in leukocytes. The crimson red pigment seems to undergo transformation, and the result would seem to be the blue pigment.

Refutation of Some Objections. Methods of Blood Examination

Before I delve into the nature of the parasitic elements and their pathologic role, I wish to answer two objections made to me several times which probably will be presented to me again:

(*1*) Were the above-described parasitic elements really found in the blood of the patients? Were they not accidentally introduced into the slides?

(*2*) Were altered blood elements mistaken for parasitic elements?

The technique I used in all my preparations should shield me from the first of these objections. The glass slides were carefully washed in alcohol; the patient's finger was swabbed with alcohol; pure blood was examined without the addition of another fluid; and finally the slides were sealed with paraffin. It is true that all these precautions would not prevent floating air particles from entering the preparation, but how could one possibly maintain that the complicated parasites I have described were floating in the air only while I was examining the blood of malaria patients? How could one correlate the relationship I have many times ascertained between the abundance or rarity of parasites and the degree of sickness or apparent recovery of malaria patients if the inclusion of the parasites was due only to chance? Moreover, I was always careful to prepare the slides in different locations in the wards or in my laboratory, and the results were identical. I beg to dispose of this objection and to maintain that the parasites were truly in the blood of patients.

The second point seems even easier to deal with than the first. It is impossible to confuse No. 2 bodies equipped with mobile filaments with any possible normal or pathologic element of the blood. The swift movements of the filaments have nothing in common with the slow motions of leukocytes, and the pigmented granules, mobile or

arranged in a ring, should not be confused with the granulation of leukocytes. All my colleagues to whom I was able to show these No. 2 bodies in motion did not hesitate for a single second in recognizing that what was moving was indeed a parasite. One would only need a glance at Figs. 7 and 8 to become convinced that such bodies cannot be confused with leukocytes, however altered these may be. Even when they are motionless, No. 2 bodies resemble leukocytes only vaguely. They are usually smaller, the granulations are dark or crimson red and arranged in a ring, and they have no inner nuclei.

It would be just as impossible to confuse No. 1 bodies with blood elements. Erythrocytes, sometimes similar in shape to the bodies, never have any internal pigmented granules. It is true that No. 3 bodies look very much like pigmented leukocytes. They are alike in shape and measurements. Yet, the differences are great. Pigmented granules have a regular arrangement in No. 3 bodies (Fig. 11); there are no internal nuclei, and these elements do not take carmine dye as do leukocytes. Moreover, it is easy to ascertain that No. 3 bodies are the result of transformation of No. 2 bodies, the living nature of which is incontestable.

Nature and Pathologic Role Played By Parasitic Elements Found in the Blood

Bodies Nos. 1, 2, and 3 seem to represent different aspects or different phases of the evolution of the same parasite. It is evident that No. 3 bodies are the result of a transformation of No. 2 bodies after their death. It is easy to convince oneself in the following fashion. One looks for a No. 2 body with mobile filaments and after having found one that is characteristic and very lively, the slide is placed on the microscope and is observed from time to time. After a variable period (from some minutes to several hours), the movements cease and the filaments become invisible. The body changes from its Fig. 7 or 8 aspect to the one shown in Fig. 6. After a while, No. 2 body enlarges as if flattening out while the pigmented granules disassociate, forming a widening circle (Fig. 11). Finally, the parasitic organism alters its shape to the point where it is no longer recognizable. The pigmented granules become arranged irregularly. They accumulate at one point or disappear altogether with the exception of one or two. The same procedure, when applied to No. 1 bodies, give similar results. The bodies become shapeless after a while, although not so rapidly as No. 2 bodies. No. 1 bodies become first ovoid and then spherical and irregular.

Often, one finds in the slides ovoid bodies that appear to be intermediate between No. 1 and No. 2 bodies. Nevertheless, i have never witnessed a No. 1 body transforming itself into a No. 2 body even after a 36- or 48-hour period of observation.

Mobile No. 2 bodies are mostly found in the

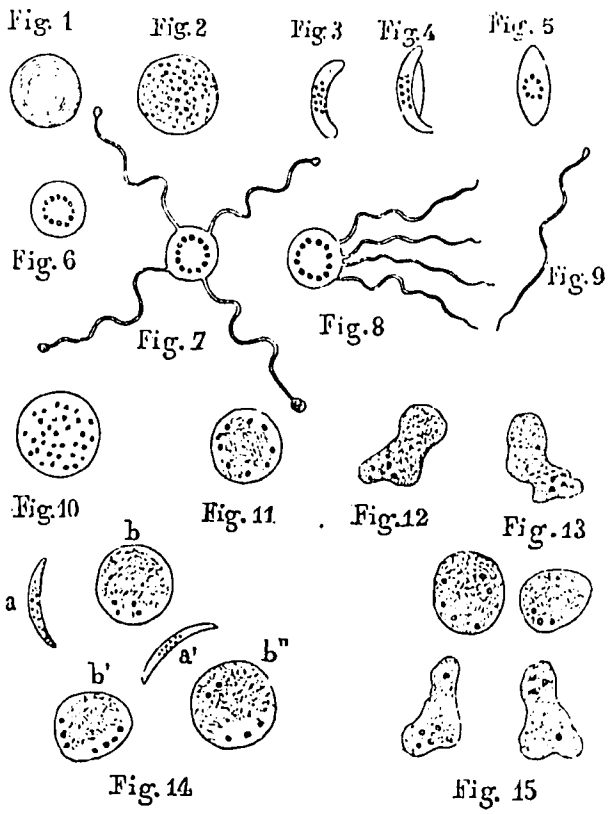

Plate 5. Key to drawings. *Fig. 1.* Blood red corpuscle. *Fig. 2.* Polymorphonuclear leukocyte. (These elements serve as points of comparison to give an idea of the measurements of the other elements; all diameters magnified [greatly].) *Figs. 3* and *4.* No. 1 bodies. *Fig. 5.* Ovoid intermediate body between No. 1 and No. 2 bodies. *Fig. 6.* No. 2 body, motionless. *Fig. 7.* No. 2 body with mobile peripheral filaments bulging at the free end. *Fig. 8.* No. 2 body with mobile filaments grouped laterally. *Fig. 9.* Mobile filament freed from the body. *Fig. 10.* Spherical body filled with mobile pigmented granules. *Fig. 11.* No. 3 body. *Figs. 12* and *13.* Distorted No. 3 body. *Fig. 14.* Pigmented elements from the blood of a man who died of pernicious fever: (*a*, *a'*) elements similar to No. 1 body; (*b*, *b'*, *b"*) elements similar to No. 3 bodies. *Fig. 15.* Elements from the spleen of a man who died of pernicious fever; elements similar to No. 3 bodies.

blood of patients who have suffered a recurrence of fever and who do not take quinine sulfate regularly.

The very fact that the parasitic organisms above described are found in an alkaline medium such as blood leads one to think that the parasites are of animal and not vegetable origin. The rapid and very varied movements of the filaments of No. 2 bodies, as well as the modifications of form they go through, lead the researcher to think of an organism like an infusoria. Is it as I first thought, an amoeba, or could bodies No. 1 and No. 2 be the result of an agglutination of cystlike parasites formed by normal elements in the blood? Could these parasites, fully developed, be the mobile filaments of No. 2 bodies, that sometimes leave the bodies to lead independent lives? This last hypothesis seems to me the most probable one. Once free, the mobile filaments are very much like filariae; and several researchers, Hallier among them, think filariae play an important part in the pathology of swamp fevers. The small, mobile, bright bodies, almost always present in the preparations, may be the first phase of an evolution of an organism. Quite often, one of these little bodies attaches itself to a red corpuscle and makes the effort, if I may say so, to penetrate into the interior.

The important role played by the parasites above described in the pathogenesis of swamp fevers may be evaluated as follows:

(*1*) These parasites are found only in the blood of patients suffering from malaria. It is fair to add that they are not always found there but, since only one or two drops of blood are examined, it is obvious that when the parasites are very scarce, their presence is difficult to establish.

(*2*) These parasites, while abundant in the blood of patients who have suffered from the fever for some time and who received no regular treatment, vanish from the blood of those treated for a long time with quinine sulfate, and who may be considered cured. Many of the patients I examined had received quinine sulfate for several days, and that could explain the high percentage of negative results I obtained.

(*3*) In the blood of patients who have died of pernicious fever, one finds a great number of pigmented elements that look very much like No. 3 bodies or, in rarer instances, No. 1 bodies. The presence of these elements in capillaries of all tissues and of all organs, particularly of the spleen and liver, is characteristic of acute malarial infection. Fig. 14 shows pigmented bodies found in the blood of a man who died of pernicious fever, and Fig. 15, similar bodies found in spleen tissue in another case of pernicious fever. The resemblance of these bodies to those I described as No. 1 bodies and No. 3 bodies, and whose parasitic nature I believe to have established, is striking.

From where come these parasitic elements found in the blood of malaria patients? How do they get into the human system? How do they cause intermittent fever and other signs of malaria? Only now is one able to pose these important questions.

Conclusion

Parasitic elements are found in the blood of patients who are ill with malaria. Up to now, these elements were thought incorrectly to be pigmented leukocytes. The presence of these parasites in the blood probably is the principal cause of malaria.

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THE INFECTIOUS DISEASES SOCIETY held its organizational meeting on October 26, 1963, at the Airlie House in Warrenton, Virginia. For several years prior to this, there had been increasing interest in the formation of such a society. A community of investigators interested in laboratory and clinical aspects of infectious diseases was becoming increasingly defined in many major academic centers. Certain of these investigators were meeting each year at Atlantic City at an informal dinner club, and a similar group had begun to meet for dinner and discussion at the time of the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Finally a decision was made to explore various ways in which an organization could be formed that would articulate the broad interests of those working in infectious diseases. An Organization Committee was formed and was charged with the responsibility of calling the first meeting, arranging for scientific program, and nominating the first slate of officers. A number of pharmaceutical firms provided financial assistance.

The organization clearly has met an important need. Its growth, its relationship to national and international activities in infectious disease, its unusual and broad scientific programs, and its relationship to the Interscience Conference have given the Society a unique and useful place in the academic and scientific community. Its decision to constitute itself as a meeting place for scientists from all of the Americas has also given it a potentially important role in unifying scientific activity in many neighboring countries.

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