STUDY WEEK

ON:

THE INTERACTION OF PARASITIC DISEASES AND NUTRITION

October 22-26, 1985
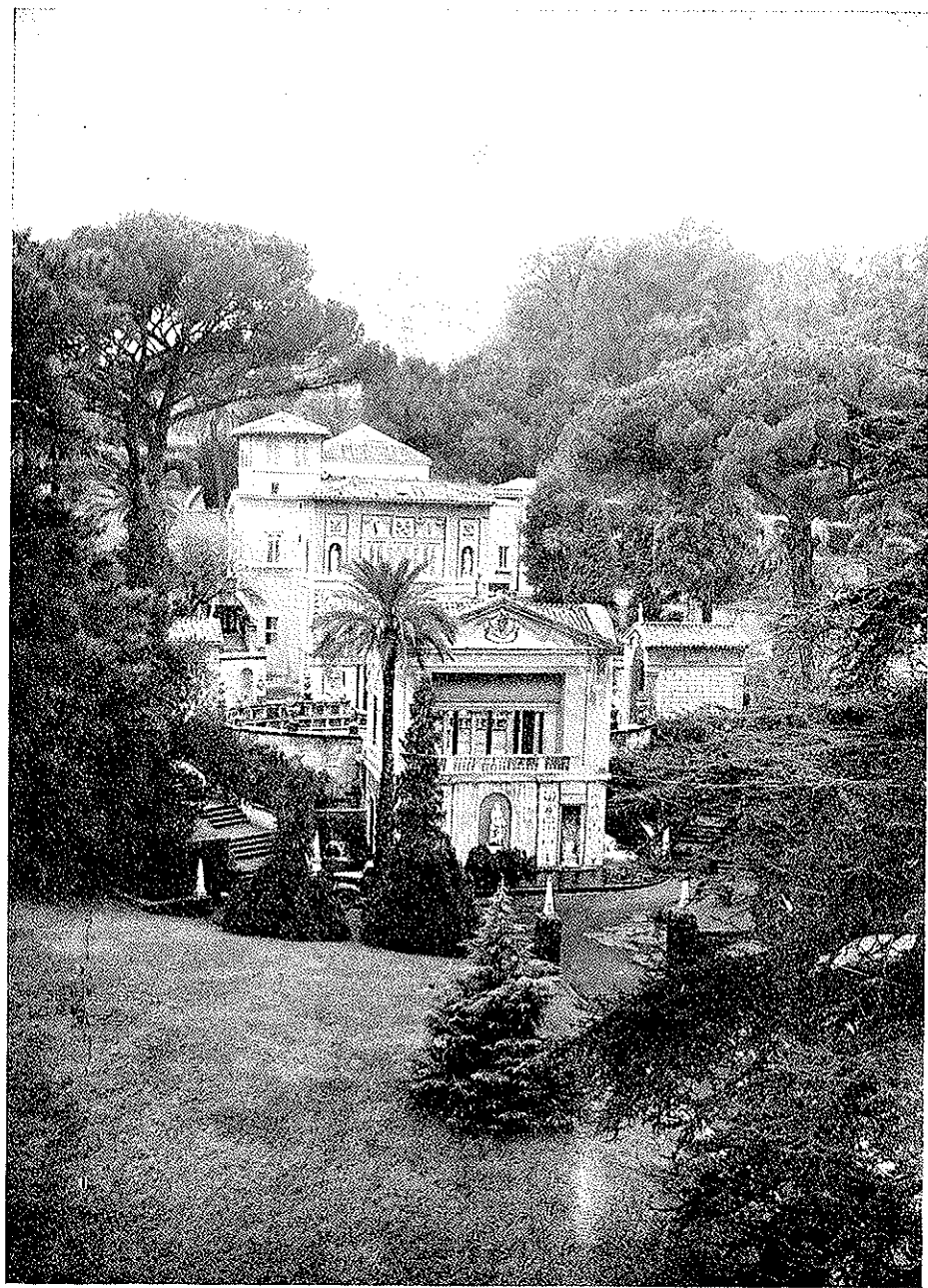
EDITED BY

CARLOS CHAGAS and GERALD T. KEUSCH

PONTIFICIA ACADEMIA SCIENTIARVM

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**PONTIFICIA
ACADEMIA
SCIENTIARVM**

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PREFACE

The Study Week on the Interaction of Parasitic Diseases and Malnutrition dealt with a very important global problem. One may associate malnutrition and parasitic diseases with economic, social and cultural factors, and it is clear that a positive action can be taken in order to minimize or eradicate both.

It is easy to accept that by malnutrition a series of pathogenic states will appear, due at least partly to the lessening of the immunological defense. Malnutrition is certainly one of the specters which haunt all of those interested in the welfare of humankind. So many studies have been made in developing countries about this relationship that it seemed not necessary to organize the Study Week which was held, and which in a certain way was a continuation of a former one held in Bellagio six years ago. The richness of the contents of the papers presented showed that the meeting had its place. All the aspects of the question were treated in our recent meeting, as, for instance, global food production, the availability per capita of energy, and other aspects of the problem.

The most fundamental conclusion of the meeting was, however, that even when dietary intake meets the accepted standards there may be a deterioration produced by the host cell as a response to the parasitic attack. This response is due to the release of interleukin and cachectin, small proteins that are well defined in their molecular constitution.

The meeting was organized and chaired by Professor Gerald T. Keusch, Chief of the Division of Geographic Medicine at Tufts University School of Medicine, Boston. I want to express not only my gratitude but also my admiration for Prof. Keusch's work. High esteem and thankfulness are due also to all the participants, who with great good will

came to Rome in search of a label which I think will certainly benefit children, women and men all around the world. I would like to thank warmly the Banco Piccolo Credito Valtellinese for the generous contribution offered towards the publication of the present volume.

I want also to present my thanks to Father Enrico di Rovasenda, and to Mrs. Michelle Porcelli and Gilda Massa, as well as Silvio Devoto for their help in the preparation of this volume.

CARLOS CHAGAS
President of the Pontifical Academy of Sciences

FOREWORD

In 1980, a conference to examine the interactions between parasitic diseases and malnutrition was held at the Rockefeller Foundation Conference and Study Center in Bellagio, Italy, with the support of the World Hunger Programme of the United Nations University, the Fogarty International Center of the U.S. National Institutes of Health, and the Rockefeller Foundation. Based on the assigned nutritional importance of each of six parasitic diseases discussed at the meeting and the feasibility of interventions, a prioritized list of recommendations was presented: malaria control, iron supplementation for hookworm disease, water and sanitation projects, periodic antihelminthic therapy for ascariasis, and targeted mass chemotherapy for schistosomiasis.

In the five years since this seminal meeting, new information has become available concerning mechanisms of malnutrition during infection, nutritional consequences of parasitic diseases, and strategies for their control. The Pontifical Academy of Sciences, under its President, Professor Carlos Chagas, decided to hold a meeting to review this new information and to update the recommendations for action. Therefore, a multidisciplinary group of experts was called together at the Academy in Vatican City, from October 22-26, 1985. During an intensive Study week, four topics were considered in great detail by presentation of papers followed by extensive discussions: 1. Mechanisms of malnutrition; 2. Interactions of parasitic infections and nutritional status; 3. Strategies for control of parasitic infections; 4. Policy implications and recommendations. This volume consists of these papers and is published in the hope it will prove useful as a resource document for those interested in the definition of future research questions and in the formulation of policy.

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SCIENTIFIC PAPERS

I.

MECHANISMS OF MALNUTRITION

FOOD SUPPLY AND ENERGY INTAKE:
A GLOBAL PERSPECTIVE *

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SUMMARY

World per capita dietary energy supply has increased by 12% from an average of 2,130 kcal per day during 1969-71 to 2,350 kcal per day during 1979-81. The improvement was particularly small in Africa and although the Far East had greater gains than Africa, its per capita dietary energy supplies remained the lowest among the regions at 2,150 kcal per day during 1979-81. During the early 1980s there was practically no growth in dietary energy supply in Latin America and in Africa the per capita dietary energy supply has actually declined. The countries with fastest population growth had the most difficulty in maintaining per capita energy supply. The consumption pattern between developed and developing countries also did not change much during this period.

Although a direct link between under-nutrition and energy intake can only be established at the individual level, there is substantial evidence that families consuming a lower amount of energy have a higher number of malnourished children and countries with a lower level of energy supply have more under-nourished people than those with higher per capita supplies. Available data on food consumption of vulnerable groups from developing countries also reveals very low intake of energy and high prevalence of malnutrition.

1. INTRODUCTION

For convenience of discussion this paper is divided into three parts. The first discusses the trends in world food supplies and changes in pattern of consumption on the basis of the latest supply data available from food balance sheets. The second deals with factors that affect energy consumption, urban-rural differentials in energy consumption and energy consumption by vulnerable groups. The third examines the broad linkages between energy consumption and malnutrition at individual, household and national level. The content is mainly drawn from FAO's Fifth World Food Survey (FAO, 1985).

1.1 *Trends in food supplies during 1960s and 1970s*

Since 1946 FAO has periodically assessed the nutritional adequacy of global food supply by comparing aggregate food supply data obtained from food balance sheets with available recommendations on energy requirement. Over the years a substantial improvement has occurred in the quality and coverage of the data and progress has also been made in our knowledge of energy requirements. A summary of the most recent prospective analysis of the change in per capita dietary energy supply (DES) from 1961-1981 is provided in Table 1. More recent trends in per capita DES during 1981-83 on the basis of preliminary data are given in Table 2. The major features of this analysis are as follows.

World per capita food supplies measured as DES improved by 12% from 2,340 kcals per day in 1961-63 to 2,620 in 1979-81. The gap between developed and developing countries, though still wide, has narrowed. There has been a substantial drop in the rate of increase in DES during the 1970s in developed countries and a slight deceleration in the high rate of increase in developing countries. The per capita food supplies have improved for each developing region and economic group in the 1970s, except for the least developed countries. The smallest increases were in Africa. In general, the gap between the developed and middle to high income developing countries has narrowed while the gap between both of these groups and low income developing countries has widened.

Examination of individual data from 112 developing countries for which recent food balance sheets are available reveals that in 26 countries (with 8% of the total population) per capita DES declined in the 1970s in 11 countries (2% of the population) there was virtually no change, but

TABLE 1 - *Per capita dietary energy supply (DES) by region and economic group 1961-63, 1969-71 and 1979-81.*

Region or economic group	1961-63	1969-71	1979-81	Average annual rate of increase	
				1961-63 to 1969-71	1969-71 to 1979-81
	(kcals per capita/day)			..... (%)	
DEVELOPED COUNTRIES	3 110	3 280	3 390	0.7	0.3
Developed market economies	3 090	3 260	3 380	0.7	0.4
North America	3 280	3 480	3 620	0.8	0.4
Western Europe	3 150	3 300	3 440	0.6	0.4
Oceania	3 160	3 270	3 150	0.4	—0.4
Eastern Europe & U.S.S.R.	3 170	3 330	3 420	0.6	0.3
DEVELOPING COUNTRIES	1 980	2 140	2 350	1.0	0.9
Developing market economies	2 060	2 160	2 320	0.6	0.7
Africa	2 120	2 170	2 260	0.3	0.4
Far East	1 940	2 020	2 160	0.5	0.7
Latin America	2 370	2 500	2 620	0.7	0.5
Near East	2 230	2 400	2 840	0.9	1.7
Asian centrally planned economies	1 830	2 100	2 430	1.7	1.4
Economic group of developing countries					
Least-developed	1 980	2 060	2 070	0.5	0.1
Low-income food-deficit	1 920	2 070	2 270	1.0	0.9
Low-income	1 910	2 060	2 240	1.0	0.8
Middle- to high-income	2 150	2 310	2 590	0.9	1.1
WORLD	2 340	2 470	2 630	0.7	0.6

Note: Per capita dietary energy supply (DES) is measured as energy equivalents of quantities of food available for human consumption.

Source: The Fifth World Food Survey.

TABLE 2 - *Per capita dietary energy supply (DES) by region and economic group* 1979-81 *and* 1981-83.

Region or economic group	1979-81	1981-83	Average annual rate of increase	
			1969-71 to 1979-81	1979-81 to 1981-83
	(kcals per capita/day)		......(%	
DEVELOPED COUNTRIES	3 390	3 390	0.3	0.0
DEVELOPING COUNTRIES	2 350	2 400	0.9	1.1
(Excluding China)	(2 320)	(2 340)	(0.7)	(0.5)
Developing market economies	2 320	2 340	0.7	0.5
Africa	2 260	2 230	0.4	−0.7
Far East	2 160	2 190	0.7	0.9
Latin America	2 620	2 620	0.5	0.0
Near East	2 840	2 900	1.7	1.1
Asian centrally planned economies	2 430	2 540	1.4	2.2
(Excluding China)	(2 320)	(2 380)	(0.3)	(1.2)
Economic groups of developing countries				
Least-developed	2 070	2 080	0.1	0.2
Low-income food-deficit	2 270	2 320	0.9	1.2
(Excluding China)	(2 160)	(2 180)	(0.5)	(0.5)
Low-income	2 240	2 300	0.8	1.4
(Excluding China)	(2 080)	(2 110)	(0.2)	(0.7)
Middle- to high-income	2 590	2 610	1.1	0.4
WORLD	2 630	2 660	0.6	0.6

Source: The Fifth World Food Survey.

in 75 countries (90% of the population) there was at least some increase in per capita food supplies. The greatest increase occurred in middle to high income developing countries.

Declines in per capita DES were concentrated in countries with low income and with already low food supply and occurred primarily in Africa. Of 30 countries with per capita DES of 2,300 kcals or less in 1969-71, 17 (14 in Africa) showed no improvement by 1979-81. In middle to high income countries, however, only 7 of 34 countries with DES of 2,300 kcals or less in 1969-71 failed to increase this measure by 1979-81.

1.2 *Dietary energy supply and population*

When changes in DES are compared by classifying countries by population growth rate, those with population growth of 2% or less fare better than countries with higher rates. Of the former group, 6 countries (17%) had a DES growth less than population growth, in contrast to 26 (26%) of the countries with population growth greater than 2%.

1.3 *Developments in the early 1980s*

While DES leveled off at around 3,390 kcals per capita in developed countries, developing countries continued to show improvement in the early 1980s with a growth rate of around 1% a year. However, this figure is highly influenced by the performance of China, and when China is excluded the growth rate is halved. The Far East and Asian centrally planned economies (ACPE; excluding China) all registered DES growth rates close to 1% a year in the early 1980s, but there has a been a major recent slowing in growth in the Near East. Including China, the gain in per capita DES in the ACPE rose from 1.4% in the 1970s, to an impressive 2.2% a year in the early 1980s. Both Africa and Latin America, where the DES growth rate was rather low during the 1970s, experienced declining growth rate. In Latin America there was no growth and in Africa there was an actual decline of serious nature since DES was already at a low 2,260 kcal per capita during 1979-81.

The stagnant trends of the 1970s in LDCs with a very low per capita DES (2,070-2,080 kcals) persisted in the early 1980s; however, the low income-food deficit and low income groups continued a respectable rate

of growth while the growth rate of the middle to high income groups was reduced by more than half.

1.4 *Food consumption pattern*

Analysis of the contribution of major food groups to dietary energy supply also indicates changes in the food consumption pattern. These changes have generally been greater in developed than in developing countries. In developed market economies the share of cereals, roots, tubers and animal oils and fats decreased and the share of vegetable oils and fats, alcoholic beverages and meat and offal increased. In developing market economies, principal changes included declines in the share of pulses, nuts and seeds (especially in the Far East) and of roots and tubers (in Latin America) and increases in sugar, vegetable oils and fats (in the Near East). In ACPE, the contribution of cereals to dietary energy supplies continued to rise as did meat and offal. Similar changes occurred in low income developing countries, but no change was found in either least developed or middle to high income countries.

The contribution of expensive animal protein to dietary energy supplies in 1979-81 was as much as 32% in developed market economies but still only 9% in developing market economies, 8% in low-income developing countries and 11% in medium to high income countries. In contrast direct cereal consumption constituted 26%, 58%, 65% and 52%, respectively, in these four groups.

1.5 *Nutrient content of the diet*

The sources of dietary energy are shown in Table 3. The differences between diets of developed and developing countries are striking. In developed countries, the contribution of carbohydrates to DES fell from 59% in 1961-63 to 55% in 1979-81; but in developing countries it remained essentially constant.

The per capita energy supply from protein remained approximately at 12% and 10% in developed and developing countries, but the per capita protein supplies in developing countries were still only 56% of those in developed countries in 1979-81. The biggest increases in these supplies were in the ACPE and in the Near East, the latter having by far the highest level of all developing regions.

Differences in animal protein supplies were even greater. In

TABLE 3 - *Per capita household energy intake and body weight of preschool children* (0-5 years) *by economic class* (Indian rural district).

Economic class	Per capita household energy intake	Body weight as % of standard within each class			
		>90	75-89.9	60-74.9	<60
			percent of children		
High	2 435	32.5	54.2	13.3	----
Middle	2 306	16.2	53.0	27.9	2.9
Low	2 140	6.4	36.3	46.8	10.5

Source: Rao and Satyanarayana (1976).

developed countries, animal protein rose from 50% of total protein in 1961-63 to 56% in 1979-81. In developing countries, however, animal protein was still only 21% of that in developed countries by 1979-81. Among individual developing regions and groups, it is only in Latin America, the Near East, ACPE, and middle to high-income countries that there was much increase in animal protein. Due to a continued increase in per capita fat supply in all regions, the energy supply for fat increased from 29% to 33% in developed countries and from 14% to 16% in developing countries. In developed countries, the animal fat share in the total, however, declined slightly from 67% in 1961-63 to 63% in 1979-81. There was a large absolute decline in animal fat supplies in Oceania (20% from 1961-63 to 1979-81) and a smaller one (4% from 1969-71 to 1979-81) in North America. In developing countries, in spite of big increases in several regions, total per capita fat supplies remained only 31% of those in developed countries.

2. ENERGY INTAKE

2.1 *The main limitations of available data*

Estimates of energy supply as provided by the food balance sheets show only the supply at the retail level and do not indicate consumption within different strata of population. In fact, actual household consumption is likely to be slightly or appreciably lower according to the degree of preparation, cooking and plate waste within the household.

Most of the data on food consumption are available at household level and can be broadly classified into two types: (1) Income/expenditure/budget surveys that show quantities of food available to, or acquired by, the household, and (2) the actual food consumption survey which is ideal for nutritional purposes and which measures the actual intake of food. The scope of the second type varies and may include consumption of vulnerable groups and individuals.

A recent comparative study by FAO (1983) between energy supply (provided by food balance sheets) and energy consumption (provided by consumption surveys) from twenty countries showed wide discrepancies. In developed countries consumption surveys showed per capita energy figures which are lower than those derived from food balance sheets. The magnitude of differences was rather high and ranged from — 11.6% to — 33.9%. In developing countries no consistent pattern was found and differences were both positive and negative (range —14.8% to + 25.3%). The actual food consumption data from three countries showed that the energy supply was uniformly higher.

Household food consumption data only indicate the aggregate consumption of the household and are not an adequate direct measure for the nutritional status of the individual members of the family. Data on individual consumption within the household are scarce and limited individual data are available for only certain vulnerable groups.

2.2 *Factors that determine energy intake*

Many factors at the household level determine access to available food supply, consumption and utilization. These factors can be broadly grouped as economic, seasonal, social, cultural and environmental.

(1) *Economic factors.*   Although most malnourished people are poor, not all poor are malnourished. Income is not the only determinant of variability in food intake, and other social and environmental deprivations contribute to it. Studies have shown a positive relationship between income and energy intake and changes in the quality of diet. A security of income, even at low level, is a good insurance against malnutrition. Fluctuations in income are particularly dangerous for families with low income and may precipitate malnutrition in those with marginal food intakes and aggravate the condition of those already suffering from malnutrition. Time available to mothers for child care is sometimes more important than income in the case of infant and child-

hood malnutrition (Wolfe and Behrman, 1982; Choudhury, 1982). Even in poorer-income groups some families can satisfy their dietary energy needs better than others by reconciling food preferences with income (Périssé and Kamoun, 1981; Shah, 1980).

(2) *Seasonal factors.* Seasonal variations in food consumption also add a temporal dimension to malnutrition. Evidence suggests that in areas with unimodal rainfall, food intake is lower in the preharvest wet season. This generally coincides with high energy expenditure for farm work, high food prices, heavy indebtedness and the lowest seasonal levels of food intake when stocks have been depleted. The harmful effects are borne by all-men, women and children. Adults lose weight (up to 8 to 10% of body weight) and even pregnant women in their last trimester lose as much as 1.4 kg in some countries (Rowland *et al.*, 1981). Children suffer most, as their body stores are less and they are more liable to functional impairment. Nutritional status deteriorates, past weight gains are frequently lost and child mortality peaks in the pre-harvest period. Seasonal labour demands on women, who, especially in Africa, carry a heavy burden of farm work along with their household chores, often curtail their time available for child care and thus further aggravate child malnutrition.

(3) *Social factors.* Urbanization has greatly altered the demographic structure of populations in many parts of the developing world. In Africa and the Far East the dependency ratio (the number of very young and elderly directly supported by those of working age) has increased two or three-fold in rural areas. Thus in many areas, the elderly and the women are left in the countryside to produce food. Much depends on whether or not the migrant workers send remittances home. Recent data from Zimbabwe indicate that in rural families with an absent migrant worker, the incidence of malnutrition in children is six times as high where remittances are not sent than where they are (World Bank, 1983). Separate food consumption data in rural and urban areas are limited. Generally, per capita dietary energy intake is higher in rural than in urban areas (Table 4). In three countries (India, Tunisia and Brazil) where data are available by income groups, these urban-rural differential energy consumption patterns persist across all income groups. Comparative anthropometric data on nutritional status in rural and urban areas are also scarce and almost all the available surveys are confined to children. For each country for which data are available, incidence of child malnutrition,

TABLE 4 - *Percentage of energy supplies by major nutrients in various regions and economic groups 1961-63, 1969-71 and 1979-81.*

Region or economic group	Carbohydrate as share of total dietary energy			Protein as share of total dietary energy			Fat as share of total dietary energy		
	1961-63	1969-71	1979-81	1961-63	1969-71	1979-81	1961-63	1969-71	1979-81
DEVELOPED COUNTRIES	59	57	55	12	11	12	29	32	33
Developed market economies	56	54	52	12	11	11	32	35	37
North America	48	47	47	12	12	11	40	41	42
Western Europe	56	54	52	11	11	11	33	35	37
Oceania	52	54	55	12	12	12	36	34	33
Eastern Europe and USSR	66	64	61	12	12	12	22	24	27
DEVELOPING COUNTRIES	76	76	75	10	10	9	14	14	16
Developing market economies	75	75	74	10	9	9	15	16	17
Africa	72	72	72	10	10	9	18	18	19
Far East	77	78	77	10	9	9	13	13	14
Latin America	70	70	69	10	9	10	20	20	21
Near East	72	71	69	11	11	11	17	18	20
Asian centrally planned economies	78	78	77	10	10	9	12	12	14
Economic groups of developing countries									
Least developed	75	75	75	11	10	10	14	15	15
Low income food deficit	77	77	76	10	10	9	13	13	15
Low income	77	77	76	10	10	10	13	13	14
Middle to high income	73	73	72	10	10	10	12	17	18
WORLD	69	68	68	10	11	10	21	21	22

TABLE 5 - *Per capita energy intakes in urban and rural areas of selected developing countries.*

Country	Rural (Energy kcal)	Urban (Energy kcal)
Tunisia 1980	2 452	2 247
Trinidad and Tobago 1970	3 011	2 850
Chad 1965	2 467	2 113
Dahomey 1966/67	2 141	1 908
Morocco 1970/71	2 888	2 521
Brazil 1960	2 640	2 428
Bangladesh 1962/63	2 254	1 732
Pakistan 1965/66	2 126	1 806
Republic of Korea 1969	2 181	1 946
India 1975	2 090	1 480
Thailand 1974	1 821	1 504
Indonesia 1976	1 885	1 633
Algeria 1978	3 210	2 138

Source: The Fifth World Food Survey, FAO.

as measured by three different indicators of nutritional status, is substantially higher in rural than in urban areas (Table 5).

Thus, the available evidence indicates that while food consumption is lower in urban than in rural areas, malnutrition in young children is markedly worse in rural children. Although the causes of this paradoxical situation are not certain, a number of reasons are suggested. It is possible that surveys do not take into account all of the food eaten outside the home in urban areas. However, it seems more likely that the higher rural consumption may actually be less adequate due to the higher energy demand for physical activity in rural populations. Food intakes of rural people also tend to be less varied and more affected than urban diets by crop failure and seasonal labour demand at the expense of the children. Less adequate medical services may also explain why rural children appear to be more vulnerable to malnutrition.

(4) *Cultural factors.* Food consumption in developing countries is still strongly influenced by many complex socio-cultural factors affecting

food behaviour. These include customary systems of sharing food within the family, cultural attitudes to different foods, methods of food preparation and child rearing practices.

2.3   *Food sharing within the familily*

Data on the distribution of food within the family are scarce, since most food consumption studies report only aggregate consumption at the household level. The qualitative evidence indicates that the distribution is generally related to hierarchical position, with the head of the household and income earning members of the family receiving preference in both quantity and quality of the food.

Recent quantitative studies from Bangladesh and New Guinea (Institute of Nutrition, 1983; Ferro-Luzzi *et al.*, 1981) as well as earlier studies from Nigeria, Ghana and Guatemala, indicate that children generally receive a smaller share of family food in relation to their nutritional requirement (Table 6). A definite sex bias in favour of male children has also been reported from some countries. In Bangladesh, when physiological factors, body size and weight, are taken into account, sex differentials in consumption disappear in adults but are still present in young children (Abdullah, 1983; Chen, Huq, Dsouza, 1981). This finding is supported by data that show larger deficits in weights and heights and higher incidence of PEM and substantially higher morality rates in female compared to male children.

In some traditional societies it is common for young children to eat from a single bowl. This often puts the youngest and weakest children at a further disadvantage in family food sharing. Consumption data available in some developing countries show that energy intake by pregnant and lactating mothers is also substantially lower than the current recommended intake.

2.4   *Cultural attitudes to different foods*

When the culturally preferred food is a root or tuber, young children are in a disadvantageous position. A weaning diet based on roots or tubers is bulky and has a low concentration of nutrients, and young children with small stomach capacity are unable to consume enough of it to meet needs. Studies from Nigeria and Uganda indicate that the bulkiness of

TABLE 6 - *Percentage of malnourished children under 5 years of age according to different indicators, rural and urban areas, selected countries.*

Country and date	Low height for age [a]		Low weight for height [b]		Low weight for age [c]	
	Rural	Urban	Rural	Urban	Rural	Urban
	......(%)......					
Brazil (Northeast) (1975)	21.9	16.6	2.2	2.3	21.9[d]	16.6[d]
Cameroon (1978)	22.4	15.5	1.1	0.7	23.0	12.2
Egypt (1978)	23.8	15.0	0.7	0.5	9.9[d]	6.1[d]
Haiti (1978)	28.6	15.7	6.4	3.8	29.5[d]	14.6[d]
Lesotho (1977)	23.7	17.2	4.3	3.0	24.9	17.3
Liberia (1976)	20.2	13.8	1.6	1.7	25.5	...
Sierra Leone (1978)	26.2	17.4	3.2	3.2	32.4	24.3
Togo (1977)	20.4	11.4	2.2	0.8	16.5[d]	8.9[d]
Yemen A.R. (1978)	42.1	33.0	6.7	2.1	47.0[d]	22.8[d]

[a] Below 90% of reference standard. Indicator of malnutrition of long duration (chronic).
[b] Below 80% of reference standard. Indicator of recent malnutrition (acute).
[c] Below 80% of reference standard. Indicator of acute, chronic or acute on chronic malnutrition.
[d] Below 75% of the reference standard.

Source: The Fifth World Food Survey.

the weaning diet may be an important cause of malnutrition in young children (Atoyebi and Hussain, 1985; Rutishauser, 1974).

Cultural beliefs and taboos, usually concerning animal food, are often applied to women and young children. Ordinarily they have little nutritional significance. However, when a child is growing poorly such cultural practices as withholding solids at the first sign of diarrhoea can precipitate PEM.

2.5 *Child rearing practices*

There has been a general decline in breast feeding, particularly in urban areas. In many rural communities introduction of supplementary feeding is delayed too long and, when introduced, it is mostly based on diluted preparations of staples which are deficient in energy, higher in

water content and inadequate for the nutritional requirements of young children. In urban areas the situation is different. Breast feeding is abruptly terminated and the bottle is promptly introduced, often under the influence of aggressive commercial advertising. As a result of the high cost, commercial milk formulas are often overdiluted. Because of the lack of facilities for cleaning and sterilization of utensils, together with the lack of appreciation by illiterate mothers of the importance of cleanliness in child feeding, they are also unhygienically prepared. Thus the whole process is not only costly to the family but extremely dangerous for the child. The inevitable consequences are gastro-enteritis, under-feeding, marasmus, and often death.

3. Relationship between energy intake and malnutrition

The energy requirements for survival take precedence over all other nutrients. Numerous animal and human experiments and experiences from disasters (both natural and man made) provide ample testimony of the obvious relationship between low energy intake (food scarcity) and undernutrition in individuals and need no further elaboration. However, the amount of energy needed can be strogly influenced by a number of health related factors.

Household level consumption data available from many countries generally indicate that malnutrition rates are higher in households which consume a comparatively lower amount of energy. For example, one study from India (Rao and Satyanarayana, 1976) found that in rural households, young children with the lowest energy intake had nearly twice the malnutrition of the group with intermediate energy intake (Table 7). In another study a clear relationship among the extent of deficiency of body weight, economic class and energy intake was shown (Levinson, 1974). These findings, however, are not universal and the reasons are evident: household consumption only shows average per capita consumption while malnutrition affects individual members. Recent data from a household survey in Bangladesh did not reveal any relationship between household food adequacy and anthropometric indicators of malnutrition in young children (Table 8) (Institute of Nutrition, 1983). This suggests that the situation may vary from country to country and that other factors at the household level may exert strong influences on nutritional status.

A cross-country correlation analysis between energy supply and

TABLE 7 - *Food consumption by preschool children derived from intrafamily food distribution from selected countries, expressed as percentage of requirement.*

| Source | Age groups | | | | | |
| | Preschool children | | Adults | | Family | |
	Energy adequacy	Protein adequacy	Energy adequacy	Protein adequacy	Energy adequacy	Protein adequacy
Nicol (1979)	74-78	68-78	94-116	94-112	—	—
McFie (1967)	68	94	78	—	—	—
Davey (1962)	55-70	—	80-100	—	—	—
Nutrition Survey of Rural Bangladesh (1977)	46-64	68-98	95-123	140-156	90	125
Flories et al. (1960)	57-78	41-74	—	—	89	99
Flories et al. (1964)	65*	43	—	—	105	106
	70**	55	—	—	115	122
	65***	50	—	—	112	110

Notes: * 1-2 yrs.   ** 2-3 yrs.   *** 3-5 yrs.

TABLE 8 - *Nutritional status (weight for height) by adequacy of energy intake in rural Bangladesh.*

Adequacy of energy	Sample size		Normal		Mild		Moderate		Severe		Number of consumers
	No. of household	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	
Below 50	39	8	27	1	53	2	51	2	13	1	144
50 - 60	50	10	46	2	79	3	65	3	23	1	213
60 - 70	74	14	80	3	128	5	92	4	37	2	337
70 - 80	88	17	100	4	159	7	124	5	34	1	417
80 - 90	80	16	89	4	152	6	132	5	35	1	408
90 - 100	55	11	74	3	89	4	83	3	18	1	264
100 +	123	24	187	8	252	10	175	7	48	2	662
All	509	100	603	25	912	37	722	29	208	9	2445

Notes: Normal = less than 90%; Mild = 90-80%; Moderate = 80-70%; Severe = greater than 70, of standard weight for height.

Source: INFS, Dhaka (1983).

TABLE 9 - *Cross-country correlations between per capita dietary energy supply and indicators of malnutrition.*

Energy supply Indicators of malnutrition	Per capita dietary energy supply
Low ht for age	— 0.48 (38)*
Low wt for ht	— 0.46 (38)*
Life expectancy at birth	0.59 (98)*
Infant mortality	— 0.55 (68)*
Incidence of low birth wt	— 0.50 (65)*

Notes: * statistically significant.

( ) figures in the parentheses indicate numbers.

Source: The Fifth World Food Survey.

TABLE 10 - *Dietary energy intake and undernutrition in selected countries.*

Country	Per capita DES kcals per day	Proportion of population undernourished	
		1.2 BMR	1.4 BMR
		%	
Low income			
Bangladesh	1837	37	45
Chad	1823	39	51
Ghana	1769	38	49
Mali	2067	40	51
Mozambique	1881	37	48
Sierra Leone	1956	42	49
Haiti	1901	44	53
Afghanistan	2055	29	39
Medium to high income			
Nigeria	2445	12	18
Argentina	3367	1	3
Kuwait	3344	2	4
Egypt	3175	3	5

Notes: BRM = basal metabolic rate.
DES = dietary energy supply.

Source: FAO Statistics Division (1985).

certain indicators of malnutrition such as weight-for-height, height-for-age, life expectancy at birth, infant mortality and incidence of low birth weight, showed significant associations for all (Table 9). Although these correlations do not imply a cause and effect relationship, the fact that an association exists at such a level of aggregation strongly suggests that countries with low energy supply are more at risk of malnutrition. Data available from the Fifth World Food Survey show that undernutrition is heavily concentrated in low income food-deficit countries (Table 10). A similar study by the World Bank reported that even after controlling for the effect of both education and health factors, energy deficiency remained a better indicator than income for life expectancy, child growth, and both infant and child mortality (Berg, 1981).

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FOOD-ENERGY PRODUCTION,
AVAILABILITY AND INTAKE IN PARASITIC DISEASE

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INTRODUCTION

At the present time we know more about the numbers of hungry or malnourished individuals in most communities in the world than at any time in its history. The last few decades have seen many attempts to reduce the numbers of malnourished by national governments and international agencies and yet careful evaluations suggest that their impact is often negligible (Beaton and Ghassemi, 1982).

There were high hopes for the future, which were born of perceptions that malnutrition of individuals, families or whole communities was largely caused by inadequate production of food. The data from national food production statistics (acknowledged even by the enthusiast to be unreliable) and food consumption data (obtained from a minute section of the population) and nutritional requirements (currently under considerable debate) were used to heighten the notion that agricultural efficiency was the "technical fix" to alleviate the "problem" of malnutrition. It has indeed been possible to produce more food during intensive programmes but usually at a great cost in terms of technical expertise drafted into the area, mechanisation, farming technology and agronomy (Harriss, 1985). To the agriculturalist interested in net production of energy per hectare this was satisfactory. In La Chontalpa, Mexico, for instance, the energy yield per hectare rose sixfold as a result of an intensive agricultural development programme (Hernandez *et al.*, 1974). With high yielding crop varieties (HYVs) in India there have been dramatic increases in

crop production in some areas. Such programmes were not without consideration of the nutrient value of foods, and the development of strains of cereal with particularly high content of amino acids has received acclaim. As malnutrition was widely perceived as the result of protein deficiency, considerable attention was diverted away from energy towards the increased production of legumes (Pacey and Payne, 1985). Not surprisingly it was soon evident that there were many uneducated people in the rural food producing areas, their poor dietary intake being attributed to ignorance, for which experts prescribed nutrition education about what to eat.

However, to the nutritionist interested in availability of food, dietary intake and nutritional status of populations, these intensive programmes have been unimpressive. During the same period that crop production increased in La Chontalpa the proportion of young children with severe protein energy malnutrition actually increased from 4 to 5%. The energy available to farmers using HYVs in some parts of India actually declined, especially for the hired labour classes who could not afford the extra resources needed to farm HYVs successfully (Pacey and Payne, 1985). Thus in this review of production, availability and intake of dietary energy a more critical, cautious approach is taken and a more comprehensive analysis of the contributing causes of malnutrition is offered in which it is recognised that the interaction of social, economic, behavioural, biological and environmental (including parasites) factors may differ quite dramatically between different regions and even within one region at different times throughout an agricultural year. This includes features of the adequacy, or better termed "security", of the individual or family to produce, control, purchase, borrow or otherwise acquire food. This whole dynamic situation termed "food entitlement" is reviewed elsewhere (Sen, 1981).

Functional significance of malnutrition

A convenient starting point on the "food energy cycle" (Figure 1) is nutritional status, by which we mean the size and body composition of the individual.

Although there are currently debates on the appropriate ways of measuring nutritional status, perhaps the use of anthropometry will always be necessary for population based studies. However, there is considerable disagreement about the significance of differences in stature
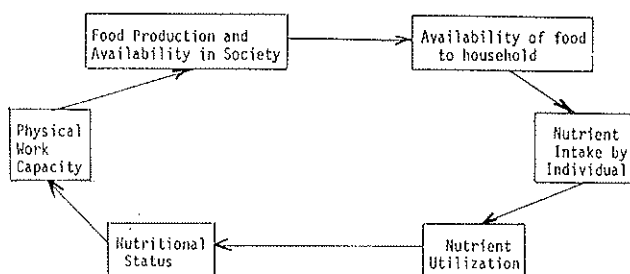
FIG. 1. A simple model of the food energy cycle.

between individuals within the same population. There is discussion about the use of international (mainly USA) standards for measurements of weight and height in view of the shorter height and lower body weight of children in developing communities. However, notwithstanding certain genetic factors or features of entire ethnic groups, the growth of children from elite families from most population groups in developing countries is indistinguishable from international standards and there seems little benefit in using local standards (Janes, 1974). The main debate, however, revolves around those that are statistically different from the elite standards. Within India there are two protagonists. Gopalan maintains that "to plead the virtues of 'smallness' is to acquiesce in the preservation of the status quo of poverty, ill health, undernutrition and socio-economic status" (Gopalan, 1983). In his estimate only 15% of the children in India are "truly healthy, physically fit, productive and intellectually capable citizens of the country". An alternative view put forward by Sukhatme (1982) is that "small is healthy" and reflects an adaptation to chronic energy shortage. In this argument consumption patterns are only regarded as seriously inadequate in 15-20% of the population of India and only those who are severely growth retarded are regarded as malnourished. The differences betweeen these two positions are discussed from the technological and ideological perspectives by Payne and Cutler (1984).

If we are to assess whether it matters to be small or not, it is necessary to examine some functional features of body size and shape. The associations between PEM, morbidity and mortality have been reviewed recently (Martorell and Ho, 1984; Tomkins, 1986a), and different categories of weight/age (W/A), height/age (H/A) and weight/

height (W/H) have been compared to rates for morbidity and mortality. Division into categories by comparison with NCHS standards into mild ($>80\%$ W/A), moderate (80-60% W/A) and severe ($<60\%$ W/A) malnutrition shows evidence of graded deterioration in immune status between mild to severe PEM but this information, while detailed, is of itself of limited value because no study has yet titrated the immune tests against subsequent disease morbidity.

Nevertheless prospective studies of nutrition and morbidity have been performed. With few exceptions the main evidence suggests that PEM does not increase the incidence of infectious disease. However, it seems clear that even moderate grades of PEM are associated with prolonged duration of symptoms (Martorell and Ho, 1984) though relatively few symptoms, mostly diarrhoea, have been studied (Tomkins, 1981). The relationship with mortality is more complex. A study in rural Bangladesh (Chen, Chowdhury and Huffman, 1980) investigating nutritional status and mortality over a 24 month period, showed that only the severely malnourished had an increased mortality whereas an analysis of the relationship over shorter periods of time (3 months) by other investigators working among the same population showed an increased mortality that was graded with decreasing nutritional status (Bairagi *et al.*, 1985). While other studies in India also showed increased risk in the moderately malnourished (Kielmann and McCord, 1978), a recent study in Zaire (Kasongo Project Team, 1983) showed no relationship between PEM and mortality. The reasons why there is a relationship between PEM and mortality risk in some areas and not others are not clear and raise the possibility that PEM may be acting as a proxy indicator for some other determinant of mortality such as maternal education, income or access to health services.

Physical work capacity

The relationship between nutrition, morbidity and mortality is probably also present among older children and adults but physical work performance and productivity which are vital parts of the "food-energy cycle" have been studied in greater detail. In general, individuals with low body weight are often noted to have lower work output (Rao, 1985). Physical work capacity (PWC) measured as the rate of oxygen consumption at maximal work may be expressed as the VO_2 max of the subject (Nelms, 1982). The trend of the results is that bigger people tend to have the greatest VO_2 max whether they be Olympic athletes or villagers

in Colombia (Spurr *et al.*, 1979), Sudan (Collins, 1982) or Nepal (Weitz and Lahiri, 1977). When close analysis of stature is performed it seems that the PWC is affected predominantly by lean body mass. The PWC of adolescents in India, studied ten or more years after a known episode of severe malnutrition, was significantly worse in those who remained small (Satyanarayana, Naidu and Rao, 1979 (Table 1). The potential implications of being small in terms of earning ability have been emphasised in India, where Satyanarayana, Naidu and Rao (1980) showed that farmers are less willing to employ boys who are small for their age because of their poorer work performance. One major variable which confuses the situation is that VO_2 max is known to be less in subjects with anaemia (Viteri and Torun, 1974). However, when differences due to varying haemoglobin levels are accounted for, the main variable affecting PWC is still lean body mass (Ferro-Luzzi, 1985).

Differentials in food-energy production

Previous analyses have tacitly assumed that those who are better nourished are able to farm more energetically and produce more food. But this reasoning neglects the factors which a farmer considers before planning his or her expenditure of effort. In particular the delicate balance between the food he produces and the food he buys or sells is critically determined by size of land, labour owned, hired or sold, market availability and price, position in society etc. In India, for example, the hired peasant has minimal land ownership (Harriss, 1983), whereas the farm owners/businessmen have considerable acreage. The former produce

TABLE 1 - *Physical Work Capacity of Adolescent Boys Malnourished in Early Life* (1-5 years) (Data of Satyanarayana *et al.*, 1979).

Nutritional Status in Early Life (W/A)	Current Body Weight (Kg)	Physical Work Capacity Kpm min⁻¹	
		Active	Sedentary
Normal	42.4	711	497
Mild	36.9	634	389
Moderate	36.7	612	425
Severe	28.5	431	328

food on their employer's land and are paid in rice and/or cash, and in situations of rapid inflation in the market price, the hired labourers have major problems in affording food. The farm owners/businessmen have produced enough rice and are able to survive wild swings in market prices (Table 2).

Similar differentials in food production exist in W. Africa where those with inherited land and better quality fields are able to produce more than the poorer families in the same village (Longhurst, 1984). He emphasised that these differences are not static. The vagaries of climate, family illness, debts etc., are such that a family which is secure one year may be insecure the next.

It is evident that there are many factors affecting availability of food to an entire family which are independent of the family's ability to produce it. During the Bengal famine of 1943 those in the marginal occupation groups — agricultural labourers, fishermen and artisans — had insufficient food because the local failure of agriculture, which was not widely experienced throughout India, led to rocketing increases in market prices which were not accompanied by increases in wages. Those with a diversified family economy could survive. Those dependent on a single economic base such as those selling the only commodity they had — labour — frequently perished.

TABLE 2 - *Production and Availability of Grain among Households in South India* (Data of Harriss, 1983).

	Hired Labourers (n=43)	Small-holding Farmers (n=95)	Farm-owners and hirers (n=56)	Business-men (n=47)
Land Holding (ha)	1.9	3.5	7.5	8.2
Production of grain on own holding (Kg/person/year)	62	141	288	456
Net Available Food Energy (Kcal/person/day)	942	1357	2608	3218
Total Income (Rupees/person)	566	645	1064	1544
Proportion of income derived from exchange (Sale of labour, crops, poultry, livestock)	62%	63%	50%	42%

Factors affecting food-energy intake

In any family there are some who eat more than others. At times there is a relatively inequitable distribution of proportions of the family food bowl to different members. Studies of this distribution in Bangladesh (Abdullah and Wheeler, 1985) show differentials in distribution between boys and girls at certain ages. However, the greatest variations appear to be those which are determined by season. The classical "hungry season" of rural W. Africa describes the period when food stores are lowest, towards the end of the rains, at a time when energy demands for weeding and collecting the next harvest are highest. Not surprisingly there are violent swings in body weight though again differentials in weight loss occur, those with the greatest food security experiencing the least seasonal weight change (Martin *et al.*, 1985). Changes in food intake during pregnancy may vary according to the trimester of pregnancy; evidence from Machakos in Kenya (Machakos Study, 1984) suggests that achieving adequate intakes from local foodstuffs may be quite difficult during the last trimester, especially at certain stress seasons.

Cultural beliefs about foods to eat in abundance or avoid during pregnancy, lactation and illness may all have profound effects on the quality of energy consumed by individuals (Brown, 1984). Illness itself is particularly important because it has profound effects on intake. This is clearly documented during acute diarrhoea in Bangladesh (Molla, 1982) and Guatemala (Martorell and Yarborough, 1980) and in chronic diarrhoea in the Gambia (Tomkins, 1983a). However, in a community study in Bangladesh (Brown *et al.*, 1985) there was no link between diarrhoea and decreased food intake. This may well have been due to the fact that more severe cases were seen in the hospital based study of Molla compared with more mild cases of diarrhoea in the community studied by Brown. A key feature in these studies is the importance of breast milk as a source of energy. In a rural hospital in Bangladesh, breast milk accounted for about half the energy intake (Hoyle, Yunus and Chen, 1980).

Several factors affect the utilisation of energy. Malabsorption of nutrients occurs in a variety of intestinal infections and losses of endogenous nutrients are described (Chen and Scrimshaw, 1982). The absorption of dietary energy (normally greater than 90% even in populations eating diets containing large amounts of fibre) may be affected by intestinal parasites and is reviewed elsewhere in this symposium by Brown.

Variation in nutritional requirements

A key feature in the use of dietary energy is the energy cost of weight gain. A child of one year could be growing at rates of 1g weight gain/kg body weight/day. This is achieved by consuming about 5 kcals for each g of weight gained. In certain conditions such as zinc deficiency (Golden and Golden, 1981) the energy cost of growth is greater, the hypothesis being that zinc is so important in many aspects of protein metabolism that deficiency makes the process of body protein synthesis rather inefficient. Similarly during systemic infection there is considerable increase in the quantity of energy required to achieve unit weight gain (Tomkins, 1985).

If there are visible sources of error and debate among currently accepted dogma on the stages of the "food-energy cycle" discussed so far, these are nothing compared with the confusion surrounding nutritional requirements at the present time. There are basically two kinds of estimates for human energy requirements currently offered by expert committees. The first is a "recommended intake" or safe dietary allowance in which a figure is provided, the intake of which should be sufficient for 98% of the population. Such figures are based on overproviding for the majority of people in order to ensure that nearly everybody gets enough. The second estimate is for a minimum physiological requirement below which there is an increasing possibility that some specific symptoms or signs of deficiency will occur. The difference between these two figures is evident if we compare the "recommended intake" for a 65 kg man who according to the FAO/WHO (1973) report would require 3,000 kcal/day with his minimum physiological needs which could be as low as 1,800 kcals/day using the recommendations in the FAO report of 1977 (the Fourth World Food Survey, FAO, 1977).

Central to these recommendations is an estimate of what energy is needed for. Wood and Capstick (1928) originally partitioned requirements into those for maintenance (the majority), those for growth (about 5 kcal/g but variable) and those for activity (very variable). In calculating these figures, that for maintenance was felt to be most consistent. The Basal Metabolic Rate (BMR) defined as the sum total of the minimal activity of all tissue cells of the body under steady state conditions has been used (Schofield *et al.*, 1985) to make a detailed critique of the published data spanning the last 50 years. The impact of age, height, temperature and climate are all discussed but, as expected, the major determinant of BMR is body weight. An interesting finding was the

lower BMR per unit body weight among subjects from developing countries compared with Europeans or N. Americans. As yet the ethnic differences are not definitively explained but there are at least two possibilities. The first is that these individuals have reduced their basal energy expenditure in response to persistently low energy intakes — a form of nutritional adaptation. Experimental studies of dietary restriction would support this view. A second suggestion is that differences in body composition might be responsible; for instance a preferential reduction in muscle mass (which has a low metabolic rate at rest) in comparison with metabolically active tissues such as liver, gut, and brain might be important.

The FAO/WHO (1973) committee collated the evidence on food energy intakes at zero energy and nitrogen balance in healthy western subjects — they were consistently about 1.5 times greater than the BMR. However, there was much evidence that many people in developing countries were eating considerably less than this and yet remained apparently healthy. Hence a figure of 80% of BMR×1.5 was taken as the minimal energy requirement.

It is hardly surprising therefore that there are considerable ranges in response in terms of body weight changes among farmers in developing communities who experience different dietary intakes and energy expenditure at different seasons of the year. Nevertheless, the striking seasonal changes in adult men and women in W. African farming communities is quite characteristic. Seasonal weight changes also occur among their children (Rowland, Cole and Whitehead, 1977). The associated problems of increased temperature, rainfall and humidity contribute to the contamination of food supplies and water, facilitating the spread of intestinal infection together with increased transmission of malaria. This occurs at the very time that agricultural activity is at its peak. Parents are forced to be away from home for long hours on the fields leaving young children in the care of siblings. Child care, and with it food intake, can only deteriorate in these situations.

An obvious question is whether these stresses compromise the success of the farmers in any way. In other words, would the availability of a little extra food enable them to produce more? There is surprisingly little data on this. Viteri and Torun (1974), in Guatemala, noted that supplements enable the farmers to play more football at the end of a day's work and Prentice (1984) noted that energy-supplemented pregnant and lactating women in the Gambia felt better and participated more in social activities than before supplementation. However, whether either group

produced more food has not been answered. It seems likely that with the few exceptions of intense, research-oriented food supplement schemes, the net result of the different stages in the "food energy cycle" is that those who are poor and hungry to begin with have major difficulties in improving their own nutritional status and/or food production within existing social systems.

Impact of parasites on the food-energy cycle

It is well recognised that the majority of poor rural communities experience parasitic infection in their blood (malaria), intestines (round-worm), viscera (bilharzia), muscles (guinea worm) and skin (onchocer-ciasis). And yet we cannot necessarily assume that these are detrimental to health or nutritional status, physical work capacity or energy production. For instance, millions of children excrete ova of *Ascaris lumbricoides* without evidence of growth impairment, and for many children bilharzia is more a way of life than an illness. Nevertheless, if we examine the different stages of the food-energy cycle we may examine the impact of a few specific parasitic infections.

Bilharzia

The VO_2 max among sugar cane cutters in the Guneid plantations on the Blue Nile has been examined in three groups — those without infection, those with light infection and those with heavy infection (Collins *et al.*, 1976) (Table 3). Despite the presence of hepatosplenomegaly in the heavily infected group there was no evidence of reduction in VO_2 max. Even more surprisingly, when the mean productivity rates (in terms of quantities of sugar cane cut down per day) were measured on a normal day and on days on which a financial bonus was given to encourage maximal production, those who were severely infected cut down more than those without infection. Evidently the explanation for this apparent paradox is that the heavily infected had been working in the area as cane cutters for many years acquiring parasites and skill as cane cutters as they did so. Training and fitness have to be taken into consideration of the impact of parasites on productivity. When the cane cutters were compared with a group of canal cleaners, heavily infected with bilharzia and anaemic, it was noted that the canal cleaners had significantly lower VO_2 max per kg lean body mass but there was no

TABLE 3 - *Physical Work Capacity in Sudanese Cane Cutters on the Guneid Sugar Plantation infected by S. Mansoni* (Data of Collins *et al.*, 1976).

Group	VO₂ max		
	Absolute (l/min)	Weight (ml/Kg/min)	LBM (ml/Kg/min)
Controls	2.88	48.3	53.9
Infected	2.84	50.7	55.7
Heavily Infected (signs)	2.83	49.8	55.1

suitable test to compare productivity. When the infected cane cutters were treated with hycanthone there was about 10% increase in VO_2 max compared with weight and considerable symptomatic improvement. Perhaps the increase in haemoglobin following treatment was responsible for the change in VO_2 max (Collins, 1982). Unfortunately there was no information on productivity.

Other studies have also failed to show much link between changes in prevalence of bilharzia and productivity (Andreano, 1976). However, Cheng (1971) has claimed that in areas where *Schistosoma japonicum* is present the disease can cause an average loss of 40% of the capacity of an adult to work. Others such as Wright (1972) and Farooq (1967) infer a major economic advantage from parasite control programmes and indeed Fenwick and Figenschou (1972) showed that non-infected workers earned at least 10% more in bonuses than those infected with *Schistosoma mansoni*. The decreased productivity in the infected workers appears to be due to increased rates of absenteeism. In all these studies the relationship between anaemia associated with bilharzia and impaired physical work capacity or production may be a critical factor. Viteri and Torun (1974) have emphasised the functional importance of even mild anaemia in Guatemala.

The painful abscesses which develop in muscle affected by guineaworm are frequently so severe that entire villages may have major problems in weeding or harvesting their crops. Similarly those populations with heavy infections with trypanosomiasis may be too debilitated to farm effectively. *Trypanosoma cruzi* is perhaps the most pernicious of this group because it is endemic among the poorest who live in the worst housing which provides ideal lodgings for the vector, the Reduviid bug.

Thus the trypanosome in Chagas' disease acts as a further factor which locks the population into a vicious cycle of downward production of food and deteriorating nutritional status.

Malaria

It is often assumed that malaria is a major illness factor which affects the ability to produce food. However, McGregor (1982), writing with many years of experience in W. Africa, where *Plasmodium falciparum* is endemic, suggests that "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...". There are evidently much greater repercussions in areas prone to infrequent epidemics of malaria. Christophers (1911) described the effects of an epidemic in Amritsar, where food vendors were so ill that they ceased to carry on their trade. "Not only was ordinary food difficult to obtain and the price excessive but owing to malaria among the cowkeeper class, milk, a necessity for the very young and the sick, was practically unobtainable".

Onchocerciasis

A most graphic description of the impact of onchocerciasis on food production is given by Bradley (1976) in the Hawal river valley, northern Nigeria, where the fast flowing streams provide ideal breeding sites for *Simulium Damnosum*. The steadily increasing prevalence of blindness among the middle aged and older farmers is associated with deteriorating food-energy production as their eyesight becomes too poor to permit proper care of their fields of guinea-corn. They are forced into eking out an existence by farming limited quantities of groundnuts or making cane baskets until even these become too difficult to perform. In certain communities the proportion who are blind is so great that they move away from the endemic focus leaving the typical "ghost villages" which are the social signs of severe stress from this parasite. The impact on nutrition is striking throughout villages studied in the Onchoceriasis Control Programme in W. Africa (Kirkwood *et al.*, 1983). There is decreasing nutritional status (as measured by the body mass index, weight/height^2) as the prevalence of blindess increases (Table 4).

TABLE 4 - *Nutritional status in Onchocerciasis* (Data of Kirkwood et al., 1983).

Age (yrs)	Males No damage	Males Damaged	Males Blind	Females No damage	Females Damaged	Females Blind
			Mean weight/height^2 (kg/m^2)			
15 —	18·3 (550)*	16·7 (7)	16·1 (10)	19·4 (579)	17·2 (5)	19·9 (5)
20 —	20·4 (382)	18·8 (9)	19·2 (11)	20·7 (508)	17·2 (3)	20·5 (7)
25 —	20·8 (422)	18·9 (4)	18·5 (20)	20·8 (543)	18·8 (10)	20·0 (2)
30 —	20·8 (407)	19·4 (11)	18·9 (18)	20·8 (499)	20·5 (15)	17·1 (1)
35 —	20·5 (445)	19·5 (19)	18·9 (33)	20·7 (436)	18·0 (15)	16·4 (9)
40 —	20·7 (349)	19·6 (19)	19·4 (23)	20·3 (284)	21·3 (12)	19·7 (8)
45 —	20·6 (323)	19·7 (25)	18·9 (50)	20·1 (334)	20·4 (20)	19·0 (19)
50 —	20·8 (243)	20·6 (36)	19·5 (44)	20·2 (222)	19·7 (41)	18·3 (34)
55 —	20·6 (197)	19·9 (46)	19·1 (53)	20·0 (141)	19·0 (29)	18·0 (26)
60 —	20·5 (101)	19·8 (40)	19·5 (31)	19·4 (73)	19·4 (33)	19·4 (20)
65 +	19·9 (62)	19·0 (45)	18·3 (41)	19·3 (34)	19·2 (38)	18·8 (24)

* No. examined in parentheses.

Some impacts of parasites on metabolism

The techniques available for measurement of food intake are critically discussed by Brown (1984). There are surprisingly few reports on food intake during specific parasitic infections. Although it is well recognised that animals infected with *Nippostronglylus brasiliensis* have decreased food intake (Keymer, Crompton and Sahakian, 1983), possibly as a result of some form of parasite-induced taste aversion, there is no data on voluntary intake in humans. Improved growth rates following deworming are described by some authors and not others (Tomkins, 1986 in press). In view of the marginal changes in nutrient absorption that follow successful deworming in all but the heaviest infections where nutrient losses may be heavy, it seems likely that anti-helminthic treatment may have its greatest nutritional impact by improving appetite, possibly by a reduction in the colicky abdominal pain and distension.

There are many metabolic responses which alter nutrient requirements during systemic infection (Beisel *et al.*, 1967). Recent studies among children in the acute stage of systemic infection in Nigeria show that rates of whole body protein synthesis and breakdown are both increased but the

rate of breakdown exceeds the rate of synthesis (Figure 3) such that there is net loss of body nutrogen with increased levels of urinary creatinine and 3-methylhistidine (Tomkins *et al.*, 1983b). The children received a formula diet which provided maintenance requirements for energy and protein. A similar metabolic response occurs in young Gambian children with acute malaria (Tomkins *et al.*, 1984). This latter group received a formula diet providing some 20% in excess of normal energy requirements. Despite the elevation of rates of synthesis and breakdown of whole body protein, the levels were approximately equal and losses of body nitrogen through catabolism were minimal in the malarious children compared with the children previously studied with various systemic infections in Nigeria. Reeds, Fuller and Nicholson (1985) have recently reviewed the contribution of energy expended in body protein synthesis as a proportion of total energy expenditure. Using the limited data available they calculate that between 7% (in undernourished infants) and 12% (in obese volunteers on energy restriction) of dietary energy is used for whole body protein synthesis. This raises the interesting ques-
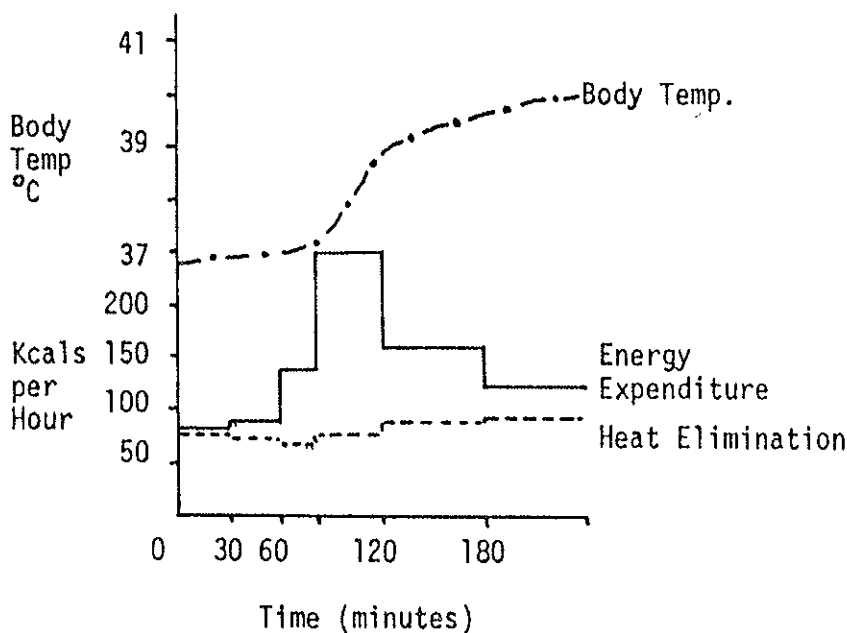

Fig. 2. Energy expenditure at different stages of malaria (Data of Dubois, 1915).
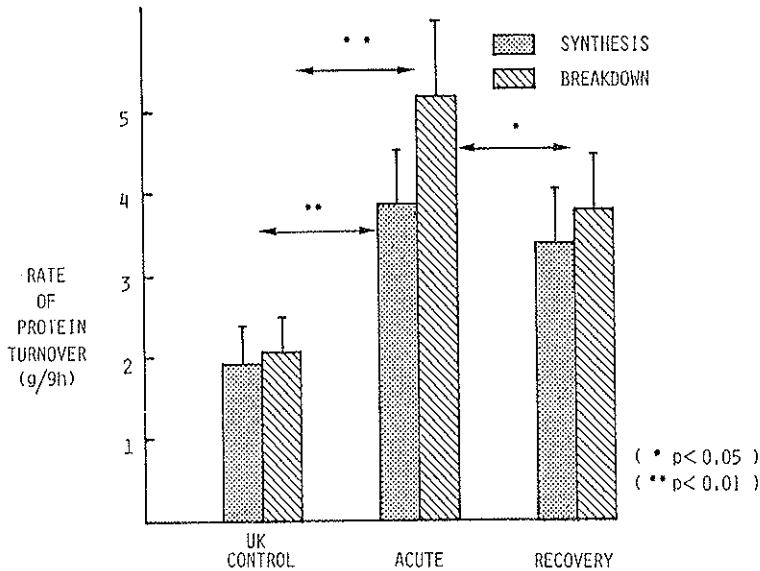
FIG. 3. Impact of infection on whole body protein metabolism (data of Tomkins *et al.*, 1983).

tion of how much energy expenditure is increased during systemic infection. Some particularly careful studies on energy metabolism in malaria were performed earlier this century (Dubois, 1915). Using indirect calorimetry to estimate heat production and a whole body calorimeter and various thermistors to measure heat loss and body temperature respectively, Dubois looked at the responses at different stages of malaria infection. Figure 2 shows the data from one patient in whom energy expenditure rose by about 100% during the early pre-chill and chill phases of the fever, the heat being generated partly, it is proposed, by shivering and partly by the effect of malaria acting as a pyrogen on the hypothalamic centres responsible for controlling metabolic rate. It is interesting that once fever is established at a high level the energy expenditure required to maintain the pyrexia is relatively small. When the energy expenditure required to produce pyrexia in malaria was compared with that required to produce fever in tuberculosis there was a striking difference, malaria being more expensive in terms of heat produced. There are obviously many variables to be considered, such as duration of fever, nutritional status, body composition and dietary intake before conclusions about the basis for these differences can be reached. However, the study highlights

the fact that febrile illness may cause quite dramatic increases in energy expenditure, especially in the early phases. More recent studies show a variety of estimates for energy expenditure in different septic conditions (Gil *et al.*, 1985). At least some of these differences must reflect diet induced changes — the greatest increase in energy expenditure occurred among infected patients who were receiving total parenteral nutrition. Calloway (1982) has calculated the nutritional cost of various infections. From the study of Marsden (1964) among children with malaria in the Gambia it seems that the restoration of the body weight that was lost as a result of repeated attacks of malaria would only require an additional 15 kcal/day throughout the year (i.e. less than 2% of the expected energy requirement). In *Ascaris* infection, studied by Stephenson *et al.* (1980), the energy cost of the growth achieved following deworming is such that only 5-6 extra kcal/day would be necessary on a daily basis throughout the year. There were somewhat higher energy costs associated with severely symptomatic giardiasis, perhaps 40 kcal/day extra being required according to the data given (Kay, Barnes and Townley, 1977). As a proportion of the total dietary intake these are small increments and it is evident from comparisons of growth rates among children at different seasons that there is enormous potential for catchup growth (Tomkins *et al.*, 1986, in press). However, for many months of the year when food is in short supply and pathogens in abundant supply it is extremely difficult to achieve even the modest increases in energy intake that have been suggested above.

A possible framework for understanding parasites and poverty

Any consideration of the ways that parasites may interact with different stages of the "food-energy cycle" must admit the complexity of the processes (Figure 4). Conventionally, these have been examined by basic science approaches in which the changes in a cell or tissue or even an individual subject are examined with respect to how parasites alter the components of metabolic systems. Social scientists on the other hand have examined the economic and behavioural changes in systems, regarding parasites as indictors of deprivation rather than contributing to the deprivation. Neither approach on its own provides conceptual frameworks which are adequate for analysing the nature of malnutrition in populations who are both poor and parasitized. If science has anything to offer, other than proclaiming its own importance, it will be judged
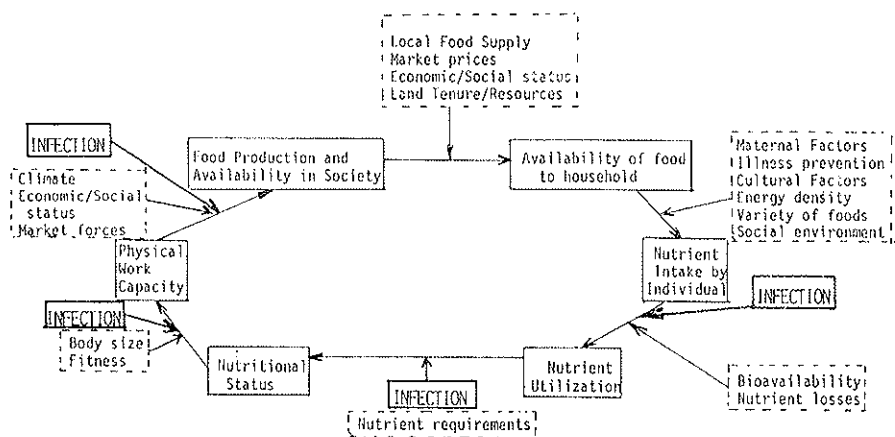
FIG. 4. An analysis of the impact of parasites and poverty on food-energy production, availability, intake and nutritional status.

according to the measure that it has contributed towards the reduction of the numbers of malnourished in poor communities. Perhaps a useful starting point for future work is a recognition that novel, interactive approaches integrating the study of metabolic and social systems are necessary before we can really comprehend something of the poverty-parasite traps currently experienced by a large proportion of the world's population.

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NUTRITIONAL CONSEQUENCES OF INFECTION

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INTRODUCTION

This discussion will review current knowledge on malnutrition-infection interactions, to provide a basis for justifiable interventions to curtail infectious diseases. Interventions should be implemented within the frame of primary health care (PHC). By doing so, malnutrition and mortality are expected to be reduced. The paradigm proposes that infectious diseases, including those caused by parasites, are in fact primary or secondary causes of malnutrition [1,2]. Malnutrition-infection interactions begin when weaning foods are given to breast-fed infants. While such foods may be nutritionally adequate, they are often contaminated with agents that cause diarrhea. Malnutrition, in turn, may be accompanied by alterations in immune response and its amplification [3, 4]. Thus, the negative effects of infection are enhanced, augmenting the risk of severe energy-protein malnutrition (EPM) and death. Good evidence that this paradigm is correct stems from the rapid change of health profiles of several traditional and transitional countries, after emphasizing control and prevention of infectious disease [5].

Just 20 years ago, the role of infection in the causality of malnutrition was mostly ignored by nutrition workers, despite the impressive body of information and the pioneer work of some enlightened authors [3]. However, the relevance of infection had been obvious to those directly involved in village work; the original descriptions of

kwashiorkor by Dr. Cicely Williams clearly showed the prominence of episodes of acute infections in children with the syndrome. The emphasis on food, with neglect for infection, stemmed from demonstration that kwashiorkor and marasmus get cured by a diet rich in protein and calories. Such clinical experience influenced scientific thought for more than three decades, with neglect of the other ecologic determinants of malnutrition. The "food paradigm" led to the belief that protein was the main limiting factor in diets of poor populations. Later, some authors convincingly demonstrated that the main deficit throughout the world was of calories more than protein [6]. Simultaneously, great skepticism arose regarding the alleged deficiency of local village diets [1, 6].

Failure to recognize the leading role of infection in the causality of malnutrition resulted in the equivocal assumption that diarrheal diseases in children were due to nutritional causes, hence the old term "nutritional diarrheas" [7]. Technological advances in the last 15 years enabled scientists to demonstrate viral and microbial entities in about 70% of diarrhea cases seen in pediatric emergency and outpatient services. It is now accepted that childhood diarrheas originate after ingestion of infectious agents present in food and water, or from direct or indirect contact with contaminated fingers, utensils or fomites [7]. Pediatricians had recognized the importance of diarrheal diseases and other infectious processes in the causality of malnutrition, thanks to their long-term association with the same children through their development.

In reviewing the scientific basis of malnutrition-infection interactions, all infectious diseases deserve consideration because the human host reacts in similar fashion to them, whether they are systemic or localized, whether they affect the skin, blood or other tissues, or whether they are due to viruses, rickettsiae, chlamydia, mycoplasma, bacteria, yeasts, fungi or parasites. However, some emphasis will be given to diarrheal diseases because they are extremely common in less developed countries, and because they have a distinct negative effect on host nutrition and growth [8].

NATURAL HISTORY OF INFECTION

In Antenatal Life

Infections affect all developmental stages of man. The human embryo and fetus are no exception, but the frequency of infection and

damage is expectedly low, in view of the formidable protection afforded by the placental barrier. Nevertheless, antenatal infections are more common in less developed than in industrial countries, particularly because women in deprived ecosystems are more frequently exposed to infection [2].

Maternal infection. Viruses, bacteria and protozoa in the mother may reach placental and fetal tissues. Pregnant women already have an increased susceptibility to many infections as a result of physiologic and endocrinologic alterations. The risk of infection is greater in traditional societies, as a result not only of inherent features of the particular tropical environment, but of behavioral and cultural factors that enhance opportunities for infection. The risk of antenatal infection is also greater for mothers in poor urban slums [9].

Prospective observations in a typical Guatemalan highland village revealed that urinary tract infection, diarrhea and lower respiratory disease were rather common during pregnancy, Table 1 [2]. Limitation in water, deficient personal hygiene, uncircumcision of men, and sexual intercourse in the last months of pregnancy, probably accounted for the high frequency of cervical and vaginal inflammation, Table 1. Cervical infection with *Mycoplasma* and *Ureaplasma* is very common among poor women in an industrial country, and appeared related to amniotic ascending infection and perinatal death in industrial and traditional societies [10-12].

Maternal infection has serious negative nutritional effects, worsened by excess physical exertion and lack of health services. Poor women generally can not rest due to a daily routine of caring for children, procuring fuel and water, cooking and washing clothes, and helping in agriculture. Infection is a cause or contributory factor of maternal malnutrition, and may favor fetal growth retardation, either directly or indirectly. Severe infections such as urinary tract infection or lower respiratory infection, may interrupt pregnancy. Microbial products released in the blood during maternal infection, can reach the fetus; their possible consequences are hitherto unknown.

On the other hand, more than one half of mothers in many tropical countries harbor parasites in the intestine, blood and other tissues; they also are repeatedly infected [13]. Migration of larvae through blood and organs is required by some parasites to complete the life cycle, and contact of larvae or metabolic products of parasites with the fetus is possible, another factor requiring investigation.

TABLE 1 - *Maternal Infections and Infectious Diseases, Santa Maria Cauque, 1964-1969.**

Infections			Diseases		
Agent	Number women examined	% positive	Class	Number women examined	Rate/ 100 pregnancies
In feces:					
E. histolytica	24	54	Lower resp. dis.	82	25
G. lamblia		8	Diarrhea		36
D. fragilis		8	Urinary tract infection		27
A. lumbricoides		83	Other **		25
T. trichiura		58			
Shigella spp.	116	9			
Salmonella spp.		5			
enteroviruses	32	25			
adenoviruses		3			
In vaginal exudate:					
T. vaginalis (a)	53	23			
C. albicans (b)		21			
a + b		17			

* After Mata *et al.* [2, 13].
** Conjunctivitis, otitis media, stomatitis, skin infection.

Infection of the fetus and membranes. An infectious agent reaching the placenta of the fetus or both, may implant and replicate therein. The outcome may be a live-born with inapparent infection or defects, or interruption of pregnancy resulting in a dead or live-born, with or without alterations. The product may be term or preterm, with or without growth retardation. Lesions can be physical, immunologic, neurologic or combinations of these. An infant may be born with embryopathy, overt infectious disease, or both. An apparently normal newborn infant may develop mild or moderate retardation or handicaps later on [14]. The mechanisms whereby infectious agents affect the fetus and surrounding membranes encompass decreased blood flow to the placenta and fetal tissues, increased permeability to metabolites and antigens, inhibition of cell multiplication, enhanced proliferation of certain cells, inflammation,

necrosis and chromosomal alterations. Decreased blood flow occurs in malaria, due to blockade of capillaries by parasites. Cell proliferation and necrosis in the placenta may result in decreased flow. In some instances, the agent virtually lyses fetal cells (*Toxoplasma*), or releases inhibitors of cell replication (rubella virus).

The Cauque study revealed a significantly greater immune fetal response to classical agents of intrauterine infection, namely, *Toxoplasma,* herpes simplex virus and cytomegalovirus, Table 2 [15]. On the other hand, a high proportion of infants, born consecutively in highland and lowland villages of Guatemala and Peru, showed very high levels of immunoglobulin M (IgM) at birth, Table 2 [16]. Similar findings were recently reported for Colombia [17]. High concentrations of IgM in cord or venous blood of newborns reflect antigenic stimulation of fetal B immunocytes under rural conditions. Whether this reflects fetal infection, or only exposure to antigens released by infectious agents (for instance, enzymes or enterotoxins) is not known. On the other hand, exposure, even without replication of the agent, could interfere with optimal fetal growth and development. This possibility deserves scrutiny, particularly in view of the prevailing high incidence of fetal growth retardation in developing countries, which can not be solely explained by deficient maternal nutrition [2, 16].

TABLE 2 - *Fetal Antigenic Stimulation and Antenatal Infection, Rural Populations of Guatemala, 1964-1973.*

Cord immunoglobulin M (IgM) *			Maternal seroconversion ***		
population	number of newborns	% with > 0.20 mg/ml	agent	number of women	% sero conv.
Cauque	263	42	cytomegalovirus	51	5.9
Xenacoj	211	38	herpes simplex virus	60	5.0
Sanarate **	132	14	rubella virus	61	0
			Treponema	61	0
			Toxoplasma	61	1.6
			Total		11.5

  * After Mata and Villatoro [16].
 ** Venous blood.
*** After Urrutia *et al.* [15].

Infection in Postnatal Life

Heavy fecal contamination of the newborn is common when child-birth occurs in the home or surrounding premises, in traditional positions like squatting or kneeling [2]. Under such conditions, infants may ingest cysts and ova of intestinal parasites, and pathogenic enteric bacteria and viruses, without necessarily becoming ill [18]. Intestinal resistance is attributable to exclusive breast-feeding from the moment of birth, favoured by tradition, optimal mother-infant interaction and bonding [19-20]. Also, rural neonates are quite free of skin and respiratory infections. If infections develop in exclusively breast-fed infants, they are mild, and if dehydration appears, it is generally corrected by breast-feeding. Breast-fed infants exhibit adequate growth curves for as long as 5 to 6 months [2], especially if mothers consume extra calories required for lactation. In contrast, infections tend to be more severe among prematurely weaned children.

Around six months of age, most breast-fed infants require additional supplements. In developing societies, the onset of weaning implies an increased risk of acquisition of diarrhea agents through contaminated foods and water [7]. This period also coincides with the exhaustion of transplacental immunity, the beginning of crawling, eruption of teeth and increased contact of the mouth of the child with the inmediate environment. The end of exterogestation in poorly sanitated and deprived environments marks the beginning of weaning diarrhea and other infectious diseases [21]. Rates of intestinal infection are very high, especially with onset of weaning, Table 3.

Force of infection. The magnitude of morbidity was unveiled by the Cauque study [2, 18]. During the study period (1946-1969), oral rehydration therapy (ORT) had not yet become available, although the staff posted in the village encouraged breast-feeding during and after diarrheal disease and other febrile and dehydrating events. Intravenous fluid therapy was available, but most mothers refused it. On the other hand, the use of drugs to treat *Shigella* and *Giardia* diarrhea was not advocated by the prevailing medical practice of the time. Finally, measles vaccine was just being developed, and that against pertussis, diphtheria and tetanus was not readily accepted by villagers. The Cauque study, therefore, showed the natural course of infectious disease, and its findings apply to contemporary villages where similar conditions prevail.

Almost nine episodes of fever per child per year occurred during

TABLE 3 - *Intestinal Infection of Preschool Children, Santa Maria Cauque, 1964-1969.*

Neonates *			Preschool children *		
agent	age, days	% prevalence	agent	age, months	% prevalence
enteroviruses	0	1.3	E. histolytica	12-14	0.7
	1	7.4		24-26	4.5
	2	8.2		36-38	10.4
Shigella spp.	2-4 weeks	3.6	G. lamblia	12-14	12.6
				24-26	17.5
				36-38	10.4
			Shigella spp.	12-17	6.8
				18-23	15.8
				24-29	19.1
			rotaviruses **	0-5	4.4
				6-11	10.0
				12-17	10.4
				18-23	11.1
				24-29	10.0

* Adapted from Mata [2].
** Incidence per 100 child months [47].

the first three years of life; ten to 15% were with 39.5°C or more. Anorexia was uncommon in the first six months of life, when infants were exclusively at the breast. Nevertheless, anorexia was as common as fever, with about six episodes per child per year, peaking in the third and fourth semesters [2, 18]. Episodes of infectious disease were complex and often consisted of clusters of clinical entities involving several agents at the same time [2]. This was evident in all singletons and in twins reared by their mother. Incidence rates for the whole cohort, expressed as episodes per 100 person-months by 6-month intervals (Table 4) were already high in the first semester of life, and increased with age to reach the peak at the turn of weaning, at 18 to 24 months of age [2, 18]. Acute respiratory infections (ARI) were more frequent in the first year of life, while diarrheal disease predominated in the second year. In the first three years of life, diarrhea accounted for 43% of all

infectious disease episodes; ARI for 35%; eye infections for 9%; and illnesses of the ear, nose and mouth for 5%. Similar rates have been found in Bangladesh [22] and Brazil [23].

Total days of morbidity. Another way of examining the force of infection is by computing total days with infectious diseases for a particular child or group of children. To illustrate, Table 5 summarizes days of illness for one typical pair of twins. Twin 124, with the more complex morbidity, was 140 days ill in the first year of life, as opposed to twin 125 who had 175 days of illness in the same period. The picture was reversed in the second and third years. The totals were, for twin 124, 37% of the time ill during his first three years of life, and for twin 125, 32% of the time. Similar figures were obtained for the whole cohort [2, 18].

Infections tend to last longer among children living under deprived

TABLE 4 - *Infectious Diseases in a Cohort of* 45 *Children Observed from Birth to Three Years of Age, Rates per* 100 *Person-Months, Santa Maria Cauque,* 1964-1969.*

Illnesses	Age in months					
	0.5	6-11	12-17	18-23	24-29	30-35
	270 **	270	270	270	255	250
Upper respiratory inf.	25.6	34.1	33.3	31.1	30.1	35.7
Lower respiratory inf.	15.9	23.0	23.7	27.4	24.3	14.0
Diarrhea and dysentery	33.3	63.0	77.8	87.4	78.0	55.0
Eye	21.9	18.5	13.7	14.4	8.9	5.0
Ear	0.7	0.4	1.5	0.4	1.9	0.8
Mouth	9.3	6.3	8.2	4.1	7.0	3.9
Skin, scalp	1.9	3.3	2.2	6.3	2.7	4.7
Measles, pertussis, rubella, exanthems	1.9	10.0	8.2	9.6	7.7	7.4
Other ***	0.7	1.1	2.2	4.1	1.2	1.9
Total	111.1	159.7	170.7	184.8	161.8	128.3

* Adapted from Mata [2].

** Number of person-months.

*** Genito-urinary tract, fevers, tenosynovitis, ringworm.

TABLE 5 - *Total Days of Infectious Diseases in Identical Twins Observed from Birth to Three Years of Age, Santa Maria Cauque, 1966-1969.*

Year of life	Quarter	Twin 124	Twin 125
first	1	43	48
	2	29	60
	3	44	30
	4	24	37
	subtotal	140	175
second	1	24	21
	2	44	28
	3	105	87
	4	0	5
	subtotal	173	141
third	1	12	12
	2	13	8
	3	34	8
	4	34	12
	subtotal	93	40
Total		406	356

Adapted from Mata and Urrutia [18].

conditions [18, 24]. *Shigella and Giardia* are shed for weeks or months [2, 18], often associated with chronic recurrent diarrhea. Persistence of measles antigen in cells of malnourished children has also been noted [25]. Chronicity may be related to an inability of the host to clear and eliminate the invader, possibly by a diminished immune response [3, 4]; it may also reflect continuous reinfection, understandable in view of the large number of carriers and ample opportunities for exposure.

NUTRITIONAL IMPACT OF INFECTIOUS DISEASES

Metabolic Consequences of Infection

American volunteers experimentally infected with agents with low virulence such as sandfly fever, Q fever and tularemia, exhibited characteristic metabolic responses, and loss of body weight, cell mass and body nutrients [26]. The "generalized acute-phase metabolic response" to in-

fection is stereotyped in the adult [27]. No comparable data to these could possibly be obtained in children, but one must asume that the generalized metabolic response is similar, especially because of the striking similarity in nitrogen balance and clinical effects observed in children with natural infections. The response in children probably is more serious, and additional factors must be considered; for instance, the nature of infection, whether it is accompanied by other infections, whether there was intrauterine growth retardation, the age and nutritional status of the child, the extent of infection, and the organs involved. One should also consider the particular ecosystem and family environment of the child, whether it provides for additional risk or stress (violence, excess heat or cold), or whether it favors neglect and abuse. Another relevant consideration is the presence of underlying pathology; for instance, chronic parasitic infection which may impair immune function, or nutritional, metabolic or degenerative processes that may complicate the outcome of infection [28].

The generalized acute-phase metabolic response consists of dozens or hundreds of discrete metabolic, physiologic and hormonal reactions triggered by a "controlling mechanism" activated by infection. Some reactions occur during the incubation period, but the majority develop quite rapidly in number and magnitude during the febrile episode and other clinical manifestations [26, 27]. The mediator (or family of mediators) of the generalized metabolic response is now referred to as Interleukin 1, a substance released by blood monocytes or tissue macrophages when stimulated, for instance, by infection [29, 30].

Interleukin 1 consists of small proteins with hormonal effects on many different cells and organs [29, 30]. In the brain, the immediate response is the onset of fever and anorexia. In the bone marrow, there is release of neutrophils for inflammation. In the liver, there is greater uptake of aminoacids and trace elements and greater synthesis of acute-phase reactant proteins. In skeletal muscle there is increased breakdown of muscle protein with release of aminoacids, then utilized for gluconeogenesis. In the pancreas, Interleukin 1 stimulates release of insulin and glucagon, enhancing glucose utilization by cells for maintenance of fever; insulin, in turn, diminishes utilization of free fatty acids and ketone bodies as sources of energy. Immunocytes become rapidly activated and responsive to invading microorganisms [30].

The first clinical response to infection in adults is the appearance of anorexia, fever, or both. There is an acceleration of metabolic processes of body cells, leading to marked loss of muscle mass, weakness and fatigue.

Also, there is leukocytosis. In prolonged and chronic infections, the breakdown of skeletal muscle results in marked weight loss (wastage, emaciation), and accentuated responses by endocrine glands [30]. Anemia is common in recurrent illnesses (diarrheas, urinary tract and acute respiratory infections), and it is even more evident in recurrent otitis media, malaria, hookworm infection, kala-azar, and other "tropical diseases".

Cachexia may develop in individuals infected with certain organisms. Studies have shown the existence of another hormone-like substance, named cachexin, which is released by immune cells of animals bearing low levels of parasitemia [31, 32]. The release and function of this hormone in humans, and whether it explains cachexia in certain patients with chronic infections in tropical areas, deserves investigation.

The generalized acute-phase response is a host defense mechanism necessary to cope with implantation, replication and metabolic effects of alien infectious entities. However, such defense mechanism has a nutritional and functional cost, reflected in considerable wasting, loss of stored body nutrients, loss of body cells, muscle and fat, and loss of body weight [30]. Thus, the greater the rate of infection in a given population, the greater the nutritional cost of the responses. In acute and chronic infections, there is also a stunting effect. Body weight and length can be seriously affected even by isolated episodes of tuberculosis, typhoid fever, hookworm infection, Shiga dysentery, otitis media, pielonephritis and others.

Death can be an outcome of many infectious diseases, both in well nourished individuals who fail to cope with them, and even more in persons with enhanced risks, inherent in either the unsanitary environment or in malnutrition, immune deficiency, congenital defects or other handicaps. The lack of health services undoubtedly plays a crucial role in determining the outcome of infection.

Nutrient Losses

Nitrogen loss is probably the most important effect of infection, along with anorexia and reduced food consumption. In well nourished adults, losses are detected with onset of fever [27, 30], varying according to severity and duration of infection. Accumulated losses represent a large and costly amount of nitrogen, not easy to recover; depletion is steady and reaches maximum values after clinical recuperation. Nutritional losses take a long time to recover, and during the intervening

period, individuals in poor areas usually become exposed to new infections.

A child who had recovered from EPM and who was inoculated with vaccinia virus, showed a positive nitrogen balance, even though immunization induced a febrile reaction with temporary weight loss; as soon as symptoms disappeared, weight gain resumed [3]. However, a different situation was noted in another child, also previously recovered from EPM, after an attack of measles. A marked negative nitrogen balance was observed, despite the fact that the child had been retaining nitrogen prior to onset of measles. The period of fever coincided with nitrogen losses which extended for 20 days; there was minimal loss of body weight probably due to water retention [33]. During the 20 day period, the child should have retained 100 milligrams of nitrogen per kilogram of body weight per day; instead, 50 mg/kg/day were lost. The accumulated loss was 30 g for a 10 kg child, a considerable waste preventable by vaccination.

Other losses. Nitrogen loss is accompanied by proportional losses of other intracellular elements and substances such as magnesium, potassium, phosphorus, zinc and iron, regardless of the kind of microorganism involved [27]. Marked changes in serum albumin and hydroxyproline were observed in children with acute episodes of infectious diseases [34], which might explain the increased susceptibility of some of them to develop edema and kwashiorkor after an attack of measles or other systemic viral or bacterial infections. Vitamins are utilized at a faster rate during infection, resulting in losses from bodily stores; iron and zinc and other elements are "sequestered" in the early stages of infection, within cells in storage sites, even in the presence of adequate deposits [27, 28, 30, 35, 36]. In the particular case of iron, blood levels become so low that they may limit bacterial growth, since iron is a growth factor required for bacterial replication. The steady sequestration of iron in prolonged or chronic infections may explain their anemizing effect. The phenomenon casts some doubt on the validity of the term "nutritional anemias" which has been indiscriminately given to all iron-deficiency anemias in less developed countries. It should be noted that in Cauque, a village free of indigenous hookworm and malaria, anemia cured "spontaneously" once children survived "the dirty age of infection", that is, infancy and pre-school age [2]. Consumption of iron supplements or changes in the simple and monotonous village diet were not recorded.

Aminoacids are lost through breakdown of muscle protein, and are

then utilized as energy source with the cooperation of an increased output of glucagon and insulin [27, 28, 30]. Water and electrolytes are lost in localized infections, for instance, intestinal and respiratory. Losses of water and electrolytes induce derangement of the acid-base balance, and all possible forms may appear. Metabolic acidosis may be the commonest in acute infection. Metabolic alkalosis develops with increased respiratory rate, for instance, during fever. In pneumonia, there is impaired oxygenation and respiratory acidosis may ensue. Conversely, impaired secretion of antidiuretic hormone in infection of the central nervous system may lead to water retention and pulmonary edema [30].

Some metabolic, immunologic and hormonal functions may become depressed during chronic infections such as tuberculosis, schistosomiasis, trypanosomiasis and kala-azar. These diseases may be complicated by cachexia and marked retardation in growth and maturation, particularly in infants and young children, but also in older persons. Cachexin and possibly other hormones must be considered potential factors in chronic infectious disease in humans [31, 32].

MEASURABLE EFFECTS OF INFECTION UNDER FIELD CONDITIONS

Reduced Food Consumption

Anorexia is a prominent feature of most infectious processes. It may last for a few hours, days, weeks or even months. Rejection of food may be partial, but children may refuse food altogether, except for fluids. Anorexia is generally accompanied by fever, and sometimes vomiting. Management of anorexia under field situations is complicated by the limited variety of foods and the low-calorie density and bulkiness of some of them. Furthermore, mothers may not have enough time to properly feed children. Anorexia then becomes one of the most important sources of food restriction. In the Guatemalan village, substantial reduction in food consumption was noted during and after epidemics of measles, pertussis, varicella and other communicable diseases [2, 13].

Anorexia is particularly important in diarrheal disease in view of the high frequency of this syndrome among young children. Anorexia occurs regardless of the etiology of diarrhea, and it is generally complicated by vomiting. Also, during diarrhea there is an accelerated transit of nutrients through the intestine. Furthermore, children may be given useless local remedies and modern dangerous or inappropriate drugs.

Finally, traditional beliefs and taboos lead to intentional restriction or supression of food for considerable periods. Children observed prospectively exhibited significant "calorie dips" (marked reduction in food consumption) coinciding with episodes of diarrheal disease; during healthy periods, they consume adequate volumes of the village diet. From the data it was estimated that about 21% of the total yearly calories and 24% of the proteins were not consumed because of the occurrence of diarrhea alone, Table 6 [8]. Similar estimates were obtained by others in Uganda [34].

Food consumption by children with diarrhea in Bangladesh was found to be deficient prior to admission. Although consumption increased during hospitalization, an adequate level was not attained until two weeks after recuperation, especially when the diarrhea was related to enterotoxigenic *Escherichia coli* or rotavirus [36]. The study is relevant to less developed countries because it shows that malnourished children can be made to consume food in excess of the village level, during and after diarrhea. A previous study had shown the benefit of feeding during diarrhea, especially breast milk [37]. Consumption of human milk during diarrhea was found to be less depressed than that of other foods [38].

TABLE 6 - *Mean Daily Protein and Energy Consumption by Children With Diarrhea, in Comparison With Consumption During Healthy Periods, Guatemala and Uganda.*

Age in months	Guatemala *				Uganda **	
	protein, g		energy, MJ		energy, MJ	
	healthy	diarrhea	healthy	diarrhea	healty	diarrhea
25-30					3.5	1.9
	25	19	3.8	3.0		
31-36					3.9	2.0
% difference healthy minus diarrhea ***	24		21		48	

* After Mata [8].

** After Whitehead [34].

*** Food not consumed (wastage).

Reduced Absorption of Nutrients

The following microbial actions result in a diminished capacity of the mucosa to digest and absorb nutrients: adhesion of bacteria to the mucosa, release of enterotoxins and cytotoxins, penetration or lysis of enterocytes and crypt cells, hydrolysis of bile acids and carbohydrates and microbial utilization of nutrients required by the host [8, 39]. Bengali workers found a decreased absorption of nitrogen, fat and carbohydrate in children with *Shigella,* rotavirus and other pathogens. The effect was partially corrected around 8 weeks after termination of diarrhea [40]. Thus, impaired absorption is not incompatible with efforts to rehydrate by mouth, or to feed regular village diet. Absorption of water and sodium is effected by either glucose, aminoacids or peptides [37, 41]. Important absorption of nutrients of the common village foods occurs as soon as the child is able to eat, generally a few hours after onset of diarrhea.

Increased Secretion

Diarrhea is a state of hypersecretion. In rotavirus infection there is movement of water from the affected segment of the lumen to the extracellular fluid (ECF), and increased sodium flux from the ECF into the lumen. These changes are related to damage and lysis of cells in villous tips, and replacement of absorptive enterocytes by immature crypt-like cells. There is no alteration of cyclic adenosine monophosphate (AMP) concentration [42]. Other causes of hypersecretion are stimulation of cyclic AMP and cyclic guanosine monophosphate by heat-labile and heat-stable bacterial toxins, respectively, by increased concentrations of bile and fatty acids from bacterial metabolism, or by hormones and neurotransmitters [43].

The hypersecretory state results in important deficits of sodium, potassium, chloride and water, and of vitamins and trace elements. Losses of zinc and vitamin A occur in children with measles and diarrhea [35], depleting part of the pool, and possibly contributing to stunting and xerophthalmia. Diarrhea seems to be an important determinant of vitamin A deficiency, enhancing the negative effects of infection on nutrition, and increasing the risk of death; expectedly, provision of vitamin A supplements to populations with high rates of infectious diseases could diminish morbidity and mortality associated with vitamin A deficiency [44, 45].

Acute Weight Loss, Wastage and Stunting

Most acute infectious diseases induce some weight loss, which may be more serious in children who are already malnourished. Malnourished children, in turn, are the product of repetitive infections, poor feeding practices or both. This is the natural history of most of the malnutrition seen in less developed countries. However, limited food supply still generates primary malnutrition in well known areas of the world [46].

Measles, pertussis, chickenpox, rubella and other communicable diseases of childhood have a clear effect on growth, even though they strike once in a lifetime. Certain bacterial infections such as recurrent otitis media, typhoid fever, urinary tract infection and scarlet fever, also have a marked effect on growth of village children. The greatest effect, however, is seen with diarrheal diseases, because they attack each child several times each year. The Cauque study clearly showed that the nutritional status of breast-fed children is rather good in the first months of life, whether infants were born at term, or whether they had experienced intrauterine growth retardation [2]. During the period of exclusive breast-feeding, diarrheas generally are not associated with weight loss. With onset of weaning, a protracted process starting at about 3 to 6 months of life and continuing through the second and third years, infections tend to lead to growth faltering. Individual growth curves of all cohort children revealed accumulated weight deficit (wastage) in connection with infections [2, 8, 13, 18]. During periods of disease, weight increments were definitely below the expected, in comparison with international growth charts.

Recurrent infectious diseases leave a mark on body length (height) as well. Figure 1 shows episodes of diarrheal disease and intestinal infection along the curve of body length of two village children, during the first two years of life. Comparison was with the 50th percentile of the National Center for Health Statistics (NCHS) curve. An etiologic association was defined as the occurrence of a pathogen one week before or one week after onset of a diarrheal episode. At the time of the study (1964-1969), *Campylobacter jejuni*, enterotoxigenic *E. coli* and *Cryptosporidium parvum* were not investigated; rotaviruses were diagnosed retrospectively [47]. Four of the nine episodes in the child born with a relatively adequate birth weight (Fig. 1a) were related to one or more pathogens; diarrhea was associated with periods of stunting, which was evident by one year of age. All six diarrhea episodes in the child with fetal growth retardation (Fig. 1b) were related to pathogens, and all
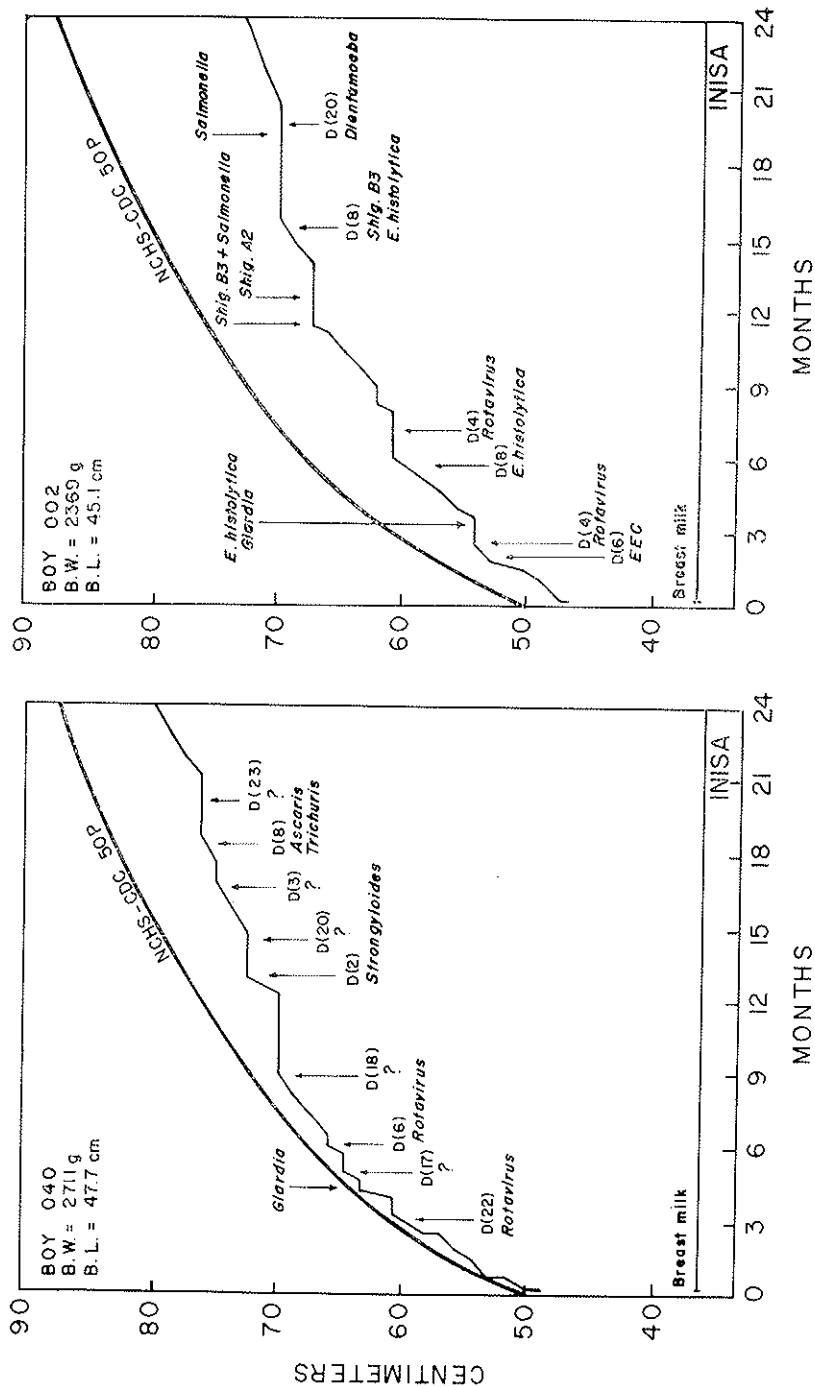
FIG. 1. Linear growth of two children from Santa Maria Cauque, Guatemala [8,56], in comparison with the 50th percentile of the curve of the National Centre for Health Statistics. *Left*: child born with 2.7 kg, grew adequately for about six months, becoming stunted thereafter. *Right*: child born with fetal growth retardation, who nevertheless had a relatively good growth velocity during the first three months of life. Physical retardation began after six months. Both children were exclusively breast-fed for about six months.

diarrhea attacks coincided with arrest in growth. The stunting effect was more evident in the child with fetal growth retardation [8, 13, 18].

The wasting effect of infection can also be seen among well nourished children from affluent societies. They may develop anorexia, weight loss and arrest in growth during attacks of diarrhea, exanthematic disease and recurrent otitis media. Growth faltering can be seen even in mild infections, for instance, of *Cryptosporidium,* where there may be dif-ficulty to feed and care for the child, even by educated and experienced mothers. It is often difficult to dissociate the anorexia of infection from behavioral manipulation of parents and attendants by children.

It can be concluded that infections in general, and diarrhea in particular, are major causes of wastage and of stunting of poor children throughout the world, especially in less developed countries. The effects are more serious when there is a background of intrauterine growth retardation. A negative effect of diarrhea on growth has been described in other studies [48, 49].

Severe Malnutrition

Wasted and/or stunted children are prone to develop chronic mal-nutrition, marasmus or kwashiorkor, and severe malnutrition may appear after epidemics of diarrhea, measles and other communicable diseases [2, 3, 34]. In the Cauque village, most cases of acute malnutrition were noted during or immediately after intense transmission of infectious diseases, which in the village coincided with the harvest of staple foods [2]. On the other hand, in a large series of cases of EPM in Uganda, other types of stress, rather than the lack of food, were primarily related to precipitation of severe malnutrition [50].

Mortality

There seems to be an increased risk of death from infectious diseases in malnourished children as compared to well nourished individuals [3, 4]. Deficits in weight or height were found to be good predictors of premature death [51, 52]. Whether such an increased risk is due to deficits carried from intrauterine life, home deficiencies to rear children, or both, remains unknown. It is possible to speculate that a deficient environment would favor maternal nutrition and fetal growth retardation,

while at the same time it would increase the risk of infection, and of inappropriate child feeding and care.

On the other hand, the immune system may become inoperative paralized during the course of certain infections [28], or as a result of prolonged deprivation of food (in famine), or possibly both. Human populations subjected to famine, exhibit exacerbation of clinical manifestations and excess mortality due to infectious diseases upon refeeding [53]. Finally, part of the increased susceptibility to infection of children in deprived environments may actually be due to crowding [54, 55], a confounded variable, generally neglected in the analysis of most studies dealing with malnutrition-infection interactions.

The important consideration is that the greatest mortality toll in developing countries is not due to deficient dietaries but to the continuous presence of infectious diseases, particularly diarrhea. Infection is the great eliminater of children, either born prematurely or with intrauterine growth retardation, or weaned prematurely, with chronic malnutrition, or else, handicapped. Also, infections prey on child populations deprived of adequate health education and health care [56, 57].

DISCUSSION

There is a clear negative effect of infection on nutrition and health, not only among malnourished individuals, but in well nourished persons as well. There may also suffer from serious, debilitating and lethal infections. Significant advances in health and medicine in certain less developed countries, resulted in control of many infectious diseases and malnutrition, and in the reduction of infant mortality, without a demonstrable improvement in the diet [58, 59]. The phenomenon supports the paradigm that to improve nutrition and health, the control of infection is required. The "infection paradigm" [58] is being supported by most international agencies, through advocation of water supply and sanitation, health education, ORT, immunizations and breast-feeding, within the concept of primary health care.

The role of food, however, can not be denied, and every individual in the world should have the right to meet his daily calorie and nutrient requirements for adequate growth, function and health. In this regard, there is evidence that requirements have been unnecessarily magnified by expert committees [1], while at the same time, adequate village diets have been equivocally classed as unsuitable in quality and quantity [1,

2]. Nutritional surveys in most developing countries reveal that food consumption levels are not too different from those of advanced industrial nations [60]. The exception to the application of the infection paradigm has already been noted, and pertains to situations of natural or man-made disaster where food is not available and malnutrition results from famine [56, 57].

On the other hand, the concept that "malnutrition predisposes to infection" was widely diffused, exerting a negative influence on public health planning in developing countries. Limited resources were shifted from effective interventions such as primary health care, sanitation and water supplies [61] to food distribution programs. The idea that well nourished children are more resistant to infection has not been substantiated, but this was not grasped by professionals in the field. What should have been said is that the effects of infection might be enlarged by a basal state of malnutrition.

The pressure from international and donor agencies to demonstrate that an improved diet would curtail infection and its effects was very strong during the 1960's. Many studies and applied programs were funded to improve the quality and quantity of local diets, and to demonstrate their impact on health. The recommendation to governments, to improve food consumption, did not await the scientific evidence as to their feasibility and benefits [62, 63]. Costly and generally ineffective programs were established in tropics and subtropics, including food distribution centers, fortification of cereals and other staple foods, supplementation of local foods, vegetable mixtures, and nutrition recuperation centers.

The Cauque Study also served to test the effect of an improved diet. For almost four years, the staple food was fortified daily during milling of corn. The fortification mixture corrected deficient levels of aminoacids, and added calories, protein and vitamins to make the food completely adequate. At the end of the intervention, no improvements were noted in any biologic parameter, including maternal nutrition and birth weight, child nutrition and growth, child morbidity or mortality [64].

Since nutrition education for mostly poor and illiterate people always appeared as an unsurmountable problem, supplementation of the local diets appeared to many as the logical solution. Also, food programs appealed to politicians for their vote-purchasing value. Billions of dollars and much effort were spent on food programs with little or no impact and with high cost/benefit. Regrettably, many nutritionists, plan-

ners, and politicians still believe in an alleged effect of food distribution programs in the absence of clear limitation in food availability.

The concept that "malnutrition predisposes to infection" disregards the basics of infectious disease epidemiology. Susceptibility is determined by lack of previous exposure and lack of immunity to the agent. Susceptible individuals from industrial nations who travel to poorly sanitated areas in the tropics are frequently exposed, infected and become ill, regardless of their good nutritional status. In fact, a great proportion acquire acute diarrheal disease, although consequences are not as serious as for natives, since tourists return to their more clean environment, and get treated. Conceivably, village children removed from their contaminated environment for proper treatment, would regain their appetite and would improve their nutrition if maintained in the village diet. Conversely, it is also possible that well nourished children, if placed in a poor village setting, will be repeatedly infected and become malnourished, even if enough food would be made available to them. These possibilities can not be tested under experimental situations, but there is indirect evidence that such is the case. For instance, growth and survival of children in the two different population settings in Central America were markedly different, despite the fact that children, and their corresponding mothers, consumed a similar diet in the two settings. The main accountable difference between the populations was the excess rates of infection in the setting where children had the lowest growth and survival [56, 57].

Furthermore, there is growing skeptcism about the existence of a universal deficit of food intake [1, 50, 58, 60, 62, 63]. It is known that children and adolescents can grow well with significantly less calories than those recommended, providing they are healthy. Finally, a remarkable improvement in nutrition and health has occurred in several poor less developed countries, namely, China, Kerala (India), Sri Lanka, Costa Rica and Chile [5, 58, 59]. Improvements have been attributed to a political decision supported by appropriate funding, which permitted implementation of some sort of primary health care and to promote education. The results in terms of health gains have been dramatic, particularly with respect to the control of infection and child mortality; they show that much can be accomplished, at relatively low cost, without necessarily undergoing industrialization and economic development. The crucial decision consists in adopting the correct paradigm, avoiding the costly, and often hopeless issue of improving food consumption.

ACKNOWLEDGMENTS

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MALABSORPTION IN ENTERIC INFECTION
A NUTRITIONAL COST IN CHILDREN
WITH DIARRHOEA

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Introduction

Since the publication of the important work of Scrimshaw *et al.* [1] demonstrating nutrition-infection interactions, knowledge about the causative factors for precipitation of malnutrition in various infectious diseases has increased. Nutritional deprivation due to enteric infections may occur through several mechanisms, and malabsorption of nutrients is probably one of the most important. Investigations have shown diarrhoeal disease to be the major contributory factor influencing the nutritional status of preschool children and causing premature death of infants and children [2, 3]. An estimated 5 million of the world's children die from diarrhoea every year and many more suffer from the serious consequences of diarrhoea, mostly in the developing countries. Previous studies to understand the nature of both the qualitative and quantitative absorption of nutrients in children with diarrhoea and parasitic infections demonstrated that intestinal absorption is commonly impaired during and after acute intestinal infections [4, 5]. Clinical studies in children with acute intestinal infections have documented malabsorption of macronutrients, including carbohydrates, fat and protein. Though the mechanisms of malabsorption in all cases were not fully understood, new techniques for evaluation and improved methods to identify the causative organisms have provided an opportunity to clarify the above phenomena. This paper will review the important findings regarding nutrient malabsorption and its possible

mechanisms in children during enteric infections. Some of the relevant data obtained from the studies carried out at ICDDR, B, on malabsorption of nutrients in children with diarrhoea due to various aetiologies will also be discussed.

Disaccharidase deficiencies

Transient carbohydrate malabsorption has been observed very often in episodes of viral diarrhoeas in infants [6, 7]. In acute adult diarrhoea, loss of intestinal disaccharidases (sucrase, lactase, maltase and palatinase activities) has also been demonstrated [8]. In the latter study the activities of the enzymes decreased significantly during the acute phase and returned to normal during the convalescent phase. Reduced disaccharidase activities in the acute stage and rapid improvement during the convalescence were considered to be the result of acute diarrhoea. However, in some of the patients lactase activity did not return to a normal level, suggesting prolonged or permanent alterations.

Malabsorption of nutrients and xylose

Marked malabsorption of fat, vitamin B_{12} and xylose were demonstrated during the acute stage and for some time after recovery from diarrhoea [9]. The mechanism for vitamin B_{12} malabsorption is not well understood, but the rapid improvement after antibiotic therapy suggests that bacterial colonization of the intestine may be one of the important factors [10]. Steatorrhoea has been demonstrated in children and adults with severe watery diarrhoea associated with Giardiasis [11]. The mechanism could be related to direct mucosal effects and/or bacterial colonization of the upper intestine associated with G. lamblia infection. Mucosal lesions may develop in human volunteers after experimental viral infection but are not necessarily accompanied by symptoms [13]. In a hospital-based study, malabsorption of fat was observed in 10 children recovering from acute infectious gastroenteritis [14] thought to be due to acids and ileal disfunction. Infants suffering from chronic diarrhoea due to unknown cause were shown to lose larger amounts of nitrogen and fat in the stool [15]. Severity of the diarrhoeal attack was related to the amount of nitrogen loss. The source of this stool nitrogen was

probably the shedding of the gastrointestinal mucosa and leakage of plasma proteins through the denuded gut wall.

The D-Xylose absorption test [16] is widely used to estimate the mucosal integrity of the small intestine. The mechanism involves active transfer of the pentose sugar, similar to the mechanism used for the transport of glucose. But studies on absorption of xylose have not shown any correlation with the absorption of food-based natural carbohydrate [17]. Xylose absorption determined in Bangladeshi children with diarrhoea due to specific aetiologies during the acute stage and two weeks after recovery is shown in Table 1. The differences between the two stages of diarrhoea were significant and particularly marked for cholera, *E. coli* and rotavirus; but, because xylose is not a nutrient or ingested as food, the test cannot reliably be used as a valid indicator of the absorption of nutrients derived from food.

Lactose malabsorption in children has long been the subject of research because of the secondary lactase deficiency during enteric infections and the possible danger of lactose intolerance in milk-fed children. Using the new noninvasive technique, breath hydrogen test (BHT), prevalence of lactose malabsorption (LM) and lactose intolerance (LI) was estimated among Bengali children in rural Bangladesh, and its relationship to the history of recent diarrhoeal diseases [18] was determined. Although more than 80% of the children over 3 years of age were diagnosed to be LM, children under 6 months of age did not suffer from LM unless there was a recent history of diarrhoea (Table 2). The

TABLE 1 - *Absorption of xylose during acute diarrhoea of different aetiologies and 2 weeks after recovery.**

AETIOLOGIES	SERUM XYLOSE LEVEL (mg%) MEAN ± ISD	
	Acute	Recovery
Cholera (25)	20.6 ± 8.4	29.4 ± 8.3
Rotavirus (15)	14.5 ± 8.7	27.8 ± 16.4
ETEC (13)	16.8 ± 6.5	26.0 ± 8.5
Shigella (9)	24.3 ± 13.4	30.0 ± 6.7

* Molla A., *et al.* (Unpublished).
Figures in the parentheses indicate number of patients.

TABLE 2 - *Prevalence of lactose malabsorption according to history of recent diarrhoea.*

	% PREVALENCE OF LACTOSE MALABSORPTION	
Age (months)	No diarrhoea in previous week (n)	Diarrhoea in previous week (n)
0 - 6	0 (18)	18 (5)
7 - 18	10 (29)*	50 (8)
19 - 36	58 (34)	70 (7)
37 - 60	85 (36)	68 (9)
61 - 84	90 (36)	70 (7)
85 - 156	80 (36)	90 (9)

This table has been adapted from Brown, *et al.*, « Am. J. Clin. Nutr. », *32*, 1962-69 (1979).
* Significantly different by Fisher Exact test.
n: No. of patients.

prevalence of LM in infants from 7-18 months old was also significantly associated with recent diarrhoea. Other studies on infants hospitalized with severe diarrhoea have also documented transient lactose malabsorption during and after the acute stage [19]. Lactose malabsorption diagnosed by BHT has to be carefully evaluated as the test is not beyond criticism with regard to its validity during diarrhoeal episodes [20]. Children of developing countries experiencing 4-6 episodes of diarrhoeal disease/year often suffer serious deterioration of nutritional status and require rehabilitative therapy. Despite the presence of lactase deficiency, studies done in Bangladesh demonstrate that such children can generally tolerate milk when fed in conjunction with other foods in the diet. Thus, consumption of milk is not contraindicated in children during and after diarrhoeal diseases, provided the clinical response to its consumption is closely monitored and the lactose load does not exceed digestive capacity.

Community-based longitudinal studies

Detailed longitudinal study of preschool children in a Guatemalan village showed progressive deterioration of the weight and height curve as a result of repeated attacks of intestinal infections [2, 21]. This study

provided evidence for the powerful negative influence of infectious diseases on nutrition and growth of children, beginning in utero. In Bangladesh, longitudinal studies were also carried out to understand the interactions between infectious diseases and the nutritional status of children [3, 22]. Morbidity and mortality were recorded and evidence of a significant adverse effect of the infectious diseases on the growth and development of the children was obtained.

Malabsorption in parasitic disease

Malabsorption secondary to intestinal parasites has been shown to vary according to the type of parasite, age of the patient and severity of infection. For example, in Bangladeshi children, malabsorption of nutrients was documented in patients with heavy ascariasis compared to those with light infection. Significant improvement of absorption was observed after treatment [23]. The mechanism is unclear.

Giardiasis is characterized clinically by a broad spectrum from asymptomatic to severe symptomatic disease. Thus, nutritional effects will also vary from minimal to severe. Severe fat malabsorption in giardiasis has been associated with deconjugation of bile salts due to small intestinal bacterial overgrowth [12, 24].

Other mechanisms of malabsorption due to parasitic infection include atrophy and blunting of villi [25, 26], intestinal damage by local irritation [27] or production of toxins that can damage the brush border. Nutrients which are reported to be affected by parasitic infection include vitamin B_{12}, fat, lactose, zinc and vitamin A [28]. The clinical significance of this malabsorption is not certain. In ICDDR,B hospital studies on absorption of vitamin A [29] during acute diarrhoeal diseases, we have observed that in spite of reduced absorption of vitamin A, eye changes due to deficiency are reversed by oral therapy.

To study the effect of parasites, we have estimated the quantitative absorption of fat, nitrogen, carbohydrate and calories derived from familiar food in children aged 1-10 years, with giardiasis. Table 3 shows the effect of giardiasis on the absorption of nutrients during admission and 2 weeks after recovery in children of different age groups (unpublished, Molla A. *et al.*). Our results do not demonstrate significant changes in absorption of nutrients from admission to post-treatment studies. There are a number of explanations why we were unable to demonstrate malabsorption in our study children.

(i) Specific effects of giardia infection were masked by residua of multiple previous enteric infections in these children.

(ii) Study children were from an older age group and not susceptible to absorptive defects associated with giardiasis.

(iii) Immunity against *Giardia lamblia* might be present because of repeated exposure.

(iv) Disease was not severe enough to demonstrate malabsorption.

Chronic carriage of *G. lamblia* without symptoms is well documented. Travellers to endemic areas are much more likely to have symptoms after infection than are long-term residents [30]. Nevertheless, protein losing enteropathy [31], which may contribute to the development of malnutrition, has been found in giardiasis patients. From the analysis of limited data it has also been suggested that giardia can interfere with linear growth and cause weight loss [32]. The precise mechanism of this impairment is uncertain but reduced intake, nutrient malabsorption and increased energy expenditure were considered to be the major contributing factors in causing malnutrition.

Malabsorption in acute diarrhoea due to known aetiological agents

Metabolic balance studies have been done at ICDDR,B to quantitatively estimate the absorption of macronutrients derived from locally available familiar foods in children with diarrhoea due to specific aetiologies. Mean coefficient of absorption of nitrogen and total calories during the acute stage and 2 weeks after recovery are shown in Table 4. In the acute stage reduced nitrogen absorptions were observed in diarrhoeas of all aetiologies, but were particularly severe in shigella infection. Nitrogen absorption in shigellosis was significantly reduced compared to the other aetiologies studied. The origin of this nitrogen in the stool could be from several sources, e.g. food, invading microbes, desquamated epithelial cells, RBC, plasma protein leakage or other secretions. Mean calorie absorption in acute diarrhoea was most affected in children infected with rotavirus. The pathophysiological mechanisms of this defect are thought to be related to the decreased glucose-mediated transportation of electrolytes and water due to dysfunction of the absorptive villus cells in rotavirus diarrhoea. From a separate study carried out in ICDDR,B it was suggested that excess acid produced in the intestine of children with rotavirus infection

TABLE 3 - *Absorption of nutrients in children of different age groups during admission and after recovery.* *

ABSORPTION (%)

Age (yrs.)	ADMISSION				RECOVERY			
	N_2	Fat	Cal	CHO	N_2	Fat	Cal	CHO
≤ 2 (6)	75.0±11.0	85.0±13.0	87.0±6.0	90.0±4.0	86.7±1.1	87.7±9.9	90.3±3.3	93.6±0.1
> 2 to 4 (10)	80.0±10.4	86.0±18.0	88.0±8.9	92.7±4.2	76.7±5.6	86.2±8.7	88.7±7.2	93.0±4.5
> 4 to 10 (17)	83.2± 6.7	93.5± 3.8	91.7±3.6	92.8±4.1	84.0±6.7	93.9±4.7	91.9±3.5	91.9±3.7

Figures in the parentheses indicate the number of patients.
* Not significant between different age groups.

TABLE 4 - *Coefficient of absorption of nitrogen and total calories (Mean ± 1SD) during acute diarrhoea of different aetiologies and 2 weeks after recovery.*

Nutrients	ACUTE				RECOVERY			
	Cholera (29)	Rotavirus (17)	E. coli (13)	Shigella (9)	Cholera (29)	Rotavirus (17)	E. coli (13)	Shigella (9)
Nitrogen	47.2±26	48.8±21	59.0±17	25.0±55	73.3±11	74.7±16	54.0±31	65.1±16
Calories	81.4±10	61.5±24	86.0±8.4	66.9±30	90.8± 4	85.8± 8	84.0±10	83.1±12

This table is adapted from Molla A., *et al.*, «Scand. J. Gastroenterology», *18*, 537-543 (1983).
* Figures in the parentheses indicate the number of patients.

could be derived from bacterial fermentation of the malabsorbed carbo-hydrates [33]. Whether the mucosal lesion in rotavirus is patchy or extensive is not known with certainty. Mean absorption of carbohydrate in rotavirus diarrhoea was 77.8% [34], which, although reduced compar-ed to other diarrhoeas, was sufficient to permit rehydration of patients with oral rehydration solution containing sucrose, glucose [7, 35-36] or cereal (Molla A.M., unpublished). Rotavirus-associated diarrhoea can certainly result in fatal dehydration if rehydration is not started promptly. ETEC and shigella-associated diarrhoea also result in high morbidity with adverse effect on the growth of children [3].

Conclusion

The association of enteric infections with the malabsorption of nutrients provides some understanding of the relative importance of acute illnesses due to bacterial, viral or parasitic infections. Based on the data obtained in Bangladesh, bacterial and viral infections cause much more profound effects than does *G. lamblia*. The cumulative effects of chronic giardiasis on growth and nutritional status are still uncertain, and the importance of possible chronic low level intestinal malabsorption remains unknown. Diarrhoeal disease mortality, due to bacterial and viral pathogens, is a major contributor to the overall mortality of children in developing countries and thus appropriately deserves urgent attention. In addition, nutrient malabsorption in diarrhoeal disease is one mechanism for precipitation of malnutrition, including mild abnormalities in chronic parasitic infection leading to growth retardation. Therefore, strategies should be defined to control enteric infection mortality and morbidity, including reversal of the adverse effect of malabsorption on the normal growth of children.

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NUTRIENT ABSORPTION IN MALNUTRITION

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The absorption of some nutrients is impaired by the gastrointestinal alterations commonly found in protein-energy malnutrition (PEM), especially in its severe edematous and marasmic forms (Table 1). Since severely malnourished persons usually live under poor hygienic conditions, it is often difficult to determine whether the gastrointestinal alterations are due to the malnutrition itself or to concomitant conditions, such as bacterial overgrowth in the small intestine [1-3] and gastrointestinal or systemic infections.

Regardless of their cause, these alterations may affect the malnourished individual because the impaired absorption interferes with the satisfaction of his nutritional requirements and/or because malabsorption of some nutrients may cause gastrointestinal dysfunction that further diminishes the absorption of those or other nutrients. For example, fat malabsorption will impair the absorption of liposoluble vitamins and lactose malabsorption may produce diarrhea that will reduce the absorption of various nutrients.

The nutritional implications of malabsorption of some nutrients are of little or no consequence under optimal therapeutic conditions, where the abundance of nutrients overwhelms the deficits in intestinal absorptive capacity. On the other hand, the provision of large amounts of certain nutrients may have undesirable effects when the gut is incapable of handling even smaller amounts of the nutrient and responds with the appearance or enhancement of diarrhea and more severe malabsorption.

It is, therefore, necessary to make a critical analysis of the relationship between malnutrition and malabsorption and of the functional and

TABLE 1 - *Gastrointestinal Alterations that Affect Nutrient Absorption in Severe Protein-Energy Malnutrition.*

Morphological abnormalities (e.g., reduction of brush border, villous atrophy) [18, 29, 62-67].

Mucosal enzyme deficiencies (e.g., lactase and other disaccharidases) [68-70].

Impaired absorptive capacity of the intestinal mucosa (e.g., glucose, vitamin B12) [4, 30, 48].

Reduced intestinal motility [64, 71].

Pancreatic and bile salt insufficiency [4, 16, 17, 20, 21].

Bacterial overgrowth, especially in the small bowel [1-3].

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therapeutic implications of the latter. This overview refers to investigations done in patients with severe PEM and with milder forms of malnutrition.

ABSORPTION OF SPECIFIC NUTRIENTS

Proteins

Studies using milk diets to treat children with severe PEM [4-6] showed that "true" nitrogen absorption (i.e., corrected for obligatory fecal nitrogen losses) is of the order of 90%, regardless of the dietary lactose content [5]. As Table 2 shows, absorption was slightly lower at the beginning of treatment, especially among children with diarrhea on admission, who only absorbed between 65 and 89% of the dietary nitrogen (mean $\pm$ s.d.: 80 ± 9) [5]. Absorption rapidly improved as nutritional treatment progressed and, on the average, fully recovered children absorbed 94% of dietary protein [5], which is similar to the absorptive capacity of healthy, well-nourished children [7].

Children 9-40 months old with mild and moderate PEM (weight-for-height deficits ranging from 5 to 18%) or who had recently attained adequate weight-for-height, were fed between 1.6 and 2.5 g protein/kg/day using Thai [8], Filipino [9], and Guatemalan [10] mixed diets, mostly with vegetable proteins. As Table 3 shows, the average "true"

TABLE 2 - *Dietary Nitrogen and Energy Absorption in Children 2-4 Years Old, at Various Stages of Treatment for Severe Protein-Energy Malnutrition (Kwashiorkor and Marasmic Kwashiorkor) Using Milk-Based Formulas.**

	Milk protein intake, g/kg/day	« True » nitrogen absorption, ** % of intake	Apparent energy absorption, % of intake
Beginning of treatment (days 2-5)	1.0 - 2.0	88 ± 9 ***	90 ± 6
Early treatment (days 12-14)	3.5 - 4.0	91 ± 5	93 ± 3
Advanced treatment (days 42-44)	3.5 - 4.0	91 ± 4	94 ± 3
Fully recovered	1.25	94 ± 4	——

* From Torún *et al.* [5, 7].
** Corrected for obligatory fecal N loss [7].
*** Mean ± standard deviation.

nitrogen absorptions ranged from 67 to 77%. These results were similar to the average "true" absorptions (ranging from 69 to 81%) of well-nousished children of the same age groups who consumed similar diets [8, 11-13].

Fats

Absorption of lipids is abnormal in severe PEM, resulting in microscopic or visible steatorrhea [4, 14-16]. The latter is not a frequent complaint, as the populations among whom PEM is highly prevalent usually eat foods with low fat contents, which generally account for only 10 or 12% of dietary energy. In children who weigh 10 kg this corresponds to a daily intake of approximately 6 to 10 g of fat.

Bile in severe PEM has a decreased concentration of conjugated bile salts and a relative increase of free bile acids [17]. There is also an impaired ileal reabsorption of bile salts with formation of more free bile acids as a consequence of bacterial overgrowth [4, 16, 17]. The increased ratio of free-to-conjugated bile acids impairs micellar formation and fat

TABLE 3 - *Nitrogen Absorption of Well-Nourished or Moderately Malnourishe Children Eating Mixed Local Diets Predominantly Made With Vegetable Foods.*

Food	Number of children	Age, months	Nutrional status *	Protein intake g/kg/day	True nitrogen absorption	Ref.
Thai	9	9-36	mild PEM or normal	1.7	67 ± 4**	8
Filipino	7	18-26	mild PEM or normal	1.7	77	9
Guatemalan	13	15-40	mild or moderate PEM	1.6-2.5	74 ± 7	10
Thai	6	8-12	normal	1.7	74 ± 2	8
Filipino	5	18-24	normal	1.2-1.5	81	11
Filipino	5	22-29	normal	1.2-1.5	69	12
Guatemalan	11	29-46	normal	1.5-2.3	79 ± 5	13

* Based on weight-for-height and, in the Filipino children, weight-for-age.
** Mean ± standard deviation.

absorption. Furthermore, the free bile acids damage the intestinal mucosa, impair cell function, increase the abnormality in ileal reabsorption of bile acids, and can cause or enhance diarrhea [17-19]. Pancreatic lipase secretion is decreased [20, 21], but this does not seem to be very important since small quantities of the enzyme are sufficient to hydrolyze triglycerides and the malnourished child is able to respond with lipase secretion when challenged with oral fat [21].

In spite of those abnormalities, fat absorption in kwashiorkor is around 95% when fed at a level of about 4 g/kg/day or 25% of dietary energy [22]. Vegetable fats appear to be better tolerated than animal lipids [23] and children with severe PEM tolerate high quantities of unsaturated fatty acids [24]. High-fat diets providing 50-70% of dietary energy as vegetable oil (80-120 g fat/day) have been successfully used to treat children with severe PEM in Jamaica [25], Costa Rica [26] and Guatemala [27, 28]. Even though there was visible fat in feces, there was no profuse diarrhea, 85 to 92% of the dietary fat was absorbed [27, 28] and the children grew well. Fat absorption improves further with protein repletion and reaches normal levels when diarrhea is absent and nutritional recovery is about 80% of the final expected value [4]. The

free bile acids decrease and conjugated acids increase to normal levels as nutritional recovery proceeds [17, 29].

Carbohydrates

Pancreatic amylase secretion is reduced [20] and absorption of glucose and D-xylose is impaired in severe PEM [4, 29, 30]. However, the carbohydrate malabsorption problem most frequently associated with diarrhea is that of disaccharides, and especially lactose malabsorption.

The effects of lactose ingestion on malnourished children have caused many apparent contradictions, most of which can be explained based on the methods used to diagnose malabsorption and assess changes in nutritional status or on the composition of the therapeutic diets (reviewed in reference 31). Although malnourished children frequently have lactase deficiency, lactose malabsorption and/or milk lactose intolerance, many investigators have reported adequate clinical and nutritional responses with milk-based therapeutic diets that provide 4-8 g lactose/kg/day or 1-1.7 g lactose/kg/meal [31].

Diarrhea has been associated with milk intakes by severely malnourished children [32-34]. On the other hand, milk has been successfully used for many years to treat children with severe PEM in countries like Jamaica [25] and Guatemala [31, 35], and diarrhea has seldom been a problem, even though in some series of patients as many as 24% passed loose stools or had a diarrheal episode without important clinical nutritional consequences [36]. In some of those patients the diarrhea could have been due to causes other than dietary lactose. It should be pointed out that in addition to being severely malnourished, all Jamaican children were black and many Guatemalan children were Mayan indians, and both these races are known to develop a genetically determined primary lactase deficiency.

Carefully controlled studies were recently done to compare the effects of intact and lactose-free milk [5, 37], and of milk- and soy-based diets (Torún, Solomons *et al.,* unpublished) in the treatment of children with severe PEM. Among the 40 children studied, the diets that contained lactose did not produce important diarrhea, and did not impair absorption of total dietary energy, nitrogen and calcium nor retard nutritional recovery.

Total Dietary Energy

The small influence of malnutrition on nitrogen, fat and carbohydrate absorption is reflected by the high levels of total dietary energy absorption. As Table 2 shows, using milk-based therapeutic diets the apparent energy absorption (i.e., without corrections for endogenous fecal energy) was about 93% in severe PEM [5]. The slightly lower degree of absorption at the beginning of treatment was probably due to the diarrhea that some patients had when they arrived at the hospital; six severely malnourished children admitted with diarrhea absorbed only 84 ± 5% (range: 77-90%) of the dietary energy at the beginning of treatment.

Using mixed Guatemalan diets, mainly with foods of vegetable origin that provided 98 ± 4 kcal/kg/day to children with mild and moderate PEM [10] and 92 ± 5 kcal/kg/day to well-nourished children [13], the corresponding apparent energy absorptions were 91 ± 2% and 92 ± 2%, respectively. These results coincide with those of studies using a Thai mixed diet with 100 kcal/kg/day [8] or Jamaican milk-based formulas with 84-108 kcal/kg/day [6], which showed apparent energy absorptions of 94% when fed to children with weights-for-height ranging from 78 to 100% of the standard.

Vitamins

Fat-soluble vitamins. The absorption of fat-soluble vitamins is impaired in children with severe PEM [4, 29, 38]. This is probably related to the impairment of micellar formation due to the low output of conjugated bile acids [4, 16, 17]. Another mechanism that may affect the absorption of certain vitamins is the impaired activity of some enzymes. This has not yet been demonstrated in humans, but defective intestinal hydrolysis and impaired absorption of vitamin A have been shown in protein-deficient rats [39] and chicks [40].

The impaired absorption of vitamin A in severely malnourished children who are otherwise healthy is not of great magnitude: using a small dose of 3,000 I.U. of vitamin A, the average absorption in children with kwashiorkor was 90%, compared with 95% in well-nourished children [41]. Using pharmacological doses of 100,000 I.U., significant increases in serum retinol levels can be seen within 4 hours [42]. However, many malnourished children have associated infections and there is evidence that vitamin A absorption is further affected by intestinal infections [43, 44] and parasites [45].

Children with mild and moderate PEM absorb about 70% of beta-carotene from green leafy vegetables, similar to well nourished children [46]. This absorption can be increased when vegetable oil is fed with the leafy vegetables [47].

Water soluble vitamins. The absorption of several water soluble vitamins, such as folic acid and vitamin B12, is also impaired in severe PEM [29]. In the case of vitamin B12, the defect is in the small intestine [48] and not necessarily associated with absence of intrinsic factor, in spite of the atrophy of gastric mucosa and hypochlorhydria seen in children with severe PEM [49]. At least for vitamin B12, absorption appears to be normal in mild and moderate forms of PEM [50].

Minerals

Iron. Absorption of iron is reduced in many, but not all, children with severe PEM [51, 52]. This led to the use of parenteral iron for the treatment of iron-deficiency anemia in kwashiorkor [53, 54]. It has been proven, however, that iron deficiency can be treated orally in a great majority of patients. The low absorptive or hematologic responses to oral iron are mainly due to an adaptation to low oxygen demands, which is secondary to reduced lean-body mass and physical activity [55, 56], or to the existence of adequate body iron stores [51, 57].

The intestinal regulation of iron absorption is preserved in severe PEM. Using a tracer technique with 59-Fe to measure absorption and stainable iron in bone marrow to assess body stores [51], it was shown that there is greater absorption when body iron stores are low than when body iron is high, and that absorption increases when body iron is depleted. The same conclusion was reached in another study that combined metabolic balance techniques to assess iron absorption and retention, and serum ferritin and blood hemoglobin levels to assess changes in circulating and total body iron [57].

Iron absorption is adequate enough to allow improvement of hematological and body iron indices of children with mild and moderate PEM fed a mixed, predominantly vegetable, diet and sugar fortified with NaFeEDTA [10].

Calcium. Its absorption seems to be unimpaired in severe PEM. Patients treated with milk diets absorbed throughout six weeks between 35 and 47% of 1.3-1.5 g of calcium provided by the daily diet [5, 58].

This was significantly more than the absorption of 20% expected in normal children with the recommended daily intake of 400 mg Ca/day [59]. The high absorption of calcium during recovery from severe PEM may be related to increased needs for calcium accretion in bone.

Other minerals and electrolytes. The loss of these elements usually seen in severe PEM seems to be related to the chronic or recurrent diarrhea that often accompanies malnutrition. However, other routes for electrolyte losses, such as urine and sweat, cannot be ruled out to explain the decrease in body potassium and magnesium often seen in severe PEM. Information about the absorption of these elements and trace minerals is scant. There are some studies, such as investigations on the role of dietary zinc to treat malnourished children [60], that suggest that the intestine is capable of absorbing these minerals, but it is not known whether the absorptive capacity is normal.

CONCLUSIONS

Gastrointestinal abnormalities impair the absorption of many nutrients in severe PEM. Furthermore, when dietary intake is only marginally adequate, chronic malabsorption may be an important limiting factor to achieve good nutritional status. These gastrointestinal alterations are not due to malnutrition alone, but are the result of an interaction between malnutrition and enteric infections or nonspecific bacterial proliferation in the small bowel.

In the absence of profuse diarrhea and intestinal infections, the ingestion of nutrients in high, therapeutic, amounts allows their absorption in sufficient quantity to permit nutritional recovery. In most cases this reduces the practical importance of malabsorption during treatment for malnutrition. Notable exceptions are food — or nutrient — intolerances that produce diarrhea and interfere with nutritional recovery. The causes of profuse or persistent diarrhea, whether of infectious or food origin, must be controlled as they may impair intestinal absorption to the extent of retarding or not allowing nutritional recovery. Since intestinal infections produce further damage and malabsorption, they should be adequately treated to facilitate nutritional rehabilitation. Whether drug treatment with antibiotics should be used in all enteric infections in children with severe PEM, is still a matter of discussion. Many such infections disappear as time and nutritional treatment progress. The

critical issue is whether those infections threaten the malnourished child's life or overall health.

The clinical and experimental evidence that is currently available in humans suggests that malabsorption disappears with nutritional recovery and that there are no important gastrointestinal sequels due to malnutrition. This must be ascertained in a definitive way since most children treated for severe PEM continue living in highly contaminated environments and resume eating a deficient or marginally adequate diet after discharge from therapy. Consequently, if their gastrointestinal functions are still impaired, they will be more prone to develop malabsorption of an important degree or diarrhea that may lead to a new episode of severe malnutrition.

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THE ROLE OF CACHECTIN IN MALNUTRITION

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Mammals infected with bacterial, parasitic, or viral organisms or bearing tumors characteristically display a catabolic state which can, if not resolved, advance to cachexia, shock and death [1, 2, 3]. Although commonly observed, the mechanism of this phenomenon has not been understood. Recently we have identified [4] and isolated [5] a protein hormone, cachectin, which we believe plays an important role in cachexia and shock. Cachectin is produced by macrophages in response to endotoxin [6] and a number of other bacterial and protozoal products [7].

The released cachectin binds to specific high affinity receptors and elicits a number of biological responses [5]. In the adipocyte, for example, several anabolic enzymes, e.g., lipoprotein lipase, are selectively suppressed [8] because of an inhibition of mRNA production [9]. A number of other cell types have been noted to have cachectin receptors; however, the full range of biological activities evoked by this hormone is still being determined. One of the more intriguing aspects of cachectin is its pivotal role in the pathogenesis of endotoxin-induced shock [10]. During the course of the chemical characterization [11] of cachectin it was realized that cachectin was identical to tumor necrosis factor (TNF), a macrophage protein that kills tumor cells. This surprising finding has added a new dimension to the biological activities associated with this protein. In the current review we will examine the chemical and biological properties of cachectin, its production and its role in cachexia and shock.

Isolation of Cachectin

The clue that was needed to unravel the biochemistry of cachexia emerged from studies of rabbits infected with the parasite, *Trypanosoma brucei* [12]. It was noted that the animals had a minimal parasite burden, but became moribund and exhibited an extreme hyperlipemia, notably a marked elevation of plasma very low density lipoprotein (VLDL). The hypertriglyceridemic state was remarkable in view of the severe wasting diathesis that accompanied this infection. Analysis of this phenomenon revealed a clearing defect of VLDL caused by a loss of the peripheral tissue enzyme, lipoprotein lipase. Subsequent studies revealed that endotoxin injected into mice could also induce the loss of this enzyme and elicit the formation of a plasma mediator that could suppress the enzyme in endotoxin resistant mice [4]. The mediator was shown to be produced by macrophages and macrophage cell lines (i.e., RAW 264.7) in response to endotoxin or other bacterial and protozoal products [6]. The monokine could also suppress the activity of LPL in the adipocyte cell line 3T3-L1, which formed the basis of the bioassay utilized during the isolation of the mediator.

The mediator responsible for the LPL suppressing activity was isolated from the conditioned media of RAW 264.7 cells previously incubated with endotoxin [5]. The purified protein had a molecular weight of 17 kilodalton and a pI of 4.7. Cachectin did not possess lymphocyte activating factor (LAF) activity, and could not be displaced from its receptor by interleukin-1 (IL-1) despite the similarity in molecular weight and isoelectric point exhibited by these two monokines. It came as a surprise when it was observed that the N-terminal amino acid sequence of mouse cachectin was strongly homologous to the reported sequence of human TNF and had complete TNF bioactivity [11]. Mouse TNF has recently been cloned and sequenced [13], and an 80% direct homology to human TNF was observed at the protein level [14]. The cloned mouse TNF sequence was in complete agreement with the sequence recently reported for mouse cachectin [15], confirming the identity of "cachectin" and "TNF". In addition to the homology noted in the translated sequence of the message, a consensus sequence (TTATTTAT) is observed [15] which is repeated several times in the 3' untranslated region of both the human TNF and the mouse cachectin. This consensus sequence is also found in the same region of several other messengers for immunoproteins including human lymphotoxin, human and mouse granulocyte-macrophage colony stimulating factor, human and mouse IL-1, human and

rat fibronectin, and most of the sequenced human and mouse interferons. There is no other homology between these various messengers and the consensus sequence is rare among mammalian messengers in general, suggesting that it may serve a specific regulatory function among messengers encoding proteins related to the inflammatory response. Assignment of a function to this sequence must await further studies.

The cachectin message encodes a protein that is much larger than the final secreted hormone. The cleavage of the prohormone occurs in a series of proteolytic cuts [16]. It is unclear, at present, whether any of these cleavage products possess distinct biological activities.

Conditions and agents that stimulate and inhibit the production of cachectin

The addition of as little as 3 pg/ml of lipopolysacharide from *E. coli* to the media of macrophage cultures prompts the production of measurable quantities of cachectin [17]. On a weight basis endotoxin is the most active inducer we have ever observed. However a number of other materials will promote cachectin production. Preparations of *C. parvum* and zymosan also elicit cachectin in a concentration dependent manner [17]. Membrane fractions of *T. brucei,* causative agent of cattle trypanosomiasis, and *Plasmodium berghei,* a mouse malaria, also elicit macrophages to produce cachectin [7]. The chemical nature of the inducer in these membrane fractions is not known, but presumably acts like endotoxin. Phorbol myristate acetate (PMA) and concanavalin A, two agents well known to stimulate macrophages to release a number of factors, are moderate elicitors of cachectin [17] but are weaker than the natural materials listed above. It appears that the macrophage has the ability to detect, by some unknown mechanism, the presence of invading organisms.

Cycloheximide added to macrophage cultures prior to the addition of endotoxin completely inhibits cachectin formation [17]. This is consistent with the observation that preformed cachectin is not present in the macrophage prior to the addition of endotoxin [8]. A series of agents utilized in the treatment of shock have been evaluated for their ability to interfere with cachectin formation [17]. The only compounds that have any activity are glucocorticoids such as dexamethasone. As little as 10^{-8} M dexamethasone could suppress the induction of cachectin production by macrophages in response to endotoxin as long as it was added to the cells prior to the addition of endotoxin. When dexamethasone

was added after the endotoxin was added, normal production of cachectin ensued. The ability of glucocorticoids to inhibit cachectin may explain their utility in the treatment of patients with endotoxin-induced shock since cachectin appears to be a major mediator in the induction of shock. The inability of glucocorticoids to prevent cachectin formation once the cells are stimulated by endotoxin offers a potential explanation of the clinical observation that steroids are only useful administered early in the course of sepsis [18].

Biological activities associated with cachectin

The biological properties associated with cachectin are only beginning to be catalogued. From the evidence available it appears to have a wide range of activities at the cellular level as well as in the whole animal. Cachectin produced by the macrophage rapidly appears in the blood of the animal, and is borne throughout the body [19]. An example of the time course of cachectin's appearance following the injection of endotoxin into rabbits is shown in Fig. 1. Within a few minutes after the injection of endotoxin there is a significant rise in the amount of cachectin activity in the blood. A peak of activity occurs at two hours, followed by a rapid decline. It has been possible using radio-labelled material to estimate the half-life of the released hormone to be between six and seven minutes in mice. This value is similar to that measured for other hormones such as insulin. Utilizing radio-labelled cachectin it has been possible to demonstrate high affinity receptors on the membranes of a number of cells. For example, adipocytes and muscle cells are estimated to have 10^4 receptors with a binding constant of 3×10^9 [5]. Liver cell membranes are particularly rich in receptors. Distribution studies of radio-labelled cachectin in mice confirm the importance of the liver as a major target of cachectin, since 31% of the injected hormone homes there [19]. Surprisingly, the skin is another major target for cachectin. Thirty per cent of the injected material is associated with this tissue. Assessment of the biological significance of this observation will have to await further experimentation. The kidney, lung, and spleen are other organs from which significant amounts of cachectin can be recovered.

The injection of purified cachectin into experimental animals has a number of obvious effects. In the rabbit, for example, there is the rapid induction of a brisk fever. Whether cachectin shares with IL-1 the ability to induce fever, or whether it prompts the release of IL-1 needs further

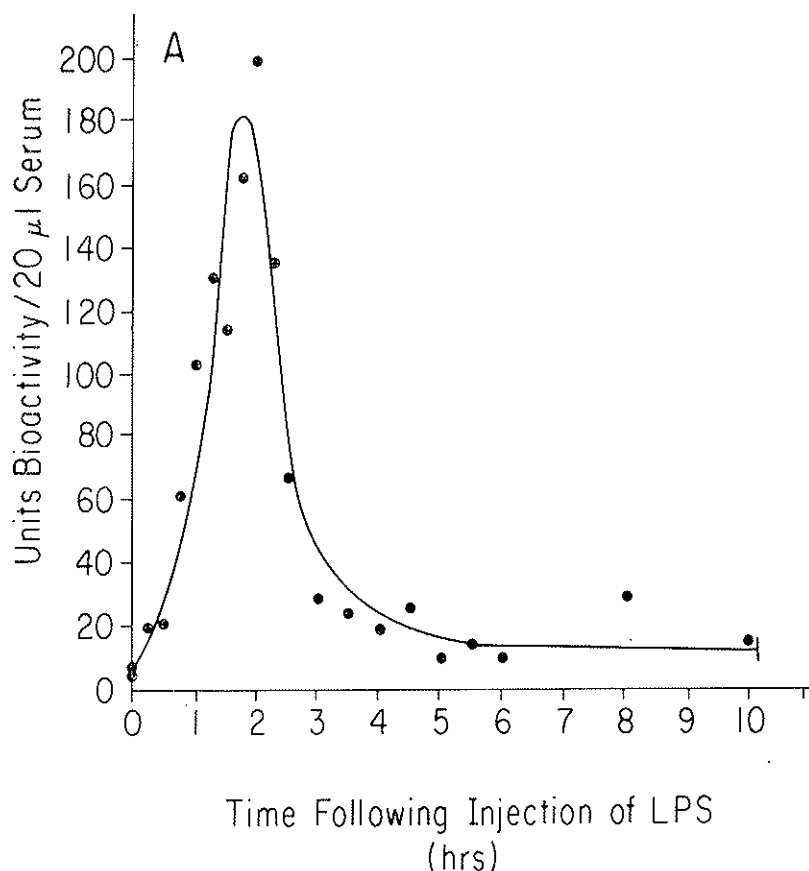# Serum Cachectin Levels in a Rabbit Following Endotoxin Administration

FIG. 1. Bioassay and receptor assay of cachectin/TNF production *in vivo*. Serum cachectin bioactivity is plotted as a function of time after injection of 30 µg of *E. coli* LPS [19].

clarification.   The most striking effect observed when mice are injected is the onset of anorexia, lethargy and an unkempt appearance, characteristics frequently observed in infected animals (see Fig. 2).   In this case the animals can be shown to be free of infection but exhibiting the biological effects of cachectin [20].   Depending on the amount given, mice frequently will develop diarrhea as well.   The administration of cachectin

on a regular basis (twice daily) over several days to mice is associated with anorexia and weight loss. If this regimen is continued, the animals will develop a shock state and die. This lethal effect can be averted by discontinuation of the cachectin injections. Following the cessation of the injections the animals slowly begin to regain their appetite and regain the weight lost. It is not known at present how much of the weight loss is due to the anorexia or the catabolic state. Studies of infected animals have frequently estimated that each contributes about one half to the weight lost [21]. Paired feeding experiments in the future should allow the determination of the role of both of these parameters.

As noted above, mice injected with cachectin eventually succumb to shock. Further evidence has recently been obtained which implicates the role of cachectin as a major mediator of shock [10]. In these experiments an anti-cachectin antibody was given to mice prior to the injection of endotoxin. Mice receiving the antibody were significantly protected from

FIG. 2. Mouse on the left was injected with 4 daily doses of 10 µg of cachectin. The mouse on the right received the same amount of heat-inactivated material.

the lethal effect of the endotoxin. In addition, it should be noted that the endotoxin-resistant mice C3H/HeJ do not produce cachectin in response to endotoxin [17]. The role of cachectin in shock will undoubtedly be investigated in detail in the future since many important questions remain.

The adipocyte is the cell that has been most investigated at present for its response to cachectin. Figure 3 presents a model explaining the effect of cachectin on the fat cell. As noted above the adipocyte has a number of receptors which, when triggered by cachectin, lead to a switching of the metabolism from an anabolic to a catabolic mode. By a mechanism that is not understood at present the DNA encoding anabolic
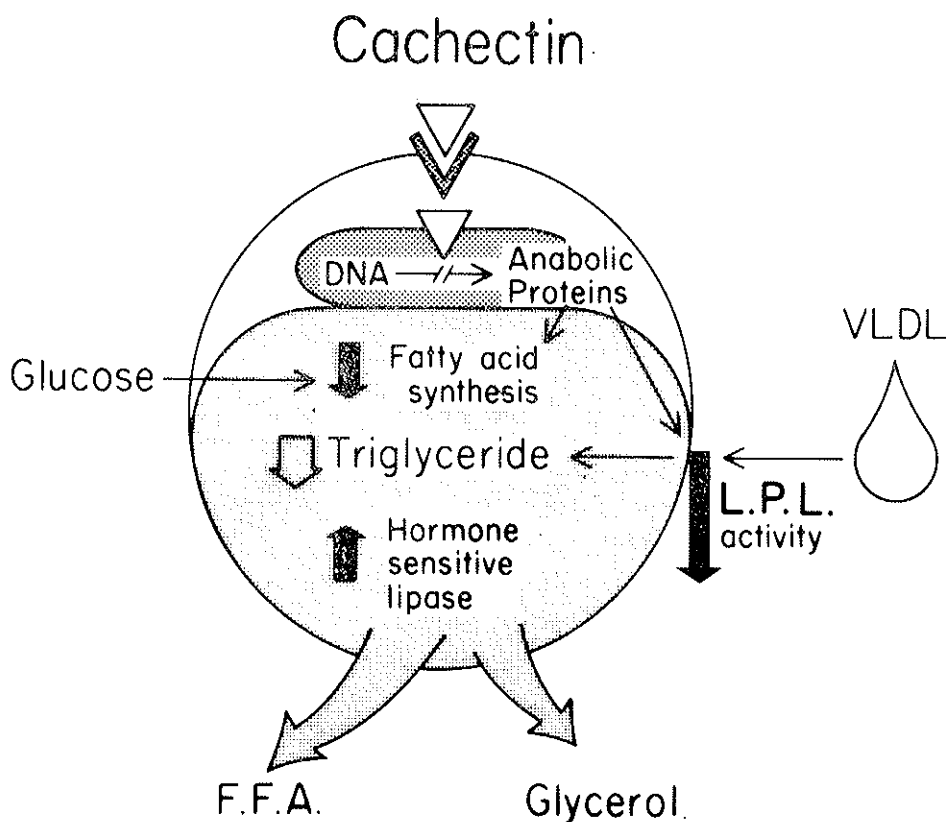
FIG. 3. Scheme of the effect of cachectin on adipocytes.

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proteins in adipocytes is not transcribed into mRNA [9]. This is a highly selective action since the transcription of other genes is not affected by cachectin. Within a few hours after the cessation of specific mRNA biosynthesis the cellular activity of the encoded enzymes begins to fall at a rate determined by the half life of each protein [8, 22]. Lipoprotein lipase, for example, falls to nearly zero activity within 5 hours. The overall outcome for the adipocyte is an inability to produce fatty acids from glucose and take up exogenous fats from the media. As a result there is a net flux of fat out of the cell. Adipocytes treated continuously *in vitro* with cachectin lose their accumulated fat over several days and display an *in vitro* cachexia.

In the fat cell cachectin is acting as an insulin antagonist. The possibility that cachectin is interfering with the insulin receptor has been examined [23]. Cachectin does not bind to the insulin receptor or prevent the synthesis of the receptor. Figure 4 displays the cachectin-induced loss of lipoprotein lipase activity with time while the number of insulin receptors remains constant. In fact, the receptor can still respond to insulin and transport increased glucose into the cell; however, once inside the cell the glucose cannot be converted into fatty acids for storage. The unused glucose diffuses back out of the cell. This situation is analogous to that observed in Type II diabetes where an unknown post-receptor defect is present. The occurrence of insulin resistance in animals is a common metabolic defect. Further understanding of the mechanism of action of cachectin should give new understanding of the mechanisms of other hormones as well.

Recently cachectin has been shown to stimulate isolated human synovial cells and dermal fibroblasts to produce collagenase and PGE_2 [24]. This is a biological activity that had previously been ascribed to IL-1 alone. It is apparent that both monokines share an activity which is believed to be responsible for the destruction and remodeling of tissues during inflammation. The released collagenase acts to disrupt the extracellular collagen matrix [25] and PGE_2 stimulates the production of intracellular proteases and triggers bone resorption by osteoclasts [26, 27]. The role of cachectin and IL-1 in arthritic diseases is an area that will attract considerable attention in the future.

One of the most interesting biological activities associated with cachectin is its ability to selectively kill tumor cells [28, 29]. By a yet unknown mechanism a number of transformed cells are selectively killed *in vitro* and *in vivo*. Presumably certain essential proteins are being
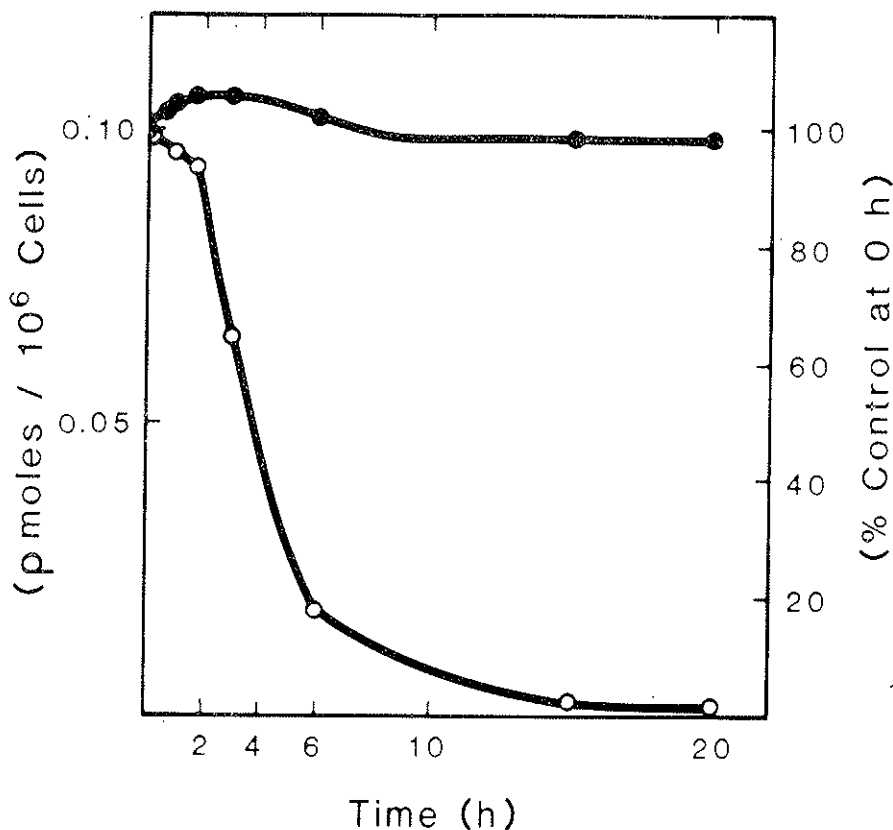
FIG. 4. Effect of cachectin on the insulin-binding capacity and lipoprotein lipase activity of adipocytes. After the indicated periods of incubation, cell surface insulin-binding capacity (●) and lipoprotein lipase activity (o) were determined [23].

selectively turned off in the susceptible tumor cells by a mechanism similar to that observed for the adipocytes. The nature of these proteins is not known, but knowledge of them would be of obvious utility in the design of new cancer chemotherapeutic agents. Considerable effort is now being expended on this property because of its potential in the treatment of human cancer. Clinical trials are currently under way to evaluate its use in various cancers.

During the course of evolution mammals have evolved a complicated series of reactions that are evoked when an animal is invaded by bacteria, viruses, parasites or tumors. These responses are mediated by the im-

mune system through a series of cytokines that can govern other somatic tissues. At present we can only presume that these metabolic alterations are advantageous to the invaded animal in its battle with the invader. IL-1, for example, has the ability to activate lymphocytes and promote the immune response [30]. Cachectin does not share this property with IL-1 but presumably in the near future other properties will be identified which offer to the infected individual an advantage for having cachectin. Figure 5 outlines a scheme of the effect of cachectin in animals. If the immune system is successful in defeating the invader, the animal convalesces. However, if the infection is overwhelming, the animal succumbs to shock. Chronic infections not resolved by the immune system lead to cachexia and death.
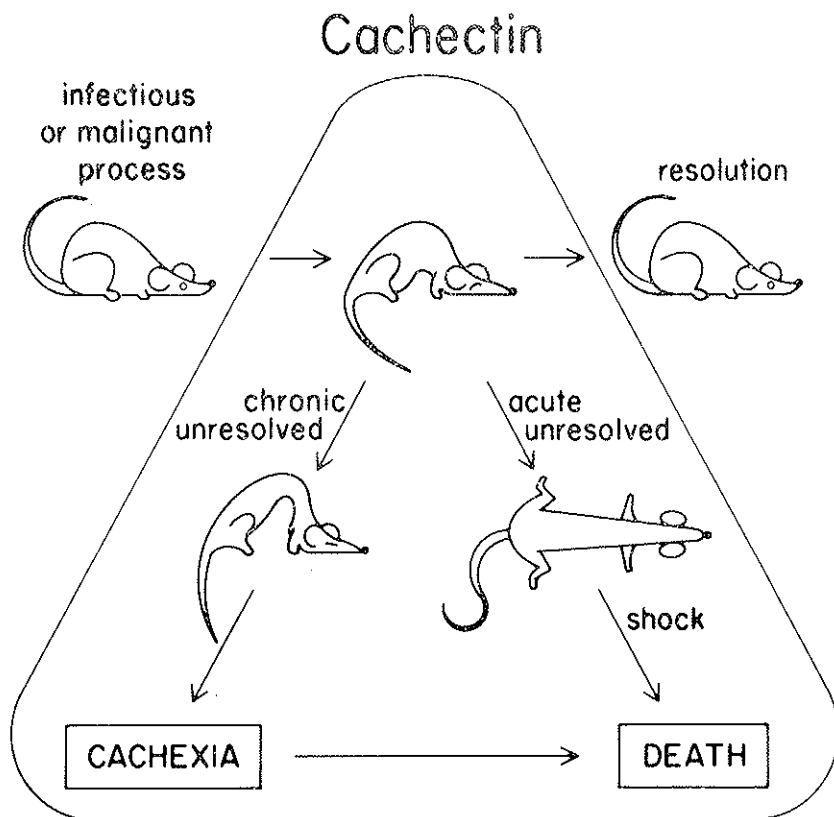

Fig. 5. Schematic representation of the role of cachectin in invaded animals.

There are several properties of cachectin, which are very puzzling. It is difficult to understand why anorexia should be such a pronounced effect of cachectin production, or how shock and death would be advantageous to the individual. One possible explanation is that the infected animal is given every chance to combat the invader, utilizing conventional immune mechanisms. However, if the individual fails to destroy the pathogen, his death could offer an advantage to the population, reducing the probability of spreading the pathogen to others. Evidence to support these speculations will have to await further experimental findings.

Although it is difficult at present to define positive actions of cachectin, it is possible to understand the negative effects it has. Foremost among these is its ability to cause cachexia in infected individuals. As noted above, this wasting reflects both the anorexia and catabolism induced by cachectin. It thus becomes possible to understand in molecular terms why individuals who undergo frequent bouts of infection display a state of malnutrition and stunted growth. This phenomenon is particularly pronounced in children who are susceptible to recurrent episodes of diarrhea, respiratory infections and other diseases. During the course of the disease they remain anorectic and catabolic, whether or not an adequate diet is available. Only after the infective episode is over can they convalesce, start eating again, and begin to rebuild the stores that were depleted during the sickness.

The importance of this biological response should be apparent to policy makers. Not only must they be concerned with increasing the quantity and quality of available food but they must also reduce the number of infectious diseases that afflict the population. If diseases are not also reduced the population will be malnourished, not because of a lack of food, but as a consequence of various infectious diseases. The specific disease entity responsible for this will vary from region to region. In some cases, multiple pathogens may be involved. The reduction of infectious diseases in the Third World should significantly reduce the impact of malnutrition.

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INTERLEUKIN 1 IN PARASITIC DISEASE
AND ITS IMPACT ON METABOLISM AND NUTRITION

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INTRODUCTION

Infectious, traumatic and immunologic challenges to the host are met within hours by stereotyped alterations in immune [1], metabolic [2], neural and endocrine [3, 4] function. Many of these "acute phase" responses are mediated by a family of polypeptides, known collectively as interleukin 1 (IL-1). This review 1) briefly summarizes the basic features of IL-1 and the acute phase response (for extensive bibliography, please refer to references 1,3 and 4), 2) presents the limited information known regarding IL-1 in parasitic disease and 3) describes the metabolic alterations mediated by IL-1 which occur during infection and which complicate the evaluation of nutritional status.

INTERLEUKIN-1 AND THE ACUTE PHASE RESPONSE

Molecular biology of IL-1

Precise information regarding the physical characteristics of the IL-1 molecules has recently emerged through the cloning of cDNAs for human monocyte-derived [5] and murine macrophage-derived [6] IL-1. At least two human forms of IL-1 exist with different isoelectric points (pI 7 and pI 5) and less than 26% homology of amino acid sequence [7]. The cDNA for the predominant form (pI 7) encodes a 33 kD precursor molecule. This precursor undergoes post-translational cleavage yielding

the 17 kd molecule which has been found in most biological conditions. Since the cDNA for IL-1 does not contain a signal or cleavage peptide sequence, the mechanisms leading to secretion of the molecule are not well understood at this time.

Phagocytic mononuclear cells are a primary source of IL-1, but other cells including B cells, large granular lymphocytes, keratinocytes, gingival and corneal epithelial cells, brain astrocytes and microglia and synovial cells produce IL-1 as well. A wide variety of microorganisms and microbial products can induce IL-1 production, although gram-negative bacteria and endotoxin have been most extensively studied. A broad spectrum of endogenous agents (bile salts, inflammatory steroids, C5A, antigens) as well as environmental agents (lectins, silica, ultraviolet radiation) also induce IL-1. Phagocytosis of particulate inducers is not necessary for IL-1 production; contact with the exterior of the producer cell is sufficient.

Since significant IL-1 activity required hours to appear in the supernatants of activated cell cultures and this appearance was blocked with inhibitors of protein synthesis, it was concluded that *de novo* protein synthesis was required for secretion. Significant quantities of IL-1 have since been found tightly bound to epidermal and monocytic tumor cell membranes which is consistent with the lack of a signal peptide indicated by the cDNA coding. This suggests that membrane-bound IL-1 may serve an autocrine function in the immediate vicinity of a localized infection.

Effects of IL-1 on the host

The most obvious of the acute phase responses is fever. IL-1 mediates fever via synthesis of prostaglandin E_2 (PGE_2) in the hypothalamus leading to regulation of body temperature at a higher set point. Moderate fever, especially in conjunction with lowered plasma iron concentrations is microbicidal for a number of pathogens. The depression of plasma iron (and zinc) is brought about by IL-1-mediated acceleration of metal transport into the liver and synthesis of metalloproteins within hepatocytes.

In addition to hypothalamic tissue, IL-1 stimulates PGE_2 production in cerebral cortex, dermal and synovial fibroblasts, chondrocytes, skeletal muscle, monocytes and macrophages. Elevated PGE_2 concentrations will inhibit IL-1 production *in vitro* suggesting a mechanism for negative feedback control of IL-1.

IL-1 acts through the central nervous system to induce, along with fever, slow wave sleep and neuroendocrine mechanisms which stimulate hepatic synthesis of acute phase plasma proteins. Systemic effects of IL-1 include anorexia, release and activation of neutrophils and procoagulant activity. Acute phase protein synthesis and trace metal alterations are also mediated at the systemic level. The acute phase proteins are thought to modulate inflammatory processes and aid in wound repair.

Localized actions of IL-1 include chemotaxis of leukocytes at sites of infection. Skeletal remodelling is mediated by IL-1 through bone resorption, cartilage breakdown, increased chondrocyte protease and synovial collagenase production and increased fibroblast proliferation. IL-1 promotes growth of new interstitial or support tissue in soft organs; glial, mesangial and endothelial cells, for example.

A major role of IL-1 during infection is modulation of the immune system. IL-1 augments the proliferative response of T cells to antigenic and mitogenic stimuli. This "lymphocyte activation" is accomplished through increased production of IL-2, which is the actual growth factor for clonal expansion of helper, suppressor and cytolytic T cells. IL-1 also induces expression of IL-2 receptors on the T cells. Humoral immune responses are augmented by IL-1 as well through increased B cell proliferation and antibody production. Natural killer cell activity is enhanced by a synergistic influence of IL-1 with interferon and by the ability of IL-1 to promote interferon production.

INTERLEUKIN-1 IN PARASITIC DISEASE

Successful occupation of the host by a parasite requires evasion of host defense mechanisms. Several protozoa and bacilli are capable of invading and multiplying within macrophages without stimulating IL-1 production. Once in residence, these parasites can influence the macrophage response to subsequent bacterial or endotoxin challenge. On the other hand, some extracellular parasites, such as *Borrelia*, are exceedingly potent inducers of IL-1 secretion and the pathology of these infections can be explained in the context of excessive acute phase responses.

Inhibited IL-1 secretion

Leishmania tropica and *Schistosoma mansoni* are examples of parasites which stimulate little IL-1 secretion themselves and inhibit IL-1 release

in response to bacteria or endotoxin. Human peripheral blood mono-nuclear cells (HMNC) infected *in vitro* with *L. tropica* failed to elaborate IL-1 activity (measured by both lymphocyte activation and fever produc-tion) into the supernatants [8]. When these infected cells were further challenged with *Staphylococcus epidermidis*, IL-1 production was signifi-cantly reduced, compared to the response of uninfected cells to the bacterial stimulus. The inhibitory effects of *Leishmania* on monocytes may be selective since the oxidative response to *L. donovani* remains intact [9].

Egg granulomas from the livers of *Schistosoma mansoni*-infected mice likewise secreted little IL-1 into supernatants *in vitro,* either spon-taneously, or in response to *Salmonella enteritidis* endotoxin [10]. Perito-neal macrophages taken from these infected mice (not in the vicinity of the granulomas) produced IL-1 spontaneously and in response to endo-toxin. This type of schistosomiasis often causes hepatic fibrosis leading to morbidity and death. While several of the acute phase effects of IL-1 promote fibrosis, other fibroblast stimulatory factors from granuloma macrophages and from the schistosomal eggs themselves seem to play a more dominant role in this disease.

Parasites as adjuvants for IL-1 production

The hemoprotozoa *Babesia microti, Plasmodium vinckii petteri* [11] and the macrophage parasite *Mycobacterium lepramurium* [12] do not elevate serum IL-1 activity in infected mice. However, unlike *Leishmania* and *Schistosoma,* these parasites render the host's macrophages *hyper*-responsive to subsequent challenge with *Escherichia coli* or *Salmonella typhi* endotoxin. The marked anorexia, fever, myalgia and arthralgia often associated with *Babesia* may in fact be precipitated by a secondary bacterial infection. In spite of the potential for high IL-1 production, human leprosy *M. leprae* is characterized by severe reduction of cell-mediated immunity. Rather than a deficit in IL-1 production, however, the reduced cellular immunity may be due to impaired IL-2 production and utilization [13], possibly caused by a glycolipid released by *M. le-prae* [14]. Bone resorption observed in leprosy may stem from exag-gerated IL-1 production due to a secondary infection.

Intact IL-1 response to parasitic infection

Not all parasites manage to avoid stimulating macrophage production of IL-1. Adherent spleen and peritoneal cells from mice infected with

Plasmodium yoelii yield significant amounts of IL-1 spontaneously or in response to endotoxin. A more lethal form of malaria, *P. berghei,* stimulated somewhat less IL-1 *in vitro.* In spite of elevated IL-1 production, cellular and humoral immune responses are impaired in malarial infections. Diminished IL-2 production by lymphocytes and increased production of a T cell-dependent IL-2 inhibitor have been implicated in this diminished immune capacity [15]. A similar scenario of normal IL-1 production, but inhibited IL-2 production, has been reported for mice infected with *Trypanosoma cruzi* [16].

Alveolar macrophages taken from rats infected with *Nippostrongylus brasiliensis* were competent producers of IL-1, both spontaneously and following endotoxin stimulation [17]. These cells also exhibited augmented phagocytosis indices, lysosomal enzyme release and even intracellular concentrations of the acute phase protein alpha₁protease inhibitor (alPi) [18]. Hepatocytes taken from mice infected with this nematode exhibited increased synthesis of alPi as well as other acute phase proteins: complement C3, serum amyloid A and amyloid P [19].

Borrelia hermsii and spirochetes associated with Lyme disease are potent inducers of IL-1 production by HMNC *in vitro* [20, 21]. In fact, the large quantities of IL-1 induced by the Lyme disease spirochete have been implicated in the pathogenesis of arthritis observed in these patients.

METABOLIC AND NUTRITIONAL ALTERATIONS BY INTERLEUKIN-1

Energy metabolism

Energy metabolism during infection resembles the starvation-adapted state: both are catabolic conditions in which peripheral nutrient stores are mobilized and then converted by the liver to usable energy substrates (see reference 2 for extensive review). The specific tissue mobilized in each case and the substrates produced are markedly different, however. In advanced stages of starvation, some alanine and lactate from skeletal muscle contribute to hepatic gluconeogenesis, but the primary supply of carbon for gluconeogenesis comes from glycerol released from adipocytes. Furthermore, free fatty acids released by adipocytes are processed into ketone bodies by the liver. The ketones then become the major energy substrate for muscle and the central nervous system.

In contrast, infected patients exhibit variable changes in fat mobilization, but a profound outpouring of amino acids and lactate from skeletal

muscle. Hepatic gluconeogenesis is high during infection, but ketogenesis is virtually absent. Several of these differences in metabolism can be attributed to the direct action of IL-1 on cellular mechanisms during infection. Other differences are related to hormonal variations, chiefly insulin, but probably catecholamines, glucocorticoids, growth hormone and TSH as well. Plasma glucagon concentrations are high in both starvation and infection.

IL-1 appears to be a major cause of muscle proteolysis via increased PGE$_2$ production [22]. Proteolysis is augmented further at febrile temperature. The free amino acids released by skeletal muscle are taken up by hepatocytes via IL-1-accelerated transport mechanisms [23]. Some of these amino acids are incorporated into acute phase proteins, while much of the alanine and glutamine is deaminated, driving hepatic gluconeogenesis and urea production. The urea lost in the urine leads to a negative nitrogen balance.

While skeletal muscle responds to infection with substantial catabolism, the response of adipose tissue is more variable. This is probably due to mixed signals. On one hand, plasma insulin is elevated which inhibits lipolysis. On the other hand, IL-1 or other macrophage factors inhibit key enzymes in fat synthesis: lipoprotein lipase [24], acetyl-CoA carboxylase and fatty acid synthetase [25].

Although fat synthesis mechanisms appear to be quiescent in adipose cells, they are clearly active in hepatocytes. Free fatty acid incorporation into triglycerides accelerates to the point that lipid droplets accumulate within the liver cells. The reason acetyl-CoA is preferentially channelled into triglycerides rather than ketones is not known, although elevated insulin levels are probably an important factor. Ketone synthesis by streptozotocin-induced diabetic rats can be effectively suppressed by injection of exogenous insulin [26]. However, challenging these rats, which are incapable of endogenous insulin secretion, with viable *Stretococcus pneumoniae* resulted in a partial suppression of ketogenesis. This implies that some other factor in addition to insulin is contributing to suppression of ketogenesis.

There is evidence that macrophages produce both a factor with insulin-like activity and a factor which induces insulin secretion by pancreatic islets. Crude leukocyte supernatants injected into rats elevated both insulin and glucagon in the plasma [27]. Furthermore, plasma taken from rats infected with endotoxin exhibited an increase in im-

munoreactive insulin activity and a macrophage derived insulin-like activity which was not neutralized by antiserum to insulin [28]. Whether either of these factors is IL-1 has not been established.

Other hormones unquestionably contribute to the metabolic responses to infection. Infusion of a hormone "cocktail" consisting of epinephrine, glucagon and cortisol into healthy human subjects induced several metabolic changes similar to those observed during infection [29]. Furthermore, IL-1 may influence hormonal secretion. Endotoxin causes a rise in growth hormone concentrations in the blood [30]. Pharmacological manipulation of PGE_2 concentrations in the hypothalamus of rats caused parallel changes in growth hormone and TSH secretion [31].

The foregoing discussion implies that IL-1 explicitly directs the metabolic response to infection. However, it must be pointed out that experimental inflammatory responses induced in human subjects with etiocholanolone were associated with increased plasma IL-1 activity, but these increases did not correlate with metabolic or acute phase responses [32]. The biological actions of IL-1 are undoubtedly modified by other hormones [33] and by specific inhibitors [34].

Nutritional Status

Chronic dietary protein deficiency reduces the capacity of blood monocytes to produce IL-1, thus diet effects host defense. IL-1, in turn, causes anorexia and alters plasma nutrient concentrations, thus host defense affects diet and nutrition. These interdependencies may warrant consideration when developing health policies aimed at populations suffering both chronic malnutrition and parasitic infection.

Blood monocytes obtained from either protein malnourished rabbits [35] or humans [36] exhibited depressed IL-1 production relative to protein-replete controls. Protein supplementation of the diet of the human subjects restored the ability of the cells to produce IL-1; supplementing the incubation media of the rabbit cells with amino acids did not correct the deficit in IL-1 production [37]. Therefore, the protein deficiency appears to affect the synthetic mechanisms of the cells and is not merely a lack of readily available amino acids.

The impact of a reduced IL-1 response in protein malnutrition is not clear. Serum from children with kwashiorkor did not effectively support lymphocyte activation *in vitro,* but the lymphocytes from these

children functioned normally when incubated with normal serum [38]. In addition, these children exhibited elevated antibody titers. In experimental infections with laboratory animals, one study demonstrated reduced acquired resistance to *N. brasiliensis* in protein deficient rats [39], but others have not observed impaired immune responses to *Brucella abortus* or *Lysteria monocytogenes* [40].

Infection often results in a loss of appetite. IL-1 can induce anorexia after systemic injection, but central administration of IL-1 failed to elicit anorexia, although the rats did respond with fever [41]. If mediated by IL-1, does anorexia represent another host defense mechanism?

Interruption of food intake may be advantageous during infections which involve vomiting, malabsorption or diarrhea since in these conditions, nutrients will not be absorbed if eaten and instead merely contribute to the loss of fluids and electrolytes [42]. Beyond these digestive considerations, however, these is evidence that a reduced energy intake actually improves resistance to infection. Mice infected with *L. monocytogenes* were force-fed by gastric intubation to the caloric intake of noninfected mice while others were allowed to become anorexic [43]. Mortality increased and survival time shortened in the force-fed animals. Furthermore, refeeding famine victims in Africa resulted in sudden outbreaks of malaria, brucellosis and tuberculosis [44].

The mechanisms underlying this relationship between food consumption and resistance are not well understood. One dietary factor which probably contributes to these results is iron. Iron is an essential nutrient for the growth of a host of pathogens [45]. The virulence of many infections seems to depend upon whether the infecting organism is successful in extracting iron from its surroundings. An appreciation of the role of iron and other nutrients in the host-parasite relationship and host defense may lead to improved diets for famine relief distribution which promote nutritional recovery without compromising host defense mechanisms.

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APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE TO THE STUDY OF PARASITIC DISEASE

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Introduction

This paper discusses the possible applications of nuclear magnetic resonance (NMR) to the study of host-parasite biology, in particular, the details of the metabolic pathways. In addition, the development of NMR imaging techniques which can determine the distribution of water and lipids in the body of animals and humans may also provide information concerning organ distribution of infection or other systemic responses in the host.

NMR is a physical technique which has been in use for 40 years in physics and chemistry to probe the molecular and electronic structure of molecules. Its greatest strength lies in its ability to determine the details of the chemical structure surrounding a particular nucleus. A detailed exposition of the physical principles behind NMR is out of place in this review; however, a brief summary of the basis of the technique will provide an underlying structure for the following discussion.

A sample under study is placed in a very homogeneous magnetic field which serves to polarize the nuclei in the sample, thus magnetizing the specimen. This magnetization can then be excited by means of an appropriate radio frequency magnetic field generated by a coil which surrounds the sample. Following excitation the magnetization spontaneously relaxes to its equilibrium value re-radiating the absorbed radiofrequency power. By measuring the precise frequency of this re-radiated power, the chemical structure of the molecules containing the nuclei under

study can be determined. It is this ability to determine chemical structure in solution which has made NMR such a powerful tool to the chemist and biologist.

Recently it has been realized that NMR measurements can provide considerable information about *in vivo* systems as well as *in vitro* solutions. Work using the phosphorous nucleus, ^{31}P, has aided in the study of bio-energetics and its control mechanisms in numerous *in vivo* systems ranging from E. coli to man by observing the intracellular levels of ATP and other high energy phosphates. In addition to studying energetics and its control, the use of ^{13}C enriched materials enables details of the metabolic pathways in these organisms to be determined [1-3].

More recently still, it has become possible to develop anatomical images from the protons in animals and man. These images reflect not only the distribution of protons but also the details of their relaxation behavior and their division between aqueous and lipid environments. In fact, the images are of such quality that serious competition with other clinical imaging modalities has emerged, both because of the increased safety of NMR imaging as well as the increased biological information available from the signals. See [4] for further review.

Metabolic Studies

These studies can measure the levels of many internal metabolites, particularly the high energy phosphates, intracellular pH, and the catabolic distribution of products of ^{13}C labeled metabolites. In the various studies considered in this review, the levels of high energy phosphates, such as ATP, are generally taken to indicate the overall metabolic energy supply of the specimen. Either it is well supplied with energy and thus in a relatively healthy state or it is not and thus presumably in a relatively diseased or dying state. Although this is generally borne out by experience, occasionally a tissue is found to have extremely low levels of ATP from which, upon renewal of perfusion, it can recover. Intracellular pH is obviously an important parameter, particularly in a process such as phago-cytosis. Although little is known regarding the internal pH of parasites during growth, in view of the importance of pH to cell division in other systems [5], the knowledge of the pH during this period might prove to be important.

Various experimental systems can be studied with these techniques [1-3]. Typical studies on whole organisms are done by means of surface

coils which localize the radiofrequency excitation and detection of the NMR signals to specific organs. The difficulty with these techniques is that the organs must be relatively near the surface for accessibility. For example, liver is a prime candidate for study by these techniques but brain, at least in animals, can be much more difficult because of the rather thick overlaying muscle in many cases. Muscle studies are straightforward.

Because of the high cost of NMR equipment, it seems unlikely that it will have substantial clinical use in relation to parasitic diseases. More likely uses will be in research, increasing our understanding of the metabolism of the parasite, the response of the host to the parasite (systemic and local) as well as to anti-parasite drugs. We will now examine each of these possibilities.

Parasite Metabolism

An increased understanding of the differences in metabolism between parasite and host may lead to the design and discovery of new anti-parasite agents capable of destroying the parasite while having minimal effects on the host. Because of the complex life cycles of many of the important parasites (*Plasmodium, Leishmania, Trypanasoma, Schistosoma*) many of the details of their metabolism are unknown, particularly if they have an intracellular form, making it difficult to untangle host from parasite metabolism. In view of the considerable morphological and environmental changes that occur one might ask whether the metabolic details stay the same as a free-living organism changes into an intracellular one. Preliminary studies of metabolism of various parasites using both ^{13}C and ^{31}P have been done, although no attempt has yet been made to separate host from parasite metabolism or to compare the metabolism of parasites at different stages in their life cycle [6-12].

Such distinctions should be useful in the case of parasites which infect the macrophages of the immune system thus evading the normal immune responses of the host. How can the metabolism of parasites which live intracellularly be distinguished from the normal host intracellular metabolism? The intracellular pH and intraparasitic pH should be distinguishable since NMR can observe intracellular compartments which are at different pH's. Another interesting possibiilty is the application of spin echo techniques to distinguish intracellular constituents from parasitic constituents in the manner analagous to that used for distinguish-

ing erythrocyte contents from external contents by means of spin echos [15].

Another area of fruitful investigation is likely to be systemic alterations in the host metabolism due to parasite burden. A particularly interesting one is the effect of cachectin on the behavior of adipose tissue, its mode of action and its normal as well as abnormal physiological role [16, 17]. Since the functional consequences of cachectin are alterations in energy metabolism, NMR should be particularly useful in this case. In addition, the investigation of responses of tissue culture to the addition of cachectin provides one with a well controlled system in which the cellular responses, as opposed to those of the whole organism, can be determined. ATP levels, other indicators of energy metabolism and switches in metabolic pathways could be easily followed as conditions are varied. For example, how does the metabolism of an adipocyte change upon exposure to cachectin? Are the metabolic pathways the same but just the levels of enzymes different or are whole new pathways developed? Do the responses depend on pH or other extracellular conditions?

A more speculative possibility in the area of systemic responses is the development of methods to quantitate the state of malnutrition. The conceptual basis here is to use stimulus/response comparisons where the stimulus is a mild stress on the organism or individual organ involved and the response is the levels of high energy phosphates or other metabolites measured non-invasively by NMR. It seems reasonable that such measurements would correlate with the overall level of health of the organism so that a mild stimulus would produce a mild response in a healthy organism whereas in a malnourished organism it would produce a much larger response since that organism is unable to operate as efficiently.

Phagocytosis, normally employed by organisms as a defense mechanism, is defeated by many parasites. This seems an area that would be particularly fruitful for study by NMR because the processes involved in the destruction of phagocytized intruders usually involve acidic pH's and other environmental extremes within the internalized vesicles. Such extreme conditions should make the internal space of the vesicles visible to NMR. Numerous questions could be examined. For example, is the reason certain parasites are not damaged by phagocytosis because they modify the internal environment of the vesicle or are they themselves resistive to the acidic pH? Is there a common process by which different organisms defeat this mode of defense or is there a multiplicity of pro-

cesses?   To answer such questions would require the development of fairly sophisticated model systems in which the process of phagocytosis can be stimulated repeatedly in a controlled manner.   The possible increase in understanding how this normal defense mechanism is defeated seems to be worth the necessary effort.

Another natural question to examine is the relative effectiveness and mode of action of anti-parasite drugs. A small amount of preliminary work in this area has been done on some of the anti-malaria drugs and their effect upon glycolizing infected red cells [9, 18]. Experiments of this sort are straightforward where model systems using tissue culture have been developed. It is more complicated to carry out these studies of drug effectiveness by metabolic response in whole organisms because of the increased difficulty of separating out the parasite response from the host response.   Differential organ sensitivity to both drugs and parasites suggests a careful series of surface coil studies might provide useful information about differential organ responses.

Imaging

It is now possible to obtain high quality images of animals such as mice with resolutions less than 50 microns [19]. The ability to follow parasitic infection sequentially in a series of animals at such scale may provide new insights into the mode of distribution of the parasite throughout the host. Such information may be of clinical utility in cases of schistosomosis, with schistosomes in their adult stage in the bile ducts or in the bladder.   A most interesting question to answer would be whether the different life stages of parasites can be detected by any changes in the NMR imaging signals due to the very different morphology and internal structure of the parasites as they go through their live cycle. Such a question is impossible to answer theoretically because our limited ability to predict changes in contrast in NMR images is limited even when we know more concerning the possible biological changes.

In summary, a wide variety of possible NMR applications exists for the study of parasitic diseases. Such applications will probably require collaboration between those working with parasites and those working with NMR because of the complexity of both the techniques as well as the questions under investigation. In view of the importance of parasites as a public health question, such collaborations would seem to be worth fostering in spite of the somewhat speculative nature of some of the experiments proposed.

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II.

INTERACTIONS OF PARASITIC DISEASE AND NUTRITION

NUTRITION AND MALARIA:
PROTEIN-ENERGY MALNUTRITION
AND IRON STATUS (*)

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Abstract

The interaction between nutrition and malaria is illustrated by reference to protein-energy malnutrition and iron deficiency. In the short term, episodes of malaria have negative effects on the growth of young children. There is little evidence regarding the long-term effects and it is likely that infant feeding practices will have an important influence on the outcome. The effect of protein-energy malnutrition on malaria is unclear.

Although malaria causes hyperferraemia it is frequently associated with iron deficiency. There is evidence from studies in both animals and man that iron deficiency protects against malaria. However, most studies in humans are beset by design problems and there is an urgent need for controlled trials to assess the public health significance of the effect of iron deficiency on malaria.

Introduction

The asexual blood stages of malaria are obligate intracellular parasites which multiply within the host and this has a wide range of implications

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* This presentation is based, with only minor modifications, on a paper entitled « Protein-energy malnutrition, iron status and malaria » in the Papua New Guinea Medical Journal, in press.

for both the host and the parasite. On the one hand, the parasite requires an environment which supplies the nutrients required for maintenance and growth whilst, at the same time, avoiding host defence mechanisms. Intracellular localisation not only allows the parasite to evade potent host immune mechanisms, it also provides an environment rich in essential nutrients. On the other hand, the host must mount a response which, at least, modulates the virulence of the organism. If it does not the parasite will continue to multiply and, eventually, cause the death of the host. It might be expected then that the nutrition of the parasite will be affected by the nutritional status of the host and that, in common with many other infectious diseases, the parasite will affect the nutritional status of the host.

In this paper the interaction between malaria and nutrition is illustrated by reference to the two most common nutrition problems in areas where malaria is endemic — protein-energy malnutrition and iron deficiency.

Protein-Energy Malnutrition (PEM)

PEM is a broad term which refers to a general, usually chronic, deficit in protein and/or energy which, in children, results in growth retardation, the proximate causes of which are generally agreed to include low birth weight, a deficient intake of energy and protein and repeated episodes of infectious disease. The importance of each of these factors will vary depending on the specific situation. The general outcome, however, will be growth retardation.

(a) *The effect of malaria on growth.* Malaria could, conceivably, effect growth through each of the paths described above.

(i) Birth weight is an important determinant of postnatal growth [1] and the effect of malaria during pregnancy on birth weight has been investigated in a number of studies. The most complete and convincing study is that of McGregor *et al.,* [2] who investigated the effect of placental malaria on birth weight in more than 6000 births in the Gambia. Confirming the findings of previous studies, they showed that pregnant women were more likely to have parasites in the placental, than in the peripheral, blood and that malarious placentae were more frequent in primiparous than multiparous women. Dense placental infections were

also more frequent in primiparae. The relationship found between malaria infected placentae and low birth weight, however, was not as strong as reported previously. Mean singleton birth weight was depressed by 170 g in the presence of malaria but the difference was only significant for primiparae. Further, the expected inverse relationship between increasing density of parasites and birth weight was not found.

(ii) Postnatal growth. Studies of the effect of malaria on growth fall into two broad categories. In the first, the effect of individual episodes of illness on weight gain during the period (e.g., month) in which the illness occurred or the period immediately following the illness has been estimated. In the second broad category of studies the net effect of malaria on growth over a much longer period of time (e.g., 1 to 2 years) has been estimated in the context of an intervention program such as chemoprophylaxis against malaria or other malaria control measures.

Examples of studies in the first category are those of Marsden [3] and Rowland et al. [4]. Marsden, working in the Gambia identified periods of growth faltering (a check in weight gain) and then determined the extent to which this faltering was preceded by episodes of illness. Approximately 70% of the periods of growth faltering were associated with periods of clinical illness which appeared to contribute to the check in weight gain. Diarrhoea and malaria were the most frequently associated conditions.

Rowland et al. [4], again in the Gambia, studied children in the first 3 years of life. Regression analysis was used to determine the effect of episodes of various illnesses on weight and height gain in the month in which the illness occurred. Gastroenteritis was the only disease to have a significant (negative) effect on monthly height gain. However, both gastroenteritis and malaria had significant negative effects on monthly weight gain.

Whilst this study provides evidence for an effect of a clinically significant episode on growth in the short term its results are not particularly surprising. That episodes of febrile illness depress food intake is a commonplace observation within the personal experience of everyone. Pyrexia increases energy metabolism and leads to negative nitrogen balance. These events, if of sufficient magnitude, will lead to weight and a decrease in the velocity of linear growth. The more important question is whether the capacity for catch-up growth is subsequently realised. That is, what is the net effect of malaria on growth over a much longer period of time, say the first two to three years of life?

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A number of studies have attempted to assess the effect of malaria on growth in the longer term. Jelliffe and Onwumere [5] studied mean weekly weight in 26 children for 3 2-monthly periods representing the time before, during and after chemoprophylaxis against malaria. The authors of this poorly analysed study, in which no account was taken of the normal decrease in growth velocity with age, concluded that malaria appeared to interfere only slightly with growth.

A much more rigorous study of the effect of malaria on growth in young children is that of McGregor [6] in which 2 groups of 26 newborns were enrolled in a 3-year prospective study. One group was given weekly chloroquine and the other a placebo. Unprotected children, once infected, initially gained weight more slowly. However, this retardation was not permanent. They subsequently gained ground and by 36 months were just as heavy as the protected group. At no time was the difference in weight between the two groups significant. However, only 1 of the children in the protected group died compared to 5 in the unprotected group. Whilst there was no significant difference in weight between the two groups at 3 years of age there was a significant difference in height. The mean height of the protected children was more than 3 cm greater than that of the unprotected group. Although this latter finding is seldom commented upon it is quite remarkable that the difference was significant, given the relatively small numbers in each group. Given the short-term instability of weight, height would seem to be a better indicator of the long-term effect of malaria on growth.

Two other studies have assessed the effect of malaria control measures on growth. Unfortunately both have serious design flaws. Draper and Draper [7] calculated mean monthly weight increments from mixed longitudinal data before and after the reduction of malaria transmission by use of a residual insecticide. Although spraying resulted in a dramatic decrease in parasite rates, and a 2 gm/dl increase in mean haemoglobin, there was no significant impact on growth rates. Inferences from this study are limited by the absence of a control group which would have enabled evaluation of secular trends.

Molineaux and Gramiccia [8] compared the nutritional status of people in villages where malaria control measures of differing intensities were employed. Anthropometric surveys were conducted during and after, but not before, intervention. The authors reported nutritional status was slightly better in the more protected villages with differences disappearing in the post-intervention phase. Insufficient data were present-

ed in the report of this study to evaluate the conclusions drawn concerning nutritional status.

Thus, the evidence from longer-term studies for the effect of malaria on growth is equivocal, to say the least. Most suffer from design problems together with the difficulties of carrying out long-term studies. In the one well-designed study, that of McGregor [6] there was a negative effect on height but not weight. However, short-term studies of the effect of individual episodes indicate the reverse — a negative effect of malaria on weight but not on height. Part of this apparent conflict can be explained by the greater short-term variability in weight than in height. But clearly, should catch-up growth after each episode be complete, it is possible for there to be a negative short-term effect and no effect in the long-term. One of the most important factors determining the net long-term effect then, is the extent to which catch-up growth occurs.

Under favourable conditions the rate of growth following a period of illness can be very high. Whitehead [9] indicates that although the normal growth rate of a 7 kg child is aproximately 10 g/day, the rate may be up to 7 times this value in a nutrition rehabilitation centre, and has calculated the energy and protein intakes, and the corresponding protein-energy ratios, necessary to sustain these rates of growth. A summary of Whitehead's calculations is shown in Table 1.

Calloway [10] used the results of a number of studies of morbidity (including malaria) and growth to estimate the extent to which energy intake would have to be increased, on days when the child was well, to

TABLE 1 - *Theoretical protein and energy requirements and protein energy ratios for different rates of growth during recovery from protein-energy malnutrition* (adapted from Whitehead [9]).*

Requirement	Value by rate of growth (g/day)			
	10	30	50	70
Total Energy (kJ/kg body weight/day)	472	514	556	597
Protein (g/kg/day) †	1.90	2.56	3.23	3.96
Protein-Energy ratio (%)	6.7	8.6	9.7	11.1

* Calculations based on a child weighing 7 kg.
† Includes an allowance for individual variation.

restore the deficit in weight gain. In the worst case, energy intake on healthy days would have to be increased by 16% to meet normal average intakes across the full period. In most cases the increase was much less. Whitehead's results indicate that the proportion of energy provided by protein (protein-energy %) must also increase during this time. Calloway raises the question of why these increases do not occur even though the increment may be quite small.

It would seem that the answer to this question may also throw some light on why malaria may have a net negative effect in some situations and no effect at all in others. The cultural context in which the disease occurs is likely to be an important explanatory variable. The cultural context will influence not only the actual foods produced and considered food, it will also influence who receives food and when, as well as the availability of food during an illness episode.

In general, the effects of malaria on growth will be expected to vary according to the cultural context. In areas where there are low rates of maternal malnutrition and relatively early introduction of solids with a reasonable protein and fat content the effect of malaria on growth will be less than in areas with high rates of maternal malnutrition and late introduction of solids with low concentrations of energy and protein.

(b) *The effects of protein-energy malnutrition on malaria.* The effects of PEM on malaria, particularly in humans, are unclear. On the one hand there are studies which show an antagonistic relationship. Probably the most often quoted is that by Ramakrishnan [11] who reported that deaths from malaria rose 200% above a 5-yearly average a few months after famine relief operations commenced in the Bengal Famine of 1943. No information was presented on the regularity of such fluctuations in this average, whether or not the average was seasonally adjusted, or on other possibly relevant factors such as rainfall.

On the other hand, there is abundant evidence that PEM is associated with impairment of immune responsiveness, particularly of T-cell function [12] and therefore it might be expected that PEM would be associated with an increase in malaria. Only a few studies have addressed this question.

Edington [13] offers anecdotal evidence supporting statements that malnourished children, particularly those with kwashiorkor, were no more likely to have malaria than well-nourished children. Brown and Opio [14] examined records of 200 children admitted with kwashiorkor

to a large urban hospital in Uganda. They reported that 16% had at least one blood slide with malarial parasites and compared this with the proportion of cases — 19% — with indirect evidence of malaria infection in a series of paediatric autopsies. The authors concluded that children with PEM were no more susceptible to malaria than better nourished children. The appropriateness of these comparison groups for such an inference is dubious.

Hendrickse et al. [15] investigated 500 seriously ill children clinically diagnosed as having malaria on admission to an urban hospital in Ibadan, Nigeria. Only 37% had positive blood slides and these children were considered to have been correctly diagnosed as having malaria. The group with parasitaemia had better nutritional status than the others in whom it was assumed the clinical diagnosis was incorrect. Parasites were found in only 4 of the 24 children with kwashiorkor. The authors claim these data demonstrated the existence of an antagonistic interaction between malaria and malnutrition. The conclusions are weakened by serious design flaws. Cross-sectional studies of this nature cannot address questions of causality. Further, the appropriateness of the comparison groups is questionable because those children assumed to be misdiagnosed certainly had some illness and it is possible that this may have resulted in greater weight loss than did malaria.

More recently Edirisinghe et al. [16] have investigated the effect of protein intake on malaria in rats. A positive association was found between protein intake and severity of malaria. The extent to which this work can be extrapolated to humans is not known. However, there are areas in which malaria is endemic and protein intakes are known to be low. Differential intakes by age and sex categories of scarce protein resources may have an effect on survival of the parasite as well as on the host's ability to mount an effective immune response thereby altering the epidemiological pattern of the disease. This is highly speculative but Edirisinghe's interesting results should be assessed in humans.

Iron Deficiency Anaemia

(a) *Effect of malaria on iron status.* Malarial parasitaemia usually results in some degree of anaemia in the host. This anaemia is usually microcytic and consistent with iron deficiency [17]. Successful intervention studies, using either spraying or chemoprophylaxis, have resulted in increased haemoglobin levels.

However, understanding the haematologic picture in malaria is complicated by the pattern of response in indicators of iron status other than haemoglobin. Whereas the usual response in most acute infections is a decrease in serum iron and a rise in haptoglobin, in malaria there is a rise in serum iron to a point where the iron binding capacity of the serum is virtually saturated, a rise in serum ferritin and a fall in haptoglobin levels [18, 19].

Thus, although red cell morphology is consistent with iron deficiency, other measures indicate adequate iron status. The situation is summarised by McGregor [17] as follows:

"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 anaemia calls for further research". (p. 801)

Nevertheless, malaria results in hyperferraemia even though iron status may be low. Hyperferraemia is known to underlie increased susceptibility of humans to infection [20] and malaria may thus have significant effect on morbidity and mortality from other causes.

(b) *The effect of iron status on malaria.* The suggestion that iron deficiency is protective against malaria infection was proposed first by Masawe *et al.* [21] and later by Murray *et al.* [22, 23, 24]. Masawe *et al.*, studied the frequency of infections in 110 African patients with haemoglobins less than 10 g/dl admitted consecutively to an adult medical ward. All but two of the 18 patients who developed malaria had both iron deficient and dimorphic anaemia. Importantly, the malarial attacks in most of these patients followed iron replacement therapy. No details were presented about the type or timing of the iron therapy, or the number of patients who were given iron therapy but did not suffer malaria.

Murray *et al.* [22] studied the relationship between iron status and incidence of clinical malaria in people whose diet improved dramatically during famine relief operations in the Sahelian drought of the early 1970's. They reported that patients and relatives changing from famine to hospital rations experienced a high incidence (40%, 74/181) of acute malarial infections. The authors postulated that this resulted from hyper-

ferraemia, as measured by transferrin saturation, associated with the improved diet. During further relief operations in the Ogaden famine Murray et al. [23] again observed recrudescence of malarial infections during refeeding. They reported that although local villagers had experienced no malarial attacks prior to arrival at the camps, attacks were very common shortly thereafter. In the same area, Murray et al. [24] found that the incidences of malaria, brucellosis and tuberculosis were much higher in iron deficient nomads supplemented with ferrous sulphate than in a placebo group. The Murrays suggested that "it may be unwise to attempt to correct iron deficiency especially in the face of quiescent infection".

In contrast to the results of Masawe and the Murrays, McGregor [17] indicated that he had not observed greater incidence of malaria in individuals given oral iron supplements in areas where malaria is endemic. McGregor suggests that the individuals observed by the Murrays may have lacked immunity against heavy parasitic challenge because of an iron deficient diet since childhood. McGregor's experience, on the other hand, had been with populations where iron deficiency was secondary to infection with either malaria or hookworm and which had developed some immunity to infection.

A more recent study carried out by Oppenheimer et al. [25], in collaboration with the Papua New Guinea Institute of Medical Research, provides further evidence of the relationship between iron status and malaria. Infants were injected with iron supplement at two months of age. The control group received a placebo injection. In rates of both malarial parasitaemia and palpable spleens the iron injected children showed significantly greater evidence of malaria.

Although animal models have been used to investigate the interrelationship between a range of nutrients and malarial infections, iron has received very little attention. Murray et al. [22] showed that rats injected with iron dextran prior to infection with Plasmodium berghei developed higher parasitaemias and died sooner than rats not given iron before the infection. Harvey et al. [26] showed that P. chabaudi infections in NFR/N mice made anaemic by dietary iron-deficiency produce mortalities of 25% (male) and 7% (female) compared to 100% in iron sufficient controls. When iron deficient mice convalescing from the primary infection were returned to the normal diet, 100% experienced recrudescent parasitaemia. No recrudescence occurred in mice maintained on the iron deficient diet.

In vitro systems have also been used to study the effect of iron on the malaria parasite. Raventos-Suarez *et al.* [27] demonstrated that desferrioxamine, a specific iron chelator, completely inhibited the growth of *P. falciparum* in an *in vitro* culture system and that the parasite sensitivity seemed to be maximal preceding schizogony.

The mechanism whereby iron deficiency could result in protection from the malarial parasite is not clear. Nurse [28] considers that haemoglobin is an important nutrient for *Plasmodium* and that the protection from malaria observed in individuals with the minor thalassaemias and with iron deficiency is related to the lowering of mean corpuscular haemoglobin. Another mechanism proposed by Wyler [29], involves a reduction in red cell catalase, which may be needed to scavenge H_2O_2 produced intracellularly by the parasite. A further possible mechanism is suggested by the *in vitro* studies of Raventos-Suarez *et al.* [27] which indicate that availability of nonhaeme iron is important and that iron deprivation may limit DNA replication in the parasite. It seems that the biology of the relationship between the malaria parasite and an iron deficient host is not clear and requires further study.

In summary, *in vivo* studies in both man and animals suggest that low iron status is associated with reduced replication of the malaria parasite. *In vitro* studies are consistent with those that have been carried out *in vivo*. However, uncertainty over the evidence, and particularly with respect to the causal nature of the relationship, makes it difficult to develop public health policies concerning iron supplementation in areas where malaria is endemic. The role of the iron status of a population as a parameter in the epidemiology of malaria is also unknown. It is likely that any such effects will not only be age-specific, but will also depend on the extent of previous exposure to the parasite. It seems clear that some additional well-designed and carefully controlled intervention studies are needed to assess the significance of the iron-malaria relationship. One such study, in which the effect of iron supplementation of schoolchildren on their subsequent experience of malaria will be assessed, is currently being carried out by the PNG Institute of Medical Research.

Conclusion

It is clear that there are short-term negative effects of episodes of malaria on the growth of young children. However, there is little evidence regarding the long-term effects and it is likely that infant feeding practices

will be an important intervening variable. The effect of PEM on malaria is unclear.

Although malaria causes hyperferraemia it is frequently associated with iron deficiency and further work on the pathogenesis of malarial anaemia is needed. There is evidence from studies in both animals and humans that iron deficiency protects against malaria. However, most studies in humans are beset by design problems and there is an urgent need for controlled trials to assess the public health significance of the effect of iron deficiency on malaria.

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CLINICAL MANIFESTATIONS OF THE LEISHMANIASES

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Abstract

Leishmania species produce disease on every continent with the exception of Australia. It is estimated that 1.2 million new cases of leishmaniasis occur each year. Leishmaniasis has traditionally been separated into cutaneous, mucocutaneous and visceral (kala-azar) syndromes, the development of which is related to a complex and still poorly understood interaction between the human immune system and the parasites' genetically determined invasiveness, pathogenicity and tropism. *Leishmania* can be divided into four species complexes: the *L. donovani* complex produces visceral disease in Latin America, eastern Africa, the Mediterranean, India and China; the *L. tropica* complex produces cutaneous disease in Africa, the Mediterranean, and the Middle East; the *L. mexicana* complex is responsible for cutaneous ulcers in Latin America; and the *L. braziliensis* complex produces cutaneous and mucocutaneous disease in Latin America. *Leishmania* are spread by sandflies of the genera *Phlebotomus* in the Old World and *Lutzomyia* and *Psychodopygus* in the Americas. The reservoir varies depending on the *Leishmania* species and the geographic location; dogs, other canines, rodents or humans are involved in various sites. The *Leishmania* are unique among pathogenic protozoa in their diversity of species, vectors, reservoirs, and epidemiology.

They continue to pose major challenges for health care workers in endemic areas throughout the world.

Introduction

Leishmaniasis is the general term used to describe disease caused by a member of the protozoal genus *Leishmania* and has traditionally been divided into cutaneous, mucocutaneous and visceral (kala-azar) syndromes [1]. The spectrum of human disease ranges from localized, self-healing ulcers to widely disseminated progressive lesions of the skin and mucous membranes or, in the case of visceral leishmaniasis, involvement of the entire reticuloendothelial system. In humans and other mammals *Leishmania* reside as intracellular amastigotes within mononuclear phagocytes. The organism is transmitted to humans by sandflies as an extracellular, flagellated promastigote. The clinical manifestations of leishmaniasis depend on a complex interaction between the host's immune system and the parasites' genetically determined invasiveness, pathogenicity and tropism. Evidence from animal models indicates that susceptibility to *Leishmania* is genetically determined and that cell mediated immune mechanisms are primarily responsible for controlling infection [2]. The *Leishmania* which produce disease in man can be divided into four species complexes. The *L. donovani* complex is responsible for visceral leishmaniasis in South and Central America, eastern Africa, the Mediterranean, India, and China. The *L. tropica* complex produces cutaneous disease in Africa, Asia, and the Middle East. The *L. mexicana* complex and the *L. braziliensis* complex produce cutaneous ulcers, and in the case of the *L. braziliensis* complex mucocutaneous disease (espundia) in Central and South America. *Leishmania* species are found on every continent except Australia (Table 1). They are estimated to cause 1.2 million new cases of leishmaniasis a year [3].

Morphology and Life Cycle

The *Leishmania* are digenetic protozoa, that is, their life cycle involves two distinct morphologic forms. *Leishmania* amastigotes are found solely within mononuclear phagocytes in mammals. They are 2-3 μm in length, oval or round in shape, and lack an exteriorized flagellum. In Wright's- or Giemsa-stained preparations their cytoplasm is blue, the nucleus is relatively large and red, and there is a distinct rod-shaped, intensely stained kinetoplast. Multiplication is by binary fission. In its sandfly
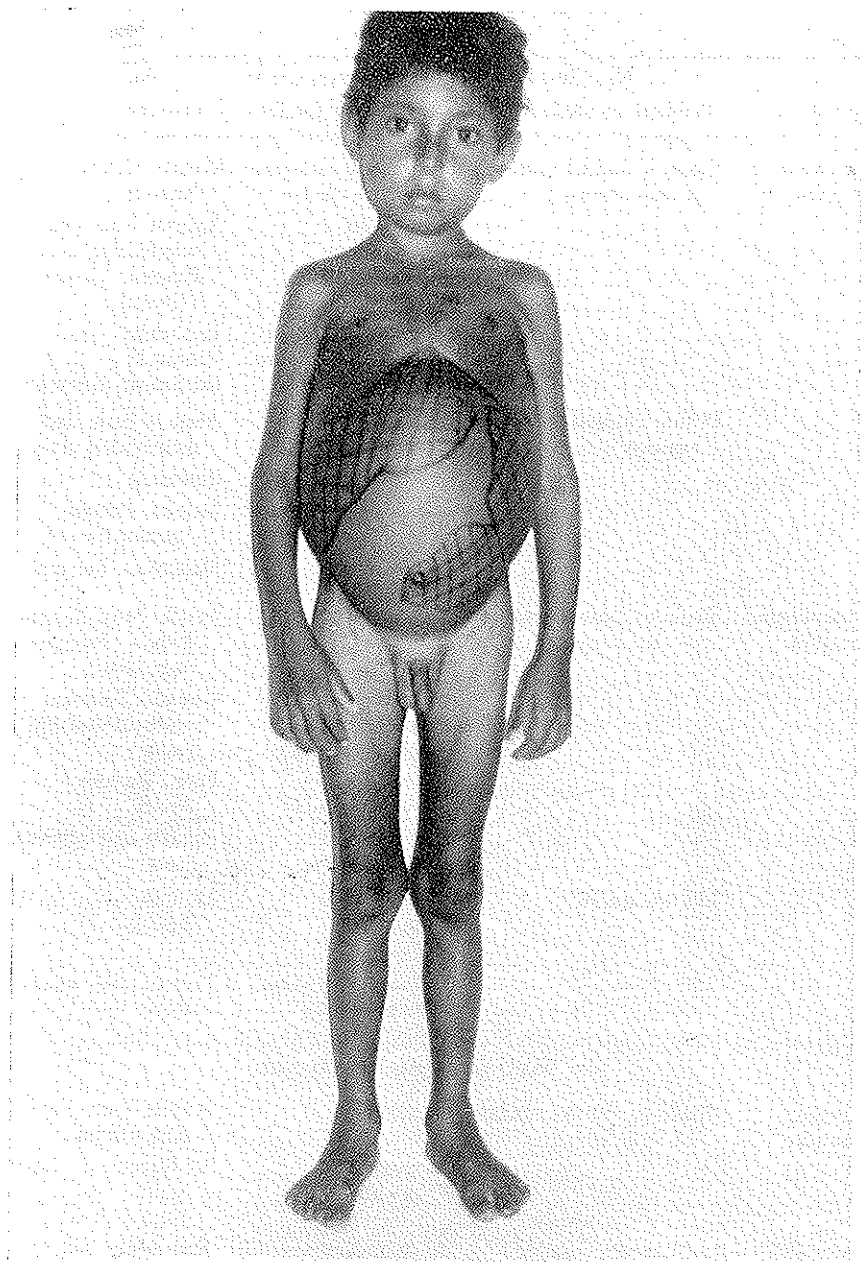
FIG. 1. Brazilian child with pronounced wasting due to *Leishmania donovani chagasi*. Marked hepatosplenomegaly is also present. (Photograph kindly provided by Dr. A.Q. de Sousa).

TABLE 1

New World Cutaneous Leishmaniasis *

Species	Clinical Syndromes	Leishmania species	Location
L. mexicana complex	Single or limited number of skin lesions	*L. mexicana mexicana* (chiclero ulcer)	Mexico, Central America
		L. mexicana amazonensis	Amazon basin and neighboring areas, Panama, Venezuela, Trinidad
		L. mexicana pifanoi	Venezuela
		L. mexicana garnhami	Venezuela
		Indeterminate	Dominican Republic
	Diffuse cutaneous leishmaniasis	*L. mexicana amazonensis*	Amazon basin and neighboring areas
		L. mexicana pifanoi	Venezuela
		L. mexicana mexicana	Mexico, Central America (rare)
		Indeterminate	Dominican Republic
L. braziliensis complex	Single or limited number of skin lesions	*L. braziliensis braziliensis*	Brazil, Peru, Ecuador, Bolivia, Paraguay, Argentina
		L. braziliensis guyanensis (pian bois, bush yaws)	Guyana, Surinam, northern Amazon basin
		L. braziliensis peruviana (uta)	Peru, Western Andes
		L. braziliensis panamensis	Panama and adjacent areas
	Mucocutaneous	*L. braziliensis braziliensis* (espundia)	Multiple areas in South America
		L. braziliensis panamensis (rare)	Panama and adjacent areas

Old World Cutaneous Leishmaniasis

Species	Clinical Syndromes	Leishmania species	Location
L. tropica complex	Single or limited number of skin lesions	*L. major*	Middle East, Central Asia, Africa
		L. tropica (oriental sore)	Mediterranean littoral, Middle East, Central Asia
		L. aethiopica	East Africa and Southwestern Africa
	Diffuse cutaneous leishmaniasis	*L. aethiopica*	East Africa and Southwestern Africa

| | Visceral leishmaniasis (kala-azar) | | |
Species	Clinical Syndromes	Leishmania species	Location
L. donovani complex	Generalized involvement of the reticuloendo-thelial system (spleen, bone marrow, liver, etc.)	L. donovani donovani	Indian subcontinent
		L. donovani infantum	Africa, China, Middle East, Mediterranean littoral, Balkans, Northwestern Iberia
		L. donovani chagasi	Widely scattered in Latin America
	Post-kala-azar dermal leishmaniasis	L. donovani donovani L. donovani infantum	Indian subcontinent Africa

* Derived from [1, 7].

vector, the organism lives as a pear- or spindle-shaped extracellular promastigote. Although the dimensions are variable, promastigotes are 10 to 15 μm in length and 1.5 to 3.5 μm in width with an anterior flagellum that ranges from 15 to 28 μm. Although minor ultrastructural differences have been described among the various *Leishmania* species, it is not possible to reliably differentiate between them in either their amastigote or promastigote stages using morphologic criteria. Initially, speciation was based on factors such as the parasites' behavior in humans, geographic distribution, epidemiological differences, involvement of specific animal reservoirs, and transmission by different species of sand-flies. More recently biochemical methods of speciation such as isoenzyme determination, analysis of kinetoplast DNA, and species-specific monoclonal antibodies have been used [1, 4-6]. Despite these sensitive and specific methods, there remains some uncertainty as to the precise taxonomic relationships among the various species and subspecies.

Sandflies of the *Lutzomyia* and *Psychodopygus* genera in the Americas and the *Phlebotomus* genus elsewhere are responsible for transmitting *Leishmania*. Sandflies tend to breed in cracks in the walls of dwellings, in rubbish, or in rubble piles. They are weak fliers, advancing in a series of small hops, and usually remain close to their breeding site. In general, a blood meal from a mammal is required by female sandflies for full development. Female sandflies ingest amastigotes when they feed on infected animals. Amastigotes then convert to promastigotes in the gut of the sandfly and parasite replication follows. After a period of time

mature promastigotes migrate to the insect's proboscis. They are inoculated into a susceptible host when the sandfly attempts to take its next blood meal. Depending on the geographic location and the *Leishmania* species, the major reservoirs of infection are rodents, wild or domestic canine species, other mammals or in some locations humans. With the exception of visceral leishmaniasis in India and under some circumstances in Africa, and anthroponotic *L. tropica* infection in urban areas of the Middle East and Asia, leishmaniasis is a zoonosis.

Visceral Leishmaniasis (kala-azar)

Members of the *Leishmania donovani* complex are responsible for visceral leishmaniasis. The disease has been termed kala-azar, dumdum fever, Assam fever, or infantile splenomegaly in various areas of the world [7]. Visceral leishmaniasis is usually characterized by a subacute or chronic course with fever, massive splenic enlargement, hepatomegaly, anemia, leukopenia, hypergammaglobulinemia, and dissemination of amastigotes throughout the reticuloendothelial system. The great majority of symptomatic cases are thought to proceed to death in the absence of treatment.

Visceral leishmaniasis occurs in widely scattered areas throughout the world. Transmission of the disease depends on: 1) an appropriate reservoir of infection; 2) a suitable vector; and 3) a susceptible human population. In South America, the Mediterranean, and China, dogs are the principal reservoirs of disease. Rats have recently been incriminated in addition to dogs in Italy [8]. In Brazil, foxes provide a wild reservoir that contributes to infection in the domestic reservoir, the dog. In East Africa, sylvatic reservoirs as well as human-to-human transmission are thought to be important. In Central Asia, wild jackals, foxes and dogs have been incriminated. Visceral leishmaniasis in India is unique in that no reservoir apart from man has been identified. In India transmission of disease is dependent on anthropophilic *Phlebotomus* species but in other regions *Leishmania* are spread by sandflies which feed on both the animal reservoir and humans. Although very rare, *L. donovani* has been transmitted by blood transfusion [9, 10] and direct person-to-person contact [11]. Congenital transmission has also been reported [12, 13]. Except for epidemics of visceral leishmaniasis that have occurred on the Indian subcontinent and on occasion in East Africa, the disease tends to be sporadic. The characteristics of susceptible human populations are variable

and incompletely understood. In East Africa, the disease is most frequent among older children and young adults, probably because they come in contact with infected sandflies as a result of occupational activities. In South America and the Mediterranean, infants and children under ten years of age are the most commonly infected. Children and young adults are the most frequently infected on the Indian subcontinent.

Susceptibility to *L. donovani* in mice is genetically determined and controlled by a single autosomal gene on chromosome 1, which has been termed *Lsh* [14]. This genetic locus is probably identical to the one which controls susceptibility to *Salmonella typhimurium* [15]. The genetic factors that determine human susceptibility to *L. donovani* have not been characterized. Greenblatt and others [16, 17] hypothesized that the *Leishmania* might use a system of camouflage or mimicry of human ABO blood group antigens to evade host defense mechanisms. However, studies in Brazil [18] and India [19] have failed to support this hypothesis.

Although not well documented, most workers in the field believe that asymptomatic infections frequently occur. Evidence for this comes from experiments in which *L. donovani* promastigotes were inoculated into human volunteers. In some, visceral dissemination occurred whereas in others localized, spontaneously healing skin lesions without dissemination were noted. In addition during a large outbreak of visceral leishmaniasis in Italy, 64% of household contacts and 40% of neighbors of patients with visceral leishmaniasis were found to have positive skin reactions to leishmanial antigens (leishmanin skin test), but remained asymptomatic [20]. Only 6% of residents of an area where *L. donovani* was not endemic were positive. Finally, the prevalence of positive leishmanin skin tests in East Africa is greater than that predicted based on the incidence of symptomatic disease [21]. Whether this is due solely or in part to asymptomatic infection with *L. donovani* or infection with *Leishmania* species that are not pathogenic for man, such as those which infect lizards, remains to be determined.

Immunology of Visceral Leishmaniasis

Although a comprehensive explanation of the immunobiology of visceral leishmaniasis is not possible, important advances have been made recently toward a better understanding of the host-parasite interaction [2]. The intracellular fate of *L. donovani* and ultimately the course of infection

appear to depend on the capacity of T lymphocytes to activate macrophages to kill the parasite [2]. Transfer of T lymphocytes from immune animals to recipient animals confers protection against infection whereas transfer of immune serum alone does not [2]. Exposure of human monocyte-derived macrophages *in vitro* to antigen- or mitrogen-elicited lymphokines or interferon-γ can effectively activate them to kill amastigotes [22]. In contrast Wyler and coworkers have noted that Lyt-1^+2^- lymphocytes, obtained from mice spontaneously healing *L. major* infections, exert antileishmanial effects *in vitro* that are genetically restricted and require direct contact of lymphocytes with leishmania-infected macrophages [23]. Experience with animal models and humans also suggests that potentially effective cell mediated immune mechanisms are suppressed during infection [2]. Delayed hypersensitivity responses in humans, as assessed by the leishmanin skin test and by *in vitro* lymphocyte blastogenic responses to leishmanial antigen [24], are absent during infection but in the majority of cases develop following successful antileishmanial chemotherapy. Paradoxically, antileishmanial antibodies are produced during visceral leishmaniasis and there is also evidence of polyclonal B lymphocyte activation to account for the observed hypergammaglobulinemia [25]. The outcome of infection appears to depend on a complex interplay between helper and suppressor mononuclear cell populations. The exact nature of the suppressor cell population(s) and the role of other factors such as circulating immune complexes [26, 27] in mediating immune suppression remain to be determined.

Relationship of Undernutrition to Development of Symptomatic Visceral Leishmaniasis

Visceral leishmaniasis is found in areas of the world where undernutrition is common, and protein-calorie malnutrition is a well known cause of secondary immunodeficiency [28]. The most severe impact of malnutrition appears to be on cell mediated immunity although humoral immunity and phagocytic function are also affected. Since control of visceral leishmaniasis is dependent on cell mediated immune responses, Harrison, Alencar, Naidu, and Pearson hypothesized [29] that undernutrition might be associated with the development of clinical visceral leishmaniasis. To test this hypothesis, they studied the relationship between undernutrition and visceral leishmaniasis in an area endemic for *L. d. chagasi* in northeastern Brazil. Mid-arm anthropometry was

used to assess nutritional status in nine patients with visceral leishmaniasis, 59 patient-housemates, and 55 randomly chosen neighborhood controls [29].

The fat areas of patient-housemates and neighborhood controls were 71% and 86% respectively those of age- and sex-matched American standards, whereas the muscle areas were 74% and 72%, respectively, of the American standards. When patient-housemates were age- and sex-matched with randomly selected neighborhood controls, the housemates had 22% less fat area (p < 0.05) than their paired neighborhood controls. This difference could not be attributed to occult visceral leishmaniasis among patient-housemates nor to an age bias in the matching procedure [29]. There was no difference in mean muscle area between housemates and controls. If one assumes that the premorbid nutritional status of patients is accurately estimated by the nutritional status of their housemates, these data suggest an association between undernutrition and development of clinically apparent visceral leishmaniasis.

Since household size might correlate with the nutritional status of individual members when food is limited in supply as it is in that area of northeastern Brazil, Harrison *et al.* compared the size of patient-households with control households. Patients came from households with a mean of 9.6 ± 1.1 members, significantly larger than the control households in which the mean was 6.8 ± 0.7 members (p < 0.05). Thus large family size as well as decreased fat area correlated with development of clinically apparent visceral leishmaniasis. Further studies are warranted to determine if there is a causal relationship between malnutrition, development of immunosuppression, and onset of visceral leishmaniasis.

Clinical Manifestations of Visceral Leishmaniasis

The clinical features of visceral leishmaniasis seem to be similar throughout the world [1, 30, 31]. The incubation period is generally in the range of three to eight months, but it may be shorter. The onset of symptoms is usually, but not always, gradual. For example, the mean duration of symptoms prior to diagnosis in children in northeastern Brazil was 3.1 months, but in some cases, it was as short as one week [31]. In subacute or chronic cases, victims experience fever, onset of vague abdominal discomfort, abdominal enlargement, pallor, weakness, loss of appetite, and progressive loss of weight (Table 2). Fever may be intermittent, remittent with twice daily temperature spikes, or less commonly, continuous. It is relatively well tolerated. In acute cases there may be

TABLE 2 - *Symptoms and Findings in Patients with American Visceral Leishmaniasis at Presentation.*

Sign or Symptom	Patients with complaint/total patients *
Fever	29/29 (100)
Lethargy	28/28 (100)
Pallor	27/28 (96)
Weight Loss	25/26 (96)
Spleen palpable	27/29 (93)
≥ 4 cm below left costal margin	25/29 (86)
≥ 7 cm below left costal margin	17/29 (59)
Anorexia	23/25 (92)
Abdominal enlargement	26/29 (90)
Anemia (Hct ≤ 30%)	26/29 (90)
Thrombocytopenia (platelet ≤ 100,000/mm³)	21/27 (78)
Leukopenia (WBC ≤ 4000/mm³)	22/29 (76)
Liver ≤ 2 cm below right costal margin	22/29 (76)
Albumin/Globulin ratio ≤ 1.0	15/25 (60)
Edema	9/28 (32)
Bleeding episodes	6/29 (21)
Jaundice	5/28 (17)

* Percentage of patients is in parentheses [31].

an abrupt onset of high fever and chills with a periodicity that suggests malaria.

As time passes, progressive enlargement of spleen and liver, anemia and profound cachexia are observed. The spleen often becomes enormous; it is usually soft and non-tender. The presence of a hard spleen suggests a hematologic disorder or another infection such as schistosomiasis The liver is also enlarged and has a soft consistency with a smooth surface. In rare instances localized lymphadenopathy has been the only clinical abnormality. The skin becomes dry, thin, and scaley. In light colored patients in India the skin of the hands, feet, abdomen and face may become grayish. This discoloration gave rise to the Indian name "kala-azar" which means black fever. Peripheral edema develops late in the disease. Hemorrhage may occur from one or multiple sites; epistaxis and gingival bleeding are the most common. Petechiae and ecchymoses are occasionally seen on the extremities. Death in visceral leishmaniasis is often due to bacterial secondary infections including pneumonia, septicemia, concurrent tuber-

culosis, dysentery, measles, or uncontrolled hemorrhage or severe anemia with its sequelae. Post-kala-azar dermal leishmaniasis follows treatment of visceral leishmaniasis in an estimated 3% of cases in Africa and up to 20% in India [32, 33].

The diagnosis of visceral leishmaniasis is documented by demonstrating amastigotes in tissue or isolating the organism in culture. Various serological methods are available to detect antibody, but these are not specific. The leishmanin skin test (Montenegro test) is negative during active visceral leishmaniasis because of the antigen-specific immunosuppression that accompanies disease [2]. In most areas the mortality rate with pentavalent antimonial therapy is thought to be in the range of three to five percent, but higher mortality rates have been reported. Relapses and occasional failures with pentavalent antimony therapy are not uncommon.

The Effects of Visceral Leishmaniasis on Nutrition

For many years physicians have observed marked wasting in patients with visceral leishmaniasis. In order to better characterize this, Harrison et al. [29] compared the nutritional status of nine patients with documented visceral leishmaniasis in northeastern Brazil to age- and sex-matched housemates or neighborhood controls [29]. Patients who had been treated less than four months prior to evaluation had 66% ($p < 0.05$) and 41% ($p < 0.01$) of the fat areas of their age- and sex-matched housemates or neighborhood controls, respectively, and 81% ($p < 0.05$) and 75% ($p < 0.05$) of the muscle areas of their age- and sex-matched housemates or neighborhood controls, respectively. Patients who had been treated twelve to twenty months before evaluation of their nutritional status did not have significantly different fat or muscle areas in comparison to either housemates or neighborhood controls. These data demonstrate that visceral leishmaniasis can have a significant effect on nutritional status resulting in depletion of both fat and muscle, but that nutritional status returns to normal after successful therapy.

Recent investigations indicate that acute infection or injury is associated with production of various factors by macrophages which can mediate catabolic processes. Interleukin 1 (IL-1), also known as endogenous pyrogen, has been shown to be responsible for accelerated proteolysis during acute infections and possibly for the anorexia which accompanies them [34-39]. It is now accepted that IL-1 is produced

by circulating blood and tissue mononuclear phagocytes as well as a number of other cell types. Production is known to be stimulated by viruses, bacteria, lipopolysaccharide endotoxin, bacterial exotoxins and immune complexes.

Recent studies have illustrated how acute infection can result in increased proteolysis [37-39]. Injection of endotoxin from *E. coli* into rats resulted in increased protein degradation of skeletal muscle and was associated with increased levels of prostaglandin E_2 (PGE$_2$). Highly purified IL-1 incubated with rat muscle *in vitro* also stimulated both PGE$_2$ production and protein degradation which was inhibitable by indomethacin [39]. Although IL-1 production by *Leishmania*-infected monocytes has not been documented, the presence of fever and acute phase proteins during visceral leishmaniasis provides circumstantial evidence for the production of IL-1. Recent data indicate that *L. major* infection of human monocytes *in vitro* does not result in production of IL-1 [40]. Further studies are needed to determine whether IL-1 is produced during visceral leishmaniasis and if so, whether IL-1 production is due directly to *L. donovani* infection of macrophages, to immune complexes, which are prelevant during disease, or to some other mechanism.

Gallin and coworkers [41] observed several years ago that acute infection can affect lipid metabolism. Cerami and his coworkers [42-47] have subsequently shown that macrophage products other than IL-1 have profound effects on lipid metabolism. Mouse peritoneal macrophages treated with lipopolysaccharide endotoxin produce a heat-labile mediator that can suppress serum lipoprotein lipase activity by greater than 90% [42-45] preventing uptake and storage of triglycerides. The same mediator has been found to inhibit the activity of fat-producing (lipogenic) enzymes involved in *de novo* fatty acid synthesis *in vitro* [45] by specifically and reversibly inhibiting expression of the corresponding genes [46]. This mediator has been termed cachectin and has recently been shown to be indistinguishable from tumor necrosis factor [46, 47]. The loss of fat stores during visceral leishmaniasis may be due to cachectin, anorexia and/ or some other mechanism(s). Future investigations should provide insight into the intriguing but complex relationship between visceral leishmaniasis and the nutritional status of the patient.

Treatment of Visceral Leishmaniasis

Pentavalent antimonial compounds remain the drugs of choice for the therapy of visceral leishmaniasis. Stibogluconate sodium (Pentostam) is available in the United States (Parasitic Diseases Drug Service, CDC) and used throughout the Old World and meglumine antimonate (Glucantime) is used in francophone and Latin American countries. They are chemically similar and appear to have comparable toxicity and efficacy. Meglumine antimonate solution contains approximately 8.5 percent pentavalent antimony (Sb^v); sodium stibogluconate contains about 10 percent Sb^v. It is recommended that the drug dosage be based on the antimony content of the compound. Both compounds are available for intramuscular and intravenous administration.

Comparative studies to determine the optimal dosage and duration of therapy for visceral leishmaniasis have not been performed in areas other than East Africa. The dosage of pentavalent antimony recommended by the World Health Organization is 20 mg of Sb^v/kg body weight daily, to a maximum of 850 mg per day, for a minimum of 20 days [48]. Pentamidine and amphotericin B are alternative drugs for patients who fail to respond to one or more courses of pentavalent antimony. Allopurinol and related pyrazolopyrimidines have been used successfully in some patients, but experience is insufficient to justify their widespread use until controlled experimental trials have been completed.

Cutaneous Leishmaniasis of the Old World

The classic form of cutaneous leishmaniasis is the "oriental sore" caused by members of the L. tropica complex [1, 30]. It occurs throughout tropical and subtropical regions of Asia Minor, China, the Mediterranean, India and in Africa in Sudan, Ethiopia, and the Congo basin. In general, oriental sores are troublesome and unsightly, but they are not a threat to life.

Epidemiology

Members of the L. tropica complex are transmitted to humans by sandflies of the genus Phlebotomus. The disease occurs in three clinical forms; each is produced by a different subspecies. The rural form is due to L. major which infects desert rodents, primarily gerbils. Humans become infected in sparsely inhabited areas or in villages on the edge of

desert areas of Central Asia, North Africa, and the Middle East. The urban form of cutaneous leishmaniasis is caused by *L. tropica* and involves dogs and humans in cities of the Middle East such as Baghdad, Teheran, and Damascus as well as cities in the Mediterranean, India and Pakistan. In cutaneous leishmaniasis due to *L. aethiopica*, which is found in Ethiopia, Kenya and South West Africa, the primary reservoirs are species of hyrax while rodents seem to constitute a secondary reservoir. In general, cutaneous leishmaniasis is a sporadic disease in endemic areas but occasionally presents an epidemic pattern, particularly when susceptible people are exposed during road construction, military maneuvers, agricultural work or refugee movements.

Clinical Manifestations

The incubation period of Old World cutaneous leishmaniasis varies from two weeks to several months and in sporadic cases has been as long as three years. The local lesion starts as a papule at the site where promastigotes are inoculated by the sandfly. The papule gradually enlarges, becomes crusted and finally ulcerates. The ulcer is usually shallow and circular with well defined, raised borders and a bed of granulation tissue. It progressively increases in size reaching a diameter of two centimeters or more. Satellite lesions which fuse with the original ulcer may be present. There is frequently a serous discharge. The manifestations of disease are quite variable. In the urban, or dry form, lesions tend to be single, grow slowly and last for a year or more, whereas in the rural or moist form lesions may be multiple, progress more rapidly and heal after several months. Ulcers may be accompanied by regional lymphadenopathy. Secondary bacterial or fungal infections at the site of the ulcer are not uncommon. After a variable period of time ranging from several months to longer than a year, the ulcer heals leaving a flat, atrophic scar.

There are two uncommon variations of cutaneous leishmaniasis. In diffuse cutaneous leishmaniasis the disease starts as a local papule which does not ulcerate. Satellite lesions develop around the initial papule and the organism subsequently disseminates throughout the skin, often to the face and extremities. The disease progresses slowly and persists for 20 years or more. The leishmanin skin test is negative indicating antigen-specific immunosuppression. Another variant is leishmaniasis recidiva, a relapsing, tuberculoid form of cutaneous disease. It is not uncommon in Iran. Lesions are often on the face and spread outward with healing at the

center. Mucous membranes may be involved with concomitant nasal destruction. Leishmaniasis recidiva is a chronic disease lasting 20 to 40 years. In contrast to diffuse cutaneous leishmaniasis, the leishmanin skin test is positive and few if any amastigotes can be identified in material from the lesions.

A definite diagnosis of *L. tropica* complex infection depends on identification of amastigotes in stained smears or scrapings from the base of the ulcer or from biopsies of its border.

Immunology of Cutaneous Leishmaniasis

In some respects the clinical spectrum of cutaneous leishmaniasis is similar to that of leprosy [49, 50]. At one end of the spectrum lies diffuse cutaneous leishmaniasis in which there is little evidence of effective cell-mediated immunity. Heavily parasitized macrophages are abundant throughout the dermis, and few lymphocytes are present. Cutaneous delayed hypersensitivity reactions to leishmanial antigen are absent. It has been hypothesized that this is due simply to poor host resistance, but it is likely that parasite factors also play a role. The histology of diffuse cutaneous leishmaniasis is somewhat analogous to that of lepromatous leprosy in which there is massive bacterial infection of macrophages and little evidence of cell-mediated immune responses. At the other extreme lies leishmaniasis recidiva in which parasites are sparse and a mononuclear cell infiltrate predominates. This is somewhat analogous to tuberculoid leprosy in which there is an intense mononuclear infiltrate with few bacteria. However, whereas the character and organization of the granuloma in leprosy are invariably characteristic of its position in the clinical spectrum, this is not true in cutaneous leishmaniasis. When amastigotes are numerous, the cell type is nearly always the macrophage, but when amastigotes are scanty, the character of the granuloma, that is the composition of the mononuclear response and its organization, is not predictive of the clinical status in contrast to leprosy [51].

Although no data are available about the genetic control of susceptibility of humans to *L. major* infection, resistance in mice is under control of autosomal genes, which are different from the *Lsh* gene (responsible for resistance to *L. donovani*), and not involved in the H-2 complex. BALB/c mice, which are susceptible to *L. major*, have progressive local disease followed by widespread dissemination and death, whereas C57BL mice, which are considered resistant, can be infected but display localized,

self-healing ulcers [52]. BALB/c mice in certain ways resemble patients with visceral leishmaniasis. The susceptibility of BALB/c mice to *L. tropica* appears to be due to induction of a suppressor T-cell population(s), which contributes to the chronicity of infection and inhibits healing of lesions [53].

The best evidence for immune suppression in human leishmaniasis comes from patients from the Dominican Republic with diffuse cutaneous leishmaniasis [54] due to a *Leishmania* species which is thought to be a member of the *L. mexicana complex.* Of those patients who were studied extensively, none had delayed cutaneous hypersensitivity reactions or lymphocyte proliferative responses to leishmanial antigens. Relatives of these parents living in the same endemic area frequently showed skin test and lymphocyte reactivity to leishmanial antigens [55]. In studies of peripheral blood mononuclear cells from patients, decreasing the number of glass-adherent mononuclear cells or the addition of the prostaglandin inhibitor, indomethacin, permitted expression of lymphocyte responses to leishmanial antigens *in vitro* thereby suggesting the presence of a population of suppressor mononuclear phagocytes. Co-cultivation of lymphocytes and monocytes from HLA-identical leishmanin responders and nonresponders also identified the suppressor cells as monocytes [55]. In contrast to those patients with diffuse cutaneous leishmaniasis, patients with localized cutaneous lesions which heal spontaneously develop delayed cutaneous hypersensitivity and blastogenic responses to leishmanial antigen [56]. Animal studies have also provided important insight into the complex interaction between helper and suppressor activities during cutaneous leishmaniasis [2]. Further discussion of the immunology of leishmaniasis as it relates to vaccine development can be found elsewhere (see "Strategies for control of visceral, cutaneous and mucocutaneous leishmaniases").

Relation to Nutrition

Little is known about the effect of malnutrition on susceptibility of humans to members of the *L. tropica* complex. The fact that the disease is encountered in presumably well-nourished army troops as well as American workers in the Middle East would indicate that malnutrition is not necessarily a predisposing factor for development of cutaneous ulcers. Whether or not the duration and extent of ulceration is affected by nutritional status has not yet been assessed. Likewise there is no evidence

to suggest that the *L. tropica* complex causes wasting. The presence of massive parasite burdens which persist for many years in patients with diffuse cutaneous leishmaniasis would suggest that the *L. tropica* complex does not have pronounced effects on nutritional status. Likewise the finding of Crawford *et al.* [40] that *L. major* fails to elicit production of IL-1 when human monocytes are infected *in vitro* is in keeping with the lack of fever in patients with Old World cutaneous leishmaniasis.

Treatment of Old World Cutaneous Leishmaniasis

The decision to treat cutaneous leishmaniasis depends on the location and extent of the lesion(s). Early, non-inflamed nodular lesions have been treated with intralesional injections of an antimonial compound or intralesional mepacrine [48]. Large or disfiguring ulcers usually are treated with a pentavalent antimonial; 10 to 20 mg Sb^v/kg body weight per day (maximum dose, 850 mg Sb^v per day) until clinical and parasitological cure are achieved, and for a few additional days. In contrast, cutaneous lesions due to *Leishmania aethiopica* often fail to respond to that dosage. Pentamidine isethionate 4 mg/kg body weight once or twice weekly until resolution is complete, or high dosage sodium stibogluconate, 20 mg/kg twice daily for 30 days, may be effective [48], but are often toxic (see "Strategies for control of visceral, cutaneous and mucocutaneous leishmaniases").

A variety of other drugs have been used to treat Old World cutaneous leishmaniasis, but because experience with them is still limited, they are not recommended for routine treatment. Cryosurgery and the application of carbon dioxide snow (dry ice) also have been reported to be effective in some cases.

New World Cutaneous Leishmaniasis

American cutaneous leishmaniasis is widespread in South and Central America, where it constitutes a major public health problem [2, 30]. The spectrum of disease ranges from single, localized cutaneous ulcers to mucocutaneous disease (espundia), which is the only form associated with mortality. In the latter disorder there may be extensive involvement of the nose, oral cavity and pharynx with tissue destruction and mutilation. Prevention of the late sequelae of mucocutaneous leishmaniasis is thought

to be possible if appropriate therapy is administered during the initial cutaneous stage of disease.

The causative agents of new world cutaneous leishmaniasis belong to the *L. braziliensis* complex and the *L. mexicana* complex. They produce different syndromes in multiple geographic areas throughout Central and South America. The species can not be differentiated on morphologic grounds but can be by species-specific monoclonal antibodies, kinetoplast DNA hybridization or isoenzyme determination [6].

Clinical Manifestations

Cutaneous Leishmaniasis. A wide variety of skin lesions are seen in American cutaneous leishmaniasis ranging from small, dry, crusted lesions to large, deep, mutilating ulcers [2, 30]. There may be a single lesion or multiple lesions located on exposed areas of the body. Lesions with different characteristics may be seen on the same patient and lesions produced by one *L. braziliensis* or *L. mexicana* species may produce different types of lesions in different people.

In localized cutaneous disease, the initial lesion usually appears two to eight weeks after the sandfly bite as a small papule. It progresses slowly to form a typical ulcer with rounded, raised borders and a granulating base, which is covered by an exudate. The ulcer may persist for months to years, but eventually heals leaving a flat, atrophic scar. Occasionally a large vegetation projects from the skin at the site stimulating a neoplasm. Rarely lesions assume a keloidal form or involve local lymphatics producing a chain of nodules which mimics lymphatic sporotrichosis.

Diffuse cutaneous leishmaniasis, which is rare, is caused by members of the *L. mexicana* complex. In this condition, there is no cutaneous ulceration but wide dissemination of amastigotes throughout the skin. The disease runs a protracted course. This is an anergic variant of cutaneous leishmaniasis and the leishmanin skin test is negative.

Mucocutaneous Leishmaniasis

In a small percentage of patients with *L. braziliensis* complex infection, amastigotes persist after disappearance of the primary ulcer and later reappear to produce mutilating mucosal lesions of the face and head. The time between healing of primary lesions and mucosal involvement is usually several years, but may be as short as one month or as

long as 24 years [57, 58]. The early signs are usually those of nasal obstruction. The process starts in the nasal septum as a slight swelling and reddening of the mucosa and progresses slowly to perforation of the septum, collapse of the nasal cartilage, and in some cases perforation through the skin of the nose or through the soft palate. The upper lip as well as tongue are frequently involved. Involvement of the trachea as well as the genital mucosa occurs, but that is very rare [59, 60]. Aspiration pneumonia is a common complication in advanced stages of mucocutaneous disease and can result in death.

Diagnosis

The diagnosis of American cutaneous leishmaniasis is based on the identification of amastigotes in tissue, isolation of the parasite in axenic culture or in hamsters, or indirect immunologic evidence in the appropriate clinical setting. Unfortunately, *L. braziliensis* grows poorly in culture and bacterial or fungal colonization of the ulcer often results in contamination. For these reasons and because amastigotes are scanty and may not be visualized in mucocutaneous lesions, a diagnosis of mucocutaneous leishmaniasis is often made on the basis of the clinical findings and a positive leishmanin skin test or the presence of antileishmanial antibodies in serum.

Relation to Nutritional Status

As in the case of cutaneous leishmaniasis, little attention has been paid to the interrelationships between malnutrition and the acquisition of American cutaneous and mucocutaneous leishmaniasis. In many instances cutaneous disease is acquired by well-nourished adults working in or traveling through endemic areas. Malnutrition is not a prerequisite for the acquisition of clinical disease. In an experimental model of cutaneous leishmaniasis due to *L. mexicana* in mice, protein restriction resulted in increased ulcer size and duration [61, 62]. Whether or not undernutrition affects the eventual size or duration of lesions in humans has not been determined. Conversely, the effects of American cutaneous leishmaniasis on nutritional status have not been assessed. With cutaneous lesions, it is unlikely that there is a major effect. In patients with advanced mucocutaneous disease and involvement of the soft palate, tongue or oral pharynx, mechanical factors can adversely influence food intake [63].

Treatment of New World Cutaneous Leishmaniasis

The decision to treat cutaneous leishmaniasis depends on the location and extent of the lesion(s) and the infecting *Leishmania* species. Small, inconspicuous lesions acquired in areas where mucocutaneous disease does not occur may be followed without therapy. Large or disfiguring ulcers usually are treated with a pentavalent antimonial; 10 to 20 mg Sb^v/kg body weight per day (maximum dose, 850 mg Sb^v per day) until clinical and parasitological cure are achieved and for a few additional days. A variety of other drugs have been used to treat American cutaneous leishmaniasis, but experience is too limited to recommend them for routine therapy. Cryosurgery and the application of dry ice also have been reported to be effective in some cases. Finally, patients with isolated cutaneous lesions or diffuse cutaneous leishmaniasis acquired in the Dominican Republic have been successfully treated with topically applied heat [64].

There is general agreement that patients living in New World geographic areas where mucocutaneous disease is prevalent should be treated even if they have only cutaneous lesions. One recommended regimen for American cutaneous disease is 10 to 20 mg of Sb^v/kg (maximum dose, 850 mg) per day until the lesion is healed, and for some days longer, for a minimum total period of three weeks [48]. Response to treatment should be monitored clinically and parasitologically. In successfully treated patients, antibody titres measured by indirect immunofluorescent assay steadily decline over four to five months and often disappear after one to two years.

Once mucosal disease has developed, 20 mg of Sb^v/kg body weight (maximum dose, 850 mg) per day is given until clinical and parasitological cure and for a little longer, for a minimum period of four weeks. Unfortunately, in some regions of South America, relapse after apparent cure has been reported to be as high as 50% within one year of treatment. Patients who relapse have been successfully treated with repeated or longer courses of antinomy or with amphotericin B. Plastic surgery may be necessary to ameliorate the sequelae of mucocutaneous leishmaniasis, but it should not be performed earlier than one year after chemotherapy because the graft may be lost if relapse occurs.

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CRYPTOSPORIDIUM DIARRHEA
IN COSTA RICAN CHILDREN

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INTRODUCTION

Coccidian parasites of the genus *Cryptosporidium* cause acute diarrhea in many vertebrates, including man. Recent reviews on the subject [1-5] were stimulated by demonstration of a chronic, debilitating and generally fatal diarrhea in immunodeficient and immunosuppressed individuals, and in persons with acquired immunodeficiency syndrome (AIDS) [6-16]. Additional interest arose after finding that cryptosporidiosis is not rare among immunocompetent or otherwise healthy children and adults, who suffer from acute diarrheal disease in industrialized and less developed countries [17, 18].

The first *Cryptosporidium* species (*C. muris*) was described by Tyzzer in 1907 [19], who found the parasite in gastric glands of the domestic mouse. Tyzzer described oocysts measuring 5-6×7 µm, with 4 sporozoites of about 12-14 µm after excystation [19, 20]. He attempted transmission of the coccidium to the white rat, without success. Later, Tyzzer described another species, *C. parvum,* with considerably smaller oocysts measuring 3.0-3.3 × 4.0-4.5 µm; excisted sporozoites measured 5.5-6.0 µm [21]. This species was found in the small intestine of the laboratory mouse, rabbit and chicken [33]. *Cryptosporidium* is currently placed in Api-

complexa, Sporozoea, Coccidia, Eucoccidiida, Eimeriina, and Cryptospori-
diidae [22].

Many years after description of these species, additional "species"
were named according to the vertebrate hosts in which they were found
[22]. Most authors regard these species unjustified for several reasons.
Oocysts found in different vertebrates are of similar size and morphology
as those of *C. parvum* [23]. Infection and cross-infection occurs with
oocysts of *C. parvum*-like strains in several vertebrate species and in man.
Antibodies to one particular strain of *Cryptosporidium* have been detected
in sera from diverse vertebrate hosts [24]. On the basis of this infor-
mation, one single species was proposed [24], in analogy with *Toxo-
plasma*, although one expert proposed one species for each of the four
groups of vertebrates harboring parasites [25].

Cryptosporidium parasites attach to the surface of human intestinal
epithelial cells of jejunum, ileum and colon [26-27]. Cells of other
epithelia may also be infected, for instance, respiratory tract and gall
bladder, of immunodeficient individuals [28-30]. Infection in immuno-
deficient or immunosuppressed persons is characterized by acute watery
diarrhea which may evolve into a chronic, emaciating and often fatal
disease [9-11]. The parasite causes serious complications in immuno-
suppressed patients or in persons with terminal degenerative disease.
Finally, *Cryptosporidium* induces a serious and lethal disease in a consider-
able proportion of patients with AIDS [13-16].

In immunocompetent individuals, cryptosporidiosis is a self-limited
acute watery diarrhea of short duration, without serious epithelial damage
or involvement of organs other than the intestine [17, 18]. The first
case in an immunocompetent individual was described in 1976 [31].
Years later, the parasite was found in an important proportion of immuno-
competent children presenting diarrhea in Australia [17] and Costa
Rica [18]. The parasite has been found in humans in Rwanda, Bangla-
desh, Venezuela, Brazil, Peru and Liberia [see 5, 32-34]. Industrial
nations reporting the parasite, in addition to Australia, are Finland, Canada,
the United States and the United Kingdom [5].

Cryptosporidium is highly pathogenic for man and most infections
are clinical. In fact, the number of carriers is small or negligible [5, 18,
35]. Infection in children and adults occurs readily by exposure to a
contaminated source, as judged from observation in the community and
accidental infections of personnel handling domestic animals [1-5]. Cryp-

tosporidiosis is less common in breast-fed than in weaned infants [18]. Infants and preschool children are more easily infected than adults [5, 18].

Cryptosporidium diarrhea in Costa Rica (located 10 degrees North of the Equator) occurs almost exclusively during the rainy season, from April through September [18, 35], a warm and humid period. The same seems to be the case in Bangladesh, where infections are more common during the rainy months, about the same time of the year [32]. The reports from Australia and Venezuela showed a high rate of *Cryptosporidium* during the warm months [17, 34]. No seasonal information is available for countries that have uniform temperature throughout the year.

The present report summarizes four years of observation of preschool children with acute diarrhea in Costa Rica. Most children were studied at the National Children's Hospital, the main child referral center, in San Jose, the capital city. Other children were studied at the Field Station of INISA, in Puriscal, a rural region in the Southern Intermountain Valley. The Field Station serves as a base for prospective field studies of mothers and children.

METHOD OF PROCEDURE

Populations. The urban and rural populations studied live at an average altitude of 1000 meters above sea level, and are of comparable ethnic background, predominantly Spanish, with varying mixtures of Amerindian and to a lesser extent, Black. The urban population was the largest, and consisted of children with acute diarrhea, who were brought to the outpatient and emergency services of the National Children's Hospital, from the metropolitan area. This encompasses the capital city, the neighboring city of Heredia and dozens of small towns (cantons and districts). The population belongs to the middle and low socioeconomic strata, and has an adequate level of health and education. All children studied were less than two years of age.

The rural population was from the districts and villages of the Puriscal region, of similar demographic, socioeconomic and education characteristics as the urban population. Children under three years of age were included, the great majority under two years. During the study period, Costa Rica had an average infant mortality of 19 per 1000, a diarrheal disease death rate of 6 per 100,000 and a life expectancy at

birth of 75 years. Medical care and preventive health services are free and widely available throughout the country [36].

A slightly lower income in the rural area is compensated by a lesser cost of food and lesser need for expensive clothing and housing. In the urban area, the rate of not breast-fed infants is larger (15%) than in the rural area (8%). Also, the rate of premature weaning is greater and the introduction of weaning foods earlier in the urban area than in Puriscal. The highest incidence and duration of breast-feeding in the rural population can be accounted for by several factors, the most prominent ones being induction in hospitals, and support to mothers early in lactation by the rural health service [37].

Clinical information. Urban children with diarrhea were included at random in the hospital, each morning, five days per week. In the rural area, all children known to have diarrhea were also included as part of a prospective study of mothers and children [37]. All children were examined by a physician, and data on clinical condition, nutritional status and other variables were collected in precoded forms. Rectal temperature was measured daily. Mothers or attendants accompanied children in the outpatient service. When severe cases required internment in the emergency service, mothers stayed with their children until recovery. Breast-feeding was encouraged to avoid interruption during illness and treatment. In weaned children, foods were withheld for a few hours, two to six, as clinical condition (anorexia, vomiting, etc.) allowed. Body weight and length were collected upon admission; post-rehydration weight was used to help estimate the degree of dehydration upon admission. Patients received oral rehydration solution by mouth whenever possible [38]; other routes were used when required. Participation in the study and collection of samples was by informed consent of the parent or guardian.

Laboratory studies. One fecal specimen was collected from each child, in sterile containers; smears were prepared at the bedside and were immediately fixed in methanol. During the first year of study [18], search for *Cryptosporidium* oocysts was after staining with slow Giemsa. All specimens of the first year were reexamined with the modified cold Ziehl-Neelsen staining (Kinyoun) [39]; results were identical as those with Giemsa [35]. Since the modified cold Kinyoun is simple and permits an easier and more rapid diagnosis of *Cryptosporidium* oocysts than Giemsa,

it was adopted thereafter. Smears were examined for oocysts with low and high power light microscopy, and oocysts were confirmed under immersion oil. All data in this report are based on acid-fast-stained specimens.

RESULTS

Frequency of Cryptosporidium infection. Fifteen hundred and fifteen children with acute diarrheal disease, all under three years of age, were studied from 1982 through 1985, Table 1. Of these, 1235 were from the urban area and 280 from Puriscal. A total 248 children without diarrhea, of comparable age and socioeconomic condition, were included in the study as controls. Of these, 159 were studied at the hospital for other reasons, and 89 were from the rural area. Since there was certain incompleteness of the data for some variables, different totals will necessarily appear in the following tables.

The overall frequency of *Cryptosporidium* oocysts in both populations was 4.9%, slightly more in urban (5.3%) than in rural children, Table 1. None of the controls were found shedding oocysts, despite the fact that

TABLE 1 - *Frequency of Cryptosporidium oocysts in stools of preschool children with and without diarrhea, Costa Rica, 1982-1985.*

Age, months	Rural *			Urban			Total		
	With		Without **	With		Without **	With		Without **
	No.	+(%)		No.	+(%)		No.	+(%)	
0-5	60	0	21	521	26(5.0)	79	581	26(4.5)	100
6-11	63	0	19	413	22(5.3)	51	476	22(4.6)	70
12-17	61	3(4.9)	22	221	13(5.9)	21	282	16(5.7)	43
18-23	54	4(7.4)	19	68	3(4.4)	7	122	7(5.7)	26
24-29	18	1(5.6)	6	12	1(8.3)	1	30	2(6.7)	7
30-35	24	2(8.3)	2	0	0	n.c.	24	2(8.3)	2
Total	280	10(3.6)	89	1235	65(5.3)	159	1515	75(4.9)	248

* Only 1982-1984.
** All controls were negative for oocysts.
n.c. No cases studied.

they were from the same populations and had been included at random throughout the study period, as were the cases. *Cryptosporidium* oocysts appeared as oval-shaped structures of strikingly homogeneous morphology, measuring, in Giemsa-stained preparations, 4.1×5 µm (Mean) with 0.5×0.4 µm (S.D.), as described previously [18]. Oocysts had a morphology and dimensions compatible with those described by Tyzzer for *C. parvum* [21]. An occasional specimen was found harboring a few larger oocysts (like *C. muris*) and was disregarded for this analysis. One case had only large oocysts and was also not included. These specimens will be eventually reexamined to determine if they are compatible with *C. muris.*

Age distribution. The age distribution of the coccidium varied between urban and rural children. Urban children had similar rates of excretion of oocysts in all six-month age periods, Table 1. Rural children under one year were virtually free of infection; later, the frequency rate was similar for each six-month period, Table 1.

Breast-feeding and infection. More than 90% of all Puriscal infants are breast-fed from the time of birth [37]. Weaning in this rural area begins between two and five months, but more than 50% of infants remain at the breast at age nine months. No *Cryptosporidium* diarrheas were recorded during infancy in the rural population. Shedding of oocysts by urban infants was not uncommon, and infections were detected since the first three months of life, especially among weaned infants, Table 2.

TABLE 2 - *Diarrhea associated with Cryptosporidium according to feeding regime at the time of examination, National Children's Hospital, Costa Rica, 1983-1985.*

Age, months	Number of children	Breast-fed		Weaned	
		No.	+(%)	No.	+(%)
0-2	214	89	2(2.2)	125	2 (1.6)
3-5	250	50	0	200	22(11.0)
6-8	189	37	0	152	8 (5.3)
9-11	161	31	0	130	6 (4.6)
12-23	282	39	0	243	16 (6.6)
Total	1096	246	2(0.8)	850	54 (6.3)

TABLE 3 - *Frequency (%) of Cryptosporidium oocysts by month, preschool children, Costa Rica, 1982-1985.*

Month	With diarrhea		Without diarrhea
	No.	+(%)	No.
January	151	0	18
February	167	4 (2.4)	21
March	128	5 (3.9)	29
April	127	11 (8.7)	19
May	176	10 (5.7)	15
June	94	19(20.2)	18
July	165	16 (9.7)	11
August	131	9 (6.9)	15
September	154	8 (5.2)	21
October	152	4 (2.6)	35
November *	96	0	6
December *	98	0	9
Total	1639	86 (5.2)	217

* Data for the period 1982-1984 only.

Only two breast-fed infants less than three months old were found excreting oocysts, for an overall prevalence of 0.8%. Cryptosporidiosis was common in weaned children, particularly after three months of age, and showed a high value of 11% in the second trimester of life; the overall frequency for weaned children was 6.3%.

Seasonal distribution. Cryptosporidiosis has a marked seasonal distribution in the Costa Rican populations studied. Table 3 shows cumulative monthly data for the four-year study period. Numbers are greater than in Table 1 because the month of occurrence of infection was available for all cases, while others were incomplete. No cases were found in January, November and December. These months are generally dryer and slightly colder than the rest. Cryptosporidiosis rose after February, to peak in the period June-August. The highest frequency was observed in June (20.2%). This month generally is the most calid and humid; the rainy season starts in May. Considering individual years, monthly frequencies of 10 to 20% at the peak of the season were common.

Clinical features. None of the children had first or second degree malnutrition (less than 75% weight/age) using the 50th percentile of the curve of the National Center for Health Statistics. There was no clinical evidence of immunodeficienty in any of the children. *Cryptosporidium* diarrhea generally was mild and short-lived (usually one to three days) in rural children. The hospital population represents a selection of moderate and severe cases, with diarrhea lasting one to four days. About 5% of these develop prolonged diarrhea of one to three weeks. The great majority of episodes were acute, with gruel-like or watery stools. These were devoid of macrophages, leukocytes and erythrocytes. Occult blood was found in 12% of 41 cases in whom it was investigated, Table 4.

The main signs and symptoms were, in addition to watery stools, vomiting, fever, and abdominal pain. Table 4 shows children in whom only one single pathogen was found after careful study of possible agents, as described elsewhere [40]. Vomiting was as common in cryptospor-

TABLE 4 - *Clinical features of specific diarrheal diseases among preschool children, Costa Rica,* 1983-1985.

Symptom or sign	Cryptosporidium		Rotavirus		Campylobacter	
	No.	+(%)	No.	+(%)	No.	+(%)
Vomiting	41	37(90)	300	268(89)	76	59(78)
Fever, C	28		214		53	
37.5-37.9		3(11)		15 (7)		5 (9)
38.0-38.4		5(18)		45(21)		13(24)
> 38.4		15(54)		87(41)		14(26)
Total		23(82)		147(69)		32(60)
Abdominal pain	37	21(57)	294	153(52)	74	36(49)
Dehydration, %	40		295		66	
< 5		30(75)		261(89)		54(82)
5-9		6(15)		29(10)		11(17)
> 9		4(10)		5 (2)		1 (1)
Total, 5+		10(25)		34(11)		12(18)
Convulsions	38	2 (5)	301	17 (6)	72	3 (4)
Occult blood	41	5(12)	301	32(11)	76	8(10)

idiosis as in rotavirus diarrhea. More cases of cryptosporidiosis had high fever and dehydration than did rotavirus and *Campylobacter* diarrheas. Abdominal pain was found in one half of the patients, as in other diarrheas. Weight loss wass as common as dehydration. However, no information on the natural course and impact of cryptosporidiosis on host nutrition can be provided, due to the prompt administration of fluid therapy. An effect on nutrition, however, was evident in some children, when individual growth charts were examined. Figure 1 shows the weight growth curve of a male child from Puriscal, who had adequate birth weight, and who was exclusively breast-fed for three months, and then completely weaned at age eight months. Growth faltering began around weaning time and the child failed to keep up in his growth track. When he was 19 months old, and after a spree of weight recovery, acute *Cryptosporidium*-associated diarrhea appeared after an attack of *Giardia* diarrhea. The episode lasted 25 days and was associated with pronounced weight loss, despite prompt and adequate oral fluid dehydration. Eventually, the child recovered to almost attain the weight he originally had at onset of infection. Information on the nutrition effect of *Cryptosporidium* diarrhea is under analysis.

Fluid therapy. At least 40 cases of cryptosporidiosis admitted to the hospital required fluid therapy. Oral rehydration therapy (ORT) is the choice in this hospital [38], and was applied as a single measure to 19 (47%) of the cases. Four additional patients required, in addition to ORT, either nasogastric rehydration (NGT) (two cases), intravenous fluid therapy (IVT) (one case), or both (one case). Due to the serious condition of 15 children, NGT had to be started at once, while two patients had to be given IVT upon admission. In the rural area, all cases were offered ORT, even though dehydration was not as common and severe as in urban children. Recuperation was successful. No deaths due to *Cryptosporidium*-associated diarrhea occurred during the study period.

DISCUSSION

The homogeneity in morphology and size of oocysts excreted by Costa Rican children suggests that infections are by one single species, probably *Cryptosporidium parvum,* compatible with the description [21] and redescription [23] of Tyzzer's species. The appearance of *Crypto-*
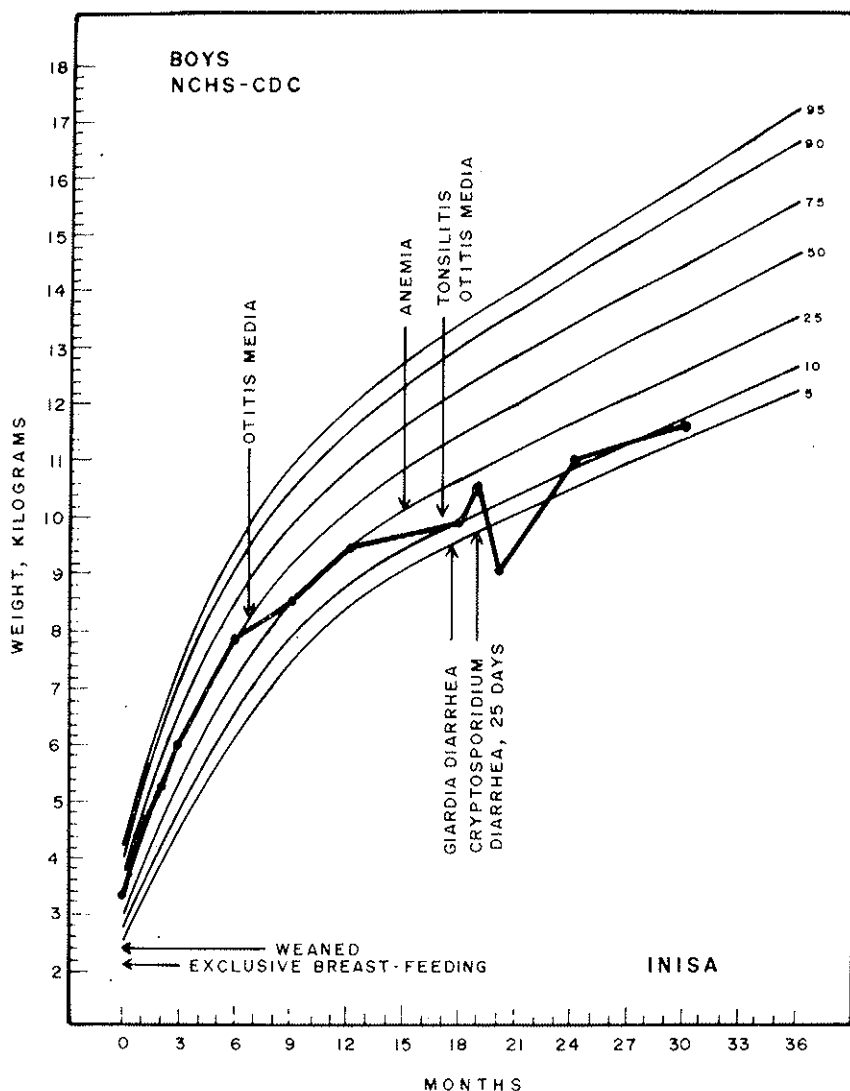
FIG. 1. Weight curve of a rural child from Puriscal, Costa Rica, in comparison with the reference curves of the National Center for Health Statistics. The child grew adequately up to 9 months of age at which point weight began faltering, to reach the 10th percentile. After an attack of *Giardia* diarrhea, and later one of *Cryptosporidium* diarrhea, the child became malnourished. After 25 days of illness, the child improved his weight, and several months later had attained the weight he had at onset of illness.

TABLE 5 - *Rehydration therapy administered to 40 children with diarrhea and dehydration associated with Cryptosporidium, National Children's Hospital, Costa Rica, 1983-1985.*

Therapy	Cases (%)
Oral rehydration therapy (ORT)	19(47)
Nasogastric rehydration therapy (NGT)	15(37)
Intravenous fluid therapy (IVT)	2 (5)
ORT + NGT	2 (5)
ORT + IVT	1 (2)
ORT + NGT + IVT	1 (2)

All treatment was given in the hospital, by health personnel supervised by pediatricians.

sporidium with large oocysts in calves with different host range [41], however, suggests the possibility of additional species or strains, morphologically similar to *C. parvum* and *C. muris*. Several laboratory concentration and staining techniques have been used to diagnose these coccidian parasites [17, 39, 43-45], but the cold acidfast Kinyoun staining seems to be the best [39]. The technique does not reveal the internal morphology of oocysts, but no other structures are found in feces that can be mistaken for *Cryptosporidium* oocysts stained with these procedures. The strong bright red of the wall of oocysts permits rapid and easy identification under low power microscopic magnification. It is convenient to examine all positives with an alternative method, for instance, with Giemsa or auramine-rhodamine.

Reliance on visual examination of oocysts, however, is not satisfactory, and methods for demonstration of small amounts of antigen are urgently needed. This is particularly important to determine if healthy and asymptomatic carriers are more common than presently realized [1-5, 46], to investigate animal reservoirs, and to better understand the phenomenon of seasonality of the parasite [18, 35]. Experimental infections can be easily induced in mice [47], embryonated hen's eggs [48], and tissue culture [49], widening the opportunity to develop better diagnostic tools.

Unpublished observations in Costa Rica indicate that contact with domestic animals, in the rural area of Puriscal, does not seem to explain most

infections in rural children. It certainly does not seem to be important in urban centers devoid of cattle and other animals, but the possibility of rodents and certain insects needs investigation. A study of high-risk populations for AIDS in Costa Rica failed to reveal *Cryptosporidium* infection in male homosexuals who were free of diarrhea at the time of sampling [unpublished]. Thus, although person-to-person transmission seems logical [5], carriers are not generally detected in homes of Costa Rican children with cryptosporidiosis. Studies elsewhere have demonstrated that asymptomatic persons are reservoirs for humans, and that transmission occurs among homosexuals [see 5].

Cryptosporidium is an ubiquitous organism which was found wherever someone looked for it [1-5, 46]. Nevertheless, there is need for information on the geographical range of infection in humans, particularly as a function of socioeconomic conditions, age, nutritional status, personal hygiene and sanitation, and seasonal distribution. Due to the relatively low rate of infection found in most studies (about 5%), and the wide variability in monthly prevalence, as shown in Costa Rica, studies should extend for prolonged periods to be fruitful. Except for the studies in Costa Rica, Bangladesh and Brazil [18, 32, 33], there is no information on this question. There is no plausible explanation for the seasonal variation of the coccidium, and particularly for the virtual "disappearance" during certain months, in analogy with seasonality of rotavirus in temperate regions, or of *Shigella* in the tropics.

The apparent variation in rate of *Cryptosporidium* by age shown in this study might be related to feeding regime more than to age. In the urban area, the rate of non breast-fed and prematurely weaned infants is considerably large, while in the rural area the situation has significantly improved in the last 7 years [36]. The hospital population most likely represents a selection of severe diarrhea cases, in whom the frequency of artificial feeding and feeding problems is greater than in children observed in the rural population. The very low rate of cryptosporidiosis in breast-fed children, in contrast with high rates in weaned children, suggests protection derived from breast-feeding. Susceptibility of colostrum-fed calves to *Cryptosporidium* [50] does not equate with the situation in infants. Human colostrum and milk contain large amounts of secretory immunoglobulin A (sIgA) and other immune and resistance factors which are either very low or absent in cow's colostrum and milk. Furthermore, while antibodies in cow's colostrum are readily absorbed by the newborn calf, those in human colostrum and milk act *in situ*.

Human sIgA is active after passing through the intestine [51]. Also, studies in adults showed lower prevalences of cryptosporidiosis than in children [46]. One study, however, revealed a rate of 2.9%, almost as in children in the tropics [52]. Data on adult infection in the tropics is badly needed. Summarizing, age does not appear as important as feeding regime, as seen from the Costa Rican data.

The relative frequency of *Cryptosporidium* infection in immunocompetent children in Costa Rica, (the most prevalent after rotavirus, enterotoxigenic *Escherichia coli* and *Campylobacter jejuni*), calls for routine investigation of this coccidium. In otherwise healthy individuals, *Cryptosporidium* diarrhea is a non-invasive process, without inflammatory cells in stools, as previously reported [53]. The coccidium could be relatively more important in industrial than in less developed nations [52, 54]. One report from the United States indicates that it is the most frequent parasite found in routine serial examinations [53]. In addition to being a common pathogen in immunocompetent persons, *Cryptosporidium* is an opportunist in immunosuppressed and immunodeficient individuals, including AIDS patients [1-5]. The role of this coccidium in chronic diarrhea and in the genesis of severe malnutrition deserves consideration in poor countries.

ACKNOWLEDGMENT

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INTERACTION OF PARASITIC DISEASES AND NUTRITION: CLINICAL IMPACT OF GIARDIASIS

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1. INTRODUCTION

Despite renewed scientific interest in the protozoan parasite *Giardia lamblia* it is still unclear whether this organism constitutes a major threat to the health and development of infants and children. *Giardia* is ubiquitous throughout the world but is particularly prevalent in under-privileged areas where living conditions are poor. The organism can cause both acute and chronic diarrhoea with intestinal malabsorption of essential nutrients. Conversely, many individuals infected by this parasite are free of symptoms and obvious detrimental effects on health. Thus the high prevalence rates of this parasite in the developing world may merely reflect widespread asymptomatic carriage; alternatively the organism could be an important cause of diarrhoeal disease morbidity. *Giardia* can certainly impair appetite and cause intestinal malabsorption of nutrients, but whether these effects are substantial enough to affect child growth at a population level is still unclear.

These key questions must be answered before specific, community-based intervention programmes should be considered. Acute diarrhoeal disease in children is a major cause of growth impairment in the developing world, but it is less certain as to which enteropathogens have the most profound effect on nutrition and growth. Similarly recurrent or chronic diarrhoea is thought to be particularly deleterious to child health but the aetiologic agents responsible and its overall impact on child development have been poorly studied. If *Giardia* was shown to be a

significant contributor to impaired nutrition and growth faltering in childhood then specific intervention programmes might be justified, particularly those directed towards the promotion of protective immunity earlier in life.

2. PREVALENCE

Prevalence of *Giardia* varies widely throughout the world. Overall prevalence in the West is between 2-7% [1-2], whereas in the developing world prevalence is generally much higher, often in excess of 20%. Data on age-specific prevalence was reported in 2099 city dwellers in Nigeria, when peak prevalence approached 14% in 1-5 year-olds [3]. Thereafter prevalence declined to approximately 5% and continued at that level for the majority of adult life. Age-specific prevalence of *Giardia* has recently been reported from Bangladesh, where peak prevalence of 21% was found in children aged 5-< 10 years [4]. Again prevalence declined during adulthood to around 5%. During an 18 month period of surveillance, 40% of Bangladeshi children less than 7 years of age acquired *Giardia* [4] and in a longitudinal study of 45 children from birth through the first three years of life in rural Guatemala, all children had had at least one *Giardia* infection [5]. This study also indicated that 30-50% of *Giardia* infections occurred in the absence of intestinal symptoms. Thus in the developing world at least, *Giardia* is highly prevalent and probably affects a large proportion, if not all, children during early life.

3. GIARDIA AS A CAUSE OF DIARRHOEAL DISEASE

Acute Diarrhoea: Despite the endemic nature of this parasite and its high prevalence in children in the developing world, it would appear to be a relatively uncommon cause of acute diarrhoea in both children and adults [6-14]. Table 1 summarizes the findings of some recent studies which have searched for the aetiologic agents responsible for acute diarrhoea. *Giardia* only accounted for 0-7% of cases of acute diarrhoea, although in the two studies that reported data on age-specific prevalence [11, 12] it would appear that *Giardia* accounted for up to 10% of acute diarrhoeal episodes in young Bangladeshi children.

The prevalence of *Giardia* in acute diarrhoeal illnesses may however have been underestimated. In the majority of these studies only a single

TABLE 1 - Giardia *in Acute Diarrhoea.*

STUDY		LOCATION	PATIENTS		CONTROLS	
			No. Studied	% prevalence	No. Studied	% prevalence
Echeverria *et al.,*	1977	Taiwan	80*	0	131	< 1.0
Maiya *et al.,*	1977	India	50*	0	30	0
Donta *et al.,*	1977	Mexico	50*	4	50	0
Pickering *et al.,*	1978	USA	255*	7	112	0.9
Pickering *et al.,*	1978	Mexico	340*	6	98	0
Echeverria *et al.,*	1978	Philippines	82*	0.5	49	0
Black *et al.,*	1980	Bangladesh	8139**	2.0***	—	—
Stoll *et al.,*	1982	Bangladesh	2246**	6.0***	—	—
Guerrant *et al.,*	1983	Brazil	150**	6.7	—	—

* children.
** children and adults.
*** vegetative forms only.

stool specimen was examined for parasites and this may reduce true prevalence by up to 50% [15]. This consideration would be supported by the usual observation that a pathogen is only detected in 70-80% of individuals with acute diarrhoea and in some series this is substantially lower at 50%. Another factor in the studies from Bangladesh is that only vegetative forms of the parasite (trophozoites) were regarded as indicative of acute infection, the presence of cysts being disregarded [11, 12]. The significance, however, of the presence of cysts and trophozoites in relation to clinically important diarrhoeal disease has not been clearly established.

Chronic Diarrhoea: The importance of *Giardia* as a cause of chronic diarrhoea worldwide is less well established. Table 2 summarizes the findings of four studies that have searched for aetiologic agents in children and adults with chronic diarrhoea [16-19]. Prevalence was substantially higher in patients with chronic diarrhoea than that reported in the acute diarrhoea studies, ranging from 11-32%. However it should be stated that only one study from Puerto Rico [16] reported data from a comparable control group which did indeed have a substantially lower

TABLE 2 - Giardia *in Chronic Diarrhoea.*

STUDY		LOCATION	PATIENTS		CONTROLS	
			No. Studied	% prevalence	No. Studied	% prevalence
Guardiola-Rotger *et al.,*	1964	Puerto Rico	72*	32	73	15
Gupte & Mehta	1970	India	62*	19	——	——
Walia *et al.,*	1971	India	200*	26	—	——
Chhuttani *et al.,*	1973	India	62**	11	—	——

* children.
** children and adults.

prevalence of *Giardia*. Studies in individuals have also shown that *Giardia* can cause diarrhoea and malabsorption which may persist for months or even years [20-26].

4. IMPACT ON NUTRITION

General Effects

Nutrient Intake: One of the most important general effects of infection on nutritional status relates to a common observation that infection reduces appetite and therefore decreases nutrient intake [27-29]. Survey of symptoms in giardiasis has been most thoroughly investigated in travellers [30, 31] who have developed acute giardiasis (Table 3). Nausea and abdominal discomfort occur in almost two-thirds of sufferers and although not reported directly, it is likely that both of these symptoms lead to reduced dietary intake. Other reports in selected groups of patients and in individuals also suggest that anorexia is an important feature of this disease [30, 32], and although reduction in nutrient intake is well documented during acute diarrhoeal disease [27-29], there are no data reported which relate specifically to giardiasis. Nevertheless, the precipitous loss of body weight that occurs so commonly during both acute and chronic giardiasis [30, 31] is likely to be due, at least in part, to reduced nutrient intake.

TABLE 3 - *Symptoms of* Giardiasis.

| | Travellers | |
	Soviet Union [1] n=324 %	Aspen, Colorado [2] n=56 %
Diarrhoea	96	93
Steatorrhoea	57	55
Nausea	60	59
Abdominal pain	61	77
Weight loss	62	73
Fever	17	NR

[1] Brodsky *et al.*, 1974.
[2] Moore *et al.*, 1969.
NR, not reported.

Fever: The presence of fever is another important factor in the metabolic and nutritional disturbance of infection [33] and although generally not regarded as a major feature of giardiasis, was reported in 17% of 324 travellers to the Soviet Union who developed giardiasis [31].

Specific Effects

Intestinal Malabsorption: *Giardia* probably has its most profound impact on host nutritional status as a result of diarrhoea and intestinal malabsorption. In severe cases a florid malabsorption syndrome is apparent with wasting, hypoalbuminaemia, steatorrhoea and failure to thrive [20-25, 34]. Various aspects of nutrient malabsorption in individuals with giardiasis have been studied (Table 4). Prevalence of abnormalities of absorption of individual nutrients varies widely [34-47], due to diverse selection criteria and variable severity of infections. Nevertheless, these data do give some indication of the extent of malabsorption in patients with giardiasis, the vast majority of whom were symptomatic. Barbieri *et al.* [39] did however study 11 Brazilian children with giardiasis who were symptom-free. It is of interest that 82% of these children exhibited malabsorption of fat and 27% had malabsorption of D-xylose, although it is uncertain as to whether all other possible

TABLE 4 - *Intestinal Malabsorption.*

STUDY	LOCATION	No. of subjects	% subjects with abnormal results				
			D-Xylose	Lactose	Fat	Vitamin B12	Vitamin A
Veghelyi, 1939	Hungary	14	—	—	71	—	—
Katsampes, 1944	USA	15	—	—	—	—	100
Cantor, 1967	Argentina	20	—	—	25	—	—
Hoskins, 1967	USA	6	50	100	40	100	—
Alp, 1969	Australia	5	20	20	100	—	—
Barbieri, 1970	Brazil	11*	27	—	32	—	—
Ament, 1972	USA	77	—	—	66	100	—
Cowen, 1973	USA	3	100	—	66	100	—
Tewari, 1974	India	30	23	—	50	6	—
Rabassa, 1975	Cuba	50	62	27	34	—	—
Wright, 1977	UK	40	45	—	35	—	—
Tandon, 1977	India	63	4	—	27	0	—
Hartong, 1979	USA	12	55	—	64	60	—
Mahalanabis, 1979	India	4	79	—	50	—	100
mean %		n = 280	47	49	55	61	100

* Asymptomatic children.

causes for malabsorption had been excluded. Nevertheless this study raises the possibility that even apparent asymptomatic carriage of *Giardia* may disturb intestinal absorptive function and potentially compromise nutritional status.

Mechanisms of Malabsorption: For many years it was proposed that malabsorption in giardiasis occurred as a result of competition by *Giardia* for host nutrients [34, 39] or that the parasite effected a physical barricade of the mucosa due to the vast numbers of adherent trophozoites [34, 35, 48]. There is no clinical or experimental evidence to support either of these hypotheses and they should now be regarded as untenable. There is however considerable evidence to support a number of other mechanisms by which *Giardia* causes intestinal malabsorption (Table 5).

Although some patients with giardiasis have histologically normal or near normal jejunal mucosa, a broad spectrum of damage has been reported

TABLE 5 - *Mechanisms of Intestinal Malabsorption in Giardiasis.*

Site of action	Mechanism
Intestinal mucosa:	Enterocyte damage
	Increased enterocyte turnover
	Invasion
	Mucosal inflammation
Intestinal lumen:	Bacterial overgrowth
	Inhibition of lipolysis
	Consumption of bile salts
Pancreatico-biliary system:	Pancreatic insufficiency
	Inflammation in gall bladder and bile ducts

from partial to sub-total villous atrophy [44, 49-51], and there does appear to be a relationship between the extent of mucosal damage and the degree of functional impairment [52]. Even when light microscopic examination of jejunal mucosa appears normal, microvillous membrane damage is apparent by transmission electron microscopy [48]. In addition, like coeliac disease, enterocyte turnover is increased [53] which results in the villus becoming populated by relatively immature enterocytes with reduced digestive and absorptive function. Direct invasion of the intestinal mucosa has been reported [54, 55], but its impact on intestinal function has not been assessed.

Infiltration of the intestinal mucosa by inflammatory cells, notably lymphocytes, occurs before villus morphological changes are apparent [53] and therefore may have a key role in disturbing intestinal function. Lymphocytes presumably enter the intestinal epithelium in response to *Giardia*-related antigen(s). The extent of mucosal inflammation correlates well with the degree of derangement of intestinal absorptive function [52]. The primary importance of the mucosal inflammatory response is also suggested by observations in experimentally infected nude (hypo-thymic) mice (*Giardia muris*) in which the changes in villous architecture are much less marked than in conventional animals, despite protracted infection by the parasite in these immunodeficient animals [56].

Bacterial overgrowth has been reported to occur in association with *Giardia infection* [45, 57], and in one study deconjugated bile salts were

detected in intestinal luminal fluid [45]. Free bile salts have also been found in patients with giardiasis in the absence of bacterial overgrowth [45], suggesting that *Giardia* itself might be responsible for bile salt deconjugation. However, we and others have failed to demonstrate bile salt deconjugation by *Giardia, in vitro* [58, 59]. Other possible intraluminal mechanisms include inhibition of lipolysis [58] and direct consumption of conjugated bile salts by *Giardia* [60, 61] which would therefore reduce bile salt bioavailability and possibly impair intestinal fat absorption.

Pancreatic insufficiency has been reported in association with giardiasis in children, although it is uncertain as to whether *Giardia* can be causally implicated [62, 63]. *Giardia* trophozoites have been found in the pancreatico-biliary system and are reported to cause cholecystitis and cholangitis [64]. *Giardia* clearly flourishes in a bile-rich environment and indeed this migration into the biliary system may reflect a specific tropism of the organism [60, 65, 66).

Faecal Nutrient Losses: Enteric loss of nutrients in giardiasis has not been systematically investigated, although small intestinal cell turnover is accelerated in acute and chronic experimental *Giardia muris* infection in mice [67], indicating that mucosal exfoliation is increased. Marked intestinal protein loss has been demonstrated in isolated case reports [68, 69] although its impact in *Giardia* infection overall has not been determined.

5. IMPACT ON GROWTH AND DEVELOPMENT

Chronic gastrointestinal disorders are known to retard growth during infancy and childhood. Crohn's disease and coeliac disease can impair child growth even in the absence of gastrointestinal symptoms [70-72]. It is now also well established that recurrent gastrointestinal infection retards growth of infants and children [73, 74]. Although *Giardia* is prevalent throughout the developing world and is now established as an intestinal pathogen, its relationship to child growth and development has not been clearly defined.

Giardia would seem to be a candidate pathogen for retarding child growth since infection, (i) occurs commonly in infants and children, with peak prevalence in the pre-school years, (ii) is known to damage the small intestine and cause intestinal malabsorption, (iii) is not always self-limiting

and may persist for many weeks or months, and (iv) causes impaired growth in young animals [75].

   Hospital-Based Studies: Since the early 1920's a number of investigators have described the effects of giardiasis on physical growth in infancy and childhood (Table 6). All of these studies were performed in patients attending hospital and therefore these data are highly biased towards more severely affected children [76-84]. The majority of studies are small and the impact of giardiasis on growth poorly documented. Veghelyi [78] studied 92 children with giardiasis in Hungary and found that 86% were below average weight and 13% below average height. Another study indicated that 31% of 154 infected Australian children had either lost weight or had failed to grow as expected [83]. 24 of these children were followed after treatment for giardiasis and 19 (79%) gained more weight than would have been expected from percentile growth charts, suggesting that *Giardia* had made a significant contribution to their weight loss or failure to thrive. Cortner in 1959 [80] provides persuasive evidence that *Giardia* can also retard linear growth in some individuals.

   Thus it would appear that in its severest form, giardiasis can reduce both weight and height velocities, which concurs with the albeit limited

TABLE 6 - Giardiasis: *Impact on Child Growth.*

Hospital based studies:

STUDY		LOCATION	No. Studied	% Growth retarded Weight	% Growth retarded Height	% Growth retarded Not spec.
Perkins,	1921	UK	7	—	—	14
Miller,	1926	UK	23	39	+	—
Veghelyi,	1938	Hungary	92	86	13	—
Boe & Rinvik,	1943	Norway	22	—	—	9
Cortner,	1959	USA	4	100	75	—
Court & Anderson,	1959	Australia	13	92	—	—
Burke,	1975	USA	7	100	—	—
Kay et al.,	1977	Australia	154	—	—	31
Pugh & Newton,	1980	UK	17	—	—	41

data from experimental animals [75]. None of these studies were performed in the developing world and may therefore reflect the florid effects of a pathogen to which individual and herd immunity is low. These studies fail to give any guidance as to whether such effects on growth are important at a community level in parts of the world where the parasite is highly prevalent.

Community-based Studies: There are few reports that tackle this key question (Table 7) and none of the available information provides a definitive answer. Rowland *et al.* in 1977 [73] reported the results of a longitudinal study of 152 Gambian children followed prospectively from three months to three years of age. The impact of a variety of infections, including gastroenteritis and giardiasis, on child growth were assessed. Gastroenteritis significantly retarded weight and height velocities, and malaria had a profound and significant effect on weight velocity. However, in this analysis, giardiasis, although reducing weight velocity the magnitude of this effect failed to achieve statistical significance. A criticism of this study with respect to *Giardia* is that diagnosis was based on microscopy of fresh stool smears and only the presence of trophozoites was noted and regarded as indicative of infection. Concentration techniques for the detection of cysts were not employed. Thus it is likely that the overall prevalence of giardiasis in this group of children was markedly underestimated.

Cole and Parkin in 1977 [85] compared growth in the same 152 Gambian children with 45 children from Uganda. In this report reduction in weight velocity due to giardiasis achieved statistical significance, as did the effects of malaria and gastroenteritis. The reasons for the disparity

TABLE 7 - Giardiasis: *Impact on Child Growth.*

Community based studies:

STUDY			LOCATION	No.	SUMMARY OF FINDINGS
Rowland *et al.*,*	1977		The Gambia	152	No effect
Cole & Parkin*	1977		The Gambia	152	↓ Weight gain (p < 0.05)
Gupta & Urrutia	1982		Guatemala	159	↓ growth with metronidazole
Farthing, Mata *et al.*,	1985		Guatemala	45	↓ Weight velocity 2nd year of life

* vegetative forms only.

between these analyses relates to the fact that in the second study [85], anthropometric data were weighted according to the frequency of observations and this was taken into account in the regression analysis (T.J. Cole, personal communication).

Gupta and Urrutia in 1982 [86] attempted to show the impact of giardiasis on child growth by a prospective, placebo-controlled study of parasite eradication. 159 children between 2 and 5 years of age were randomly allocated to twice-monthly therapy with one of four treatment regimens; (i) placebo, (ii) piperazine, (iii) metronidazole or (iv) metronidazole plus piperazine. Weight gain, linear growth and parasite prevalence were determined at regular intervals during a one year period. Piperazine reduced the prevalence of ascaris infection from 60% to 33.8% but had no impact whatsoever on growth. Metronidazole however decreased the prevalence of giardiasis from 21.5% at the beginning of the study to 2.5% at the end of the study and had small but significant effects on age-adjusted weight and height velocity, the effects being most marked in younger children, 2-4 years of age. This younger age group had a higher prevalence of giardiasis (27.5%) compared to older children (11.8%). In these younger children, the mean weight gain in those children who received metronidazole was 1.97 kg compared with 1.73 kg in those who did not; thus the extra weight gain over the study period was only 0.24 kg, or 13.8% higher than controls. The extra height gain was 1.06 cm which is a 16.6% increment over controls.

Although these findings suggest that *Giardia* does have a negative impact on child growth, metronidazole therapy is not monospecific and one cannot assume that the apparent growth-promoting effects were entirely due to its anti-giardial properties. On the other hand the results of this study may have been marred by the fact that metronidazole therapy did not eradicate *Giardia* in either of the study groups receiving this drug.

Mata in 1978 [74] reported the results of his classic prospective, longitudinal study of a cohort of 45 rural Guatemalan children from birth through the first three years of life. This study showed that prevalence of *Giardia* rose progressively during the first three years of life, reaching a peak in the third year of over 20%. Further analysis of these data shows that by the age of three years every child in the cohort had had at least one *Giardia* infection, approximately 50% of these infections lasted 2 weeks or more and in the first year of life 28% of *Giardia* infection lasted 6 weeks or more [5]. With the exception of the first 6 months of life, 50% or more of *Giardia* infections were accompanied by diarrhoea.

To assess the impact of giardiasis on child growth, weight and height velocities were compared in *Giardia*-positive and *Giardia*-negative children during each of the first three years of life. No differences in growth were observed during the first or third year of life, but in the second year weight velocity was significantly lower in *Giardia*-positive children. More detailed analysis of growth during this second year suggested that growth retardation was related to the duration of *Giardia* infections, being more profound when infection was prolonged, and also to whether infection was accompanied by diarrhoea. Although many other pathogens were isolated from these children, growth retardation was similar in children who had *Giardia* infections with or without another pathogen, indicating that *Giardia* itself played a part in impairing growth.

7. SUMMARY

(i) Giardiasis is a common infection in the developing world and probably affects the vast majority of children during the first three years of life.

(ii) Peak prevalence occurs during childhood and declines to relatively low levels in adults.

(iii) Although not a common cause of acute diarrhoea, *Giardia* may be an important aetiological factor in chronic diarrhoea in children.

(iv) In individual cases giardiasis can have a profound effect on host nutritional status, probably mediated by its detrimental effects on appetite, impairment of intestinal absorptive function and increased faecal nutrient losses.

(v) Severe giardiasis can impair growth of children but its impact at a community level remains uncertain.

8. CONCLUSIONS

Giardia is potentially an important enteric pathogen causing diarrhoeal disease, intestinal malabsorption and in some cases profound disturbances of nutritional status resulting in growth retardation of children. Clinical impact of this parasite at a community level is poorly understood and its role in the aetiology of chronic diarrhoea in children still largely unexplored. Although many individuals may apparently carry the parasite without

symptoms, the nutritional cost of carriage and its impact on intestinal function has not been assessed. Although several attempts have been made to determine the impact of this parasite on child growth at a community level, all reported studies to date have imperfections and further work is required to clarify these issues. Nevertheless the indications are such that infants and young children are vulnerable to this parasite and that during the critical pre-school years *Giardia* may be one of the contributory factors to the impairment of normal growth and development.

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INTERACTION OF PARASITIC DISEASE
AND NUTRITION: AMEBIASIS

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INTRODUCTION

Amebiasis is the infection of humans with the protozoan *Entamoeba histolytica,* which has a worldwide distribution. The trophozoite usually lives as a commensal in the lumen of the large intestine, inducing no signs or symptoms in this condition known as lumenal amebiasis. As a pathogen, it is the cause of invasive amebiasis, which is prevalent in certain countries; pathogenic strains may invade the intestinal mucosa and produce dysentery or ameboma, and through blood-borne spreading may give rise to extraintestinal lesions, mainly liver abscesses. The human being is the only reservoir and source of infection. (Sepúlveda and Martínez-Palomo, 1984 [1]).

Amebiasis is considered at present to represent the third commonest parasitic cause of death on a global scale. Walsh (1985 [2]) estimated that in 1981 probably 480 million people carried *E. histolytica* in their intestinal tracts, 36 million developed invasive forms severe enough to disable them for several days, and at least 40,000 died that year as a consequence of the infection. She also emphasized that the recent urban migration and increasing size of urban slums filled with poor people living in crowded, unhygienic conditions may accelerate the spread of amebiasis and result in even greater disability from this infection in the future. The need to develop better control strategies based on the

knowledge of parasite and host factors that determine the outcome of amebic infections is thus obvious. The purpose of this review is to extract some conclusions from the conflicting evidence on the role of the nutritional status of the host in the development of invasive amebiasis, both in experimental animals and in humans.

Little advance has been achieved in this field during the last decade, since most research efforts have concentrated on the biology of the parasite, rather than on the study of the host factors responsible for the development of invasive forms of amebiasis. However, better knowledge of the parasite has provided important information needed to understand the epidemiology of the disease, and as a consequence, has permitted a better perspective of the relative contribution of dietary factors.

Diamond (1982 [3]) reviewed the nutritional implications of amebiasis and made a rather laconic conclusion: "Clearly, the complexities of the amebic infection and disease are capable of frustrating even careful and intuitive workers who study the problems of nutrition and amebiasis". It could well be that this frustration simply reflects the fact that nutrition does not have an important role in the establishment or outcome of amebic infections. The trouble is that the demonstration of the validity of this statement proves to be equally frustrating, simply because, at least in the human being, no adequate studies have been conducted to resolve the question.

Anecdotal evidence of advanced malnutrition in cases of invasive amebiasis can be found in a poignant sketch made by the Mexican painter Diego Rivera in 1937 (Fig. 1). The drawing was used to illustrate a special issue of a medical journal dedicated to amebiasis.

One of the strongest defenders of the importance of nutrition in amebiasis was Faust. Based on experiments carried out during the 1930's he concluded that fulminating experimental amebic colitis in dogs could be controlled with raw liver, which at times even produced cure, although liver extract introduced parenterally had no effect on the progress of the lesions or symptoms. The results encouraged Faust to carry out a few experiments in patients with amebiasis, who were given raw calf liver by mouth. Even though symptoms were apparently relieved and in one instance produced apparent cure, the "unpalatable taste of the liver made it impractical to undertake a larger clinical study" (Faust, 1954 [4]. This is just an example of the type of experiments that were conducted in the past to understand the role of nutrition in amebiasis. It is possible that Faust was treating cases of cyst passers, who now are known to spon-

FIG. 1. « Amebiasis » by Diego Rivera (1937).

taneously eradicate the infection. Nanda *et al.* (1984 [5]) recently follow-ed up untreated cyst passers for a mean period of 8.6 months and observed eradication of the parasite in all patients.

It would be useless to attempt another comprehensive review of the already aged experiments on the subject, because most of them were inconclusive, were carried out with ill-characterized strains of amebas, and lacked adequate controls. Instead, I will try to support a few basic statements concerning the interaction between amebiasis and nutrition in an attempt to stimulate further study.

1. *Experimental malnutrition enhances the severity of invasive amebiasis.*

It has been shown that rats given protein deficient diets for 2 to 4 weeks and then infected intracecally with trophozoites from a case of amebic dysentery, containing the associated bacterial flora, show a greater susceptibility to infection and ulceration compared to controls. When the

low protein diet was supplemented with extra carbohydrate, an even greater infection rate was observed, but the intestinal lesions decreased in number. Whether protein deficiency acts through changes in pH, redox potential, mucus production, multiplication of the host anaerobic flora, or the bacterial flora associated with the amebas, or inducing modification of gastrointestinal structure and function is not known (Ross and Knight, 1973 [6]). A reduction in epithelial cell mitotic rate in the cecal mucosa would probably lead to an increase in the number of interglandular regions where sloughing of epithelial cells occurs; these "weak spots" are now known to be the sites of amebic penetration (Mora-Galindo et al., 1982 [7]). Whether or not protein energy malnutrition in humans predisposes to invasive amebiasis and high carbohydrate diets protect the host from tissue invasion by providing amebas with plentiful nutrients (Faust and Read, 1959 [8]) remains to be demonstrated. For the time being, the needle of the balance between synergism and antagonism with regard to nutrition and invasive amebiasis is still swinging.

2. *Individual susceptibility to amebiasis in humans does not appear to be related to the nutritional status*

Although experiments in humans specifically designed to support this statement have not been carried out, the results of at least two reports seem to validate the conclusion. The first study is the frequently quoted but seldomly read classical experiment done in 1913 by Walker and Sellars [9] in the Philippines. In one particular experiment, cysts of *E. histolytica* directly obtained from the stools of a man convalescent from a slight attack of amebic dysentery were given to 12 inmates of the Bilibid prison. Three developed dysentery, 8 became infected with the amebas but showed no symptoms, and only in one were no amebas found in the stools. The sample was relatively homogeneous because all were men serving long sentences and all ate "cooked food and drank distilled water exclusively". There are no indications that the nutritional status of those that developed symptoms was different from those who did not. More recently, Beaver et al. (1956 [10]) obtained infections in all of 42 prisoners infected with cysts from one cyst passer but none developed symptoms. It can be inferred from these experiments that, given a sufficient inoculum, lumenal amebiasis is readily established, while only a small percentage of those infected will experience invasive intestinal amebiasis. So far, there is no indication that this variation in individual susceptibility to invasive amebiasis is related to nutrition or diet.

3. The focal incidence of invasive amebiasis cannot be interpreted on the basis of nutritional differences

The fact that invasive amebiasis is a major health and social problem in only certain areas of Africa, Asia, and Latin America cannot be exclusively related to inadequate sanitary conditions and nutritional deficiencies. These conditions are common in many developing countries, which in spite of having a high incidence of lumenal amebiasis, show relatively few cases of dysentery or liver abscess. It appears that a major factor responsible for the focal incidence of invasive amebiasis is the prevalence of highly virulent strains in certain regions (Martínez-Palomo and Martínez-Báez, 1983 [12]; Walsh and Martínez-Palomo, 1985 [13]). Nonpathogenic strains of E. histolytica were first shown to differ from those isolated from cases of human invasive amebiasis in certain surface properties. It has been demonstrated that, in general, pathogenic strains have a high susceptibility to agglutinate in the presence of concanavalin A, lack a negative surface charge, show a high rate of erythophagocytosis, and lyse cultured cells (Martínez-Palomo, 1982 [11]). The analysis of isoenzyme patterns subsequently showed differences in metabolic markers between pathogenic and nonpathogenic strains. Sargeaunt and collaborators (1982 [14]) have already found that a) all species of amebas occurring in the intestine of man can be characterized by distinctive isoenzyme patterns, b) amebas from well characterized cases of invasive amebiasis are clustered into a number of well defined patterns, and c) all remaining patterns correspond to amebas isolated from probable carriers. These observations tend to support the hypothesis of Brumpt (1925 [15]) that invasive amebiasis is produced by biologically distinct species of amebas. We have recently confirmed the existence of distinct isoenzyme patterns in pathogenic strains, and showed that while most carriers harbor amebas with nonpathogenic patterns, pathogenic isoenzyme patterns may be present in some carriers (Meza et al., 1985 [16]). It should be stressed that the carriers studied by us were rigorously characterized by the absence of clinical, endoscopic, and serological findings.

The incidence of invasive amebiasis is clearly related to sanitation and socioeconomic status rather than to nutrition or climate. In Mexico high prevalence of amebic seropositivity in the general population correlates with various indices of poverty: crowding, illiteracy, lack of running water, and inadequate disposal of human excrement (Gutiérrez et al., 1976 [17]). There is poverty in food, which is scarce in quantity and deficient in quality; there is poverty in housing, which nearly always is inadequate; and there

is poverty in knowledge, education and culture; and above all there is poverty that involves the hygiene of persons, houses, and the community, which approaches real misery (Martínez-Palomo and Martínez-Báez, 1983 [12]).

4. *The degree of protein-energy malnutrition correlates with the lethality of invasive amebiasis*

During the past century, when treatment of amebic liver abscess was limited to surgery, mortality was approximately 82 per cent. The introduction of emetine in 1913 considerably decreased the mortality rate, although two decades ago it still approached 10 per cent in adults and more than 20 per cent in children. Gutiérrez *et al*. (1970 [18]) reviewed 67 cases of amebic liver abscess in children and found a mortality rate of 27 per cent. When the nutritional status was taken into account mortality was 7.7 per cent in adequately nourished children, 27.2 per cent in patients with mild malnutrition (Gómez grade I); 36.8 per cent in cases of moderate malnutrition (grade II), and 54.5 per cent in children showing severe malnutrition (grade III). It cannot be stated whether malnutrition was a consequence of the disease or was present before the establishment of the infection. In this respect it is worthwhile recalling that, in general, invasive amebiasis has a rapid course. In a series of 400 patients with amebic liver abscesses studied in South Africa the history of illness was less than 2 weeks in 59 per cent of cases. Similarly, 48 per cent of a series of 300 cases of amebic dysentery had a history of symptoms of 1 week or less (Adams and MacLeod, 1977 a, b [19-20]).

A dramatic reduction in mortality to approximately 2 per cent has been obtained in recent years in hospitals with adequate facilities (Gutiérrez-Trujillo, 1980 [21]). This improvement occurred without any intervention specifically devised to modify the nutritional status of patients; metronidazole, better diagnostic methods, and a drastic reduction in the number of aspirations of abscess contents were responsible for the decrease in the mortality rate.

5. *In terms of control of amebiasis, the only advisable measure related to nutrition is the promotion of breast feeding*

Some reports indicate that malnutrition in both animal and human hosts increases the incidence of amebic infection and potentiates the

severity of the disease, while others suggest that malnutrition protects the host against invasion (reviewed by Diamond, 1982 [3]) and that dietary regimes can alleviate symptoms and even eradicate the parasite. The strategies for the control of amebiasis recently reviewed by WHO (1985 [24]) and by Walsh and Martínez-Palomo (1985 [13]) include nonspecific measures such as the improvement of water supplies and excreta disposal, the adoption of more careful personal hygienic practices, and general social and economic development. Specific measures include community surveys and the monitoring of local conditions with regard to amebiasis; improvement of case management; and surveillance and control of situations that may favor the spread of amebiasis.

Breast feeding has been associated with a decreased incidence of diarrheal disease among young children, regardless of the etiology (Feachem and Koblinsky, 1984 [22]). In this respect, it is interesting that human milk contains a factor that kills *E. histolytica* in vitro (Gillin *et al.*, 1983 [23]); however, the clinical relevance of this is not known. It is not possible at present to make a public policy statement regarding the role of nutrition in the prevention or control of amebiasis. The only significant nutritional intervention may be the encouragement of the practice of breast-feeding.

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NUTRITIONAL EFFECTS OF INTESTINAL HELMINTHS WITH SPECIAL REFERENCE TO ASCARIASIS AND STRONGYLOIDIASIS

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INTRODUCTION

The bi-directional relationships between infectious diseases and the host's nutritional status were well described in the now classic treatise on Nutrition and Infection by Scrimshaw, Taylor and Gordon [1]. The present review will focus specifically on the adverse nutritional consequences of intestinal helminths; the effects of the host's nutritional status on the susceptibility to and severity of intestinal parasitic diseases will not be discussed. Because of the extensive experimental literature available in this field, only selected studies will be presented to illustrate specific mechanisms of parasite-induced nutritional disorders. The impact of parasites on dietary intake, intraluminal digestion and intestinal mucosal morphology, renewal, and absorptive function will be noted. Special emphasis will be given to relevant clinical and epidemiological studies that were conducted to define the magnitude of the nutritional effects of parasitic infections and to measure the impact of specific intervention programs. Most of the discussion will be directed to ascariasis and strongyloidiasis because greater research effort has been devoted to the study of these illnesses. Selected investigations of other intestinal helminth will also be cited when appropriate (See Table 1 for a classification of the major intestinal helminths of man).

When analyzing the nutritional impact of infections, the effects on

TABLE 1 - *Intestinal helminths of man.*

Biological Name	Common Name	Major Site of Infection
Nematodes		
Ascaris lumbricoides	Roundworm	Small intestine
Ancylostoma duodenale	Hookworm	Small intestine
Necator americanus	Hookworm	Small intestine
Strongyloides stercoralis	Strongyloidiais	Small intestine
Trichuris trichiura	Whipworm	Colon, rectum
Enterobius vermicularis	Pinworm	Colon, rectum
Trematodes		
Fasciolopsis buski	Intestinal fluke	Small intestine
Cestodes		
Diphyllobothrium latum	Fish tapeworm	Small intestine
Taenia saginata	Beef tapeworm	Small intestine
Taenio solium	Pork tapeworm	Small intestine
Hymenolepis nana	Dwarf tapeworm	Small intestine

single or multiple micro- or macro-nutrients can be considered separately. Alternatively, general effects on host metabolism, growth and body composition can be analyzed. With the exception of the detailed studies of the relations between hookworm and iron metabolism, between Diphyllobothrium latum and vitamin B_{12}, and between selected intestinal parasites (e.g., Giardia lamblia and Ascaris lumbricoides) and vitamin A absorption, little information is available on the effects of intestinal parasites on vitamin and mineral nutriture. Therefore, greatest attention will be directed to available literature on the effects of intestinal helminths on macronutrient metabolism and host nutritional status.

Because the negative impact of infections on nutritional status is now widely appreciated, public health specialists can rightfully consider a variety of "non-nutritional" infection-control measures as potentially valuable interventions to improve the nutritional status of populations. Large-scale efforts to eradicate enteric parasites — or, at least, to reduce the parasitic burden of a population — might be included among such potential interventions. As opposed to the wide range of pathophysiological, clinical and epidemiological studies of the nutritional effects of intestinal helminths, however, present scientific knowledge on the efficacy of

population-based parasite control programs is rudimentary, and evaluations of the relative cost-effectiveness of these programs in nutritional terms are generally lacking. Moreover, the results of rigorous experimental studies are often at odds with field observations that are by necessity less well controlled. Although these discrepancies are not entirely surprising (given the multiple factors that influence the nutritional status of free-living populations), they complicate the interpretation and practical application of the existing body of knowledge. Further applied research will be required to determine the potential nutritional value of parasite control programs in selected ecosystems.

A number of recent reviews and symposia have considered the nutritional effects of parasitic infections [2-4] and the economic implications of these infections [5]. The reader is advised to consult these papers for additional information.

General Aspects of Helminthic Infections

The life cycles of most intestinal helminths of humans do not require an intermediate host for replication, even though obligate development takes place in soil [6]. Although reinfection with larvae of *Strongyloides stercoralis* and auto-inoculation of embryonated eggs of *Enterobius vermicularis* are exceptions to the rule, intestinal helminths generally do not multiply within the host. Thus, the number of parasites can remain fairly stable over time and the worm burden is often light. Most studies that have carefully examined the functional or nutritional consequences of enteric helminths have identified quantitative relationships between the number of worms and their pathological effects. The presence of infection is not necessarily indicative of disease. Thus, it is imperative to consider parasitic infections as continuous rather than discrete variables when evaluating the nutritional effects of these infections. This concept cannot be overemphasized since failure to quantify worm burdens has been the source of much confusion in and misinterpretation of the existing literature.

Ascariasis

Most discussions of ascariasis begin with an obligatory statement regarding its ubiquitous distribution and a humble recognition of the

sizeable metabolically active mass of an adult worm. Indeed, considering that 1.3 billion of the earth's inhabitants harbor an average of six adult worms weighing approximately 5 g each, humans must share their food supply with approximately 39 millon kilograms, or 43,000 tons, of this parasite [7]. Assuming that the worms do not subsist only on food that would otherwise be unabsorbed by the host, there is a clear nutritional cost of the parasite when viewed in these macroscopic terms. Nevertheless, because this nutritional burden is shared by such a large number of individuals, it has been difficult to demonstrate major nutritional consequences for individual hosts. Except for the obstructive complications of ascariasis — which are certainly not trivial, even when considered in terms of their public health impact [8-9] — the clinical effects of ascariasis are subtle.

Driven as much by the economic consideration of feed efficiency in parasitized animals as by a concern for the health status of human populations, researchers have examined a variety of nutritional aspects of ascariasis. Pertinent studies will be presented according to the specific mechanism of potential nutrient loss. The reader is also referred to a review of this topic by Stephenson [10].

Dietary Intake

An excellent, recently published review of the influence of parasitic infection on the food intake of experimental animals concluded that "unequivocally host food intake is often altered during the course of infection with eukaryotic parasites" [11]. Although it might be concluded from the perspective of human populations that food not consumed is not really wasted since is remains available to other members of the family or community, the functional implications for individuals of reduced food intake cannot be ignored. Reduced physical activity and consequent exploration of the environment by parasitized children may be direct consequences of impaired appetite and reduced energy consumption, even if alterations in growth cannot be identified.

In addition to the presentation of individual studies of the effects of a variety of parasites, Crompton's paper [11] highlighted several general points of interest. First of all, parasite-induced alterations in dietary intake may vary according to the stage of the infection. Most animal experiments evaluate the consequences of newly acquired infections; only rarely are the effects of chronic and recurrent infections

monitored. Since the latter infectious pattern is typical of parasitic diseases encountered in human populations, the available animal studies must be interpreted with caution. Secondly, as alluded to previously, several studies have emphasized the negative and progressive relationship between parasite load and dietary intake.

Specific studies of dietary intake during ascariasis include two experimental infections of pigs and one field study of young children. Stephenson and coworkers [12] completed a series of studies of dietary intake, nutrient absorption, growth, feed efficiency and intestinal morphology of young pigs infected with *Ascaris suum* and randomized to either a low protein or high protein diet. During periods of "controlled ad libitum feeding" (i.e., animals were permitted to consume their diets freely to a maximum of 5% of body weight), there was some indication that heavily parasitized animals reduced their consumption. The interpretation of these studies was somewhat complicated, however, by the variable worm loads and the small numbers of infected animals. During one of three experiments, the three most heavily infected pigs consumed slightly less than the corresponding non-infected controls (4.38 vs 4.74% of body weight P < 0.10).

Forsum and colleagues [13] evaluated nutritional aspects of *Ascaris suum* infection during two studies of young protein-deficient pigs (Table 2). The worm burdens during the first experiment were relatively low and highly variable. No effect of the infection on dietary intake was observed. A different technique for producing infections during the second experiment yielded heavier, less variable infections. Dietary intake was significantly depressed by the infections during this latter experiment. Indeed, it was concluded that the reduction in food intake in experiment two was "probably the major factor that contributed to the growth reduction of the Ascaris-infected pigs".

A single study of the ad libitum dietary intake of free living parasitized children has been published by Hussain [14], who reported that 36 children with isolated *Ascaris lumbricoides* infections of unquantified intensity consumed 61 ± 20% of their recommended energy needs, whereas 15 uninfected children consumed 78 ± 24% of their recommended allowances (P < 0.05). Unfortunately, the age range of children infected only with ascaris (5.0 ± 3.6 years) differed markedly from the uninfected comparison group (1.6 ± 2.4 years), so it is impossible to attribute differences in dietary intake to the infection alone. Age-related differences in feeding practices can exert sizeable effects on dietary intake.

TABLE 2 - *Effect of* ascaris suum *infection on the dietary intake of young protein-deficient pigs.*

	Worm Burden (No.)	Food Intake (g total solids/ kg body weight/d)
Experiment 1		
Infected (n=5)	31 ± 25*	36 ± 2
Control (n=6)	0	34 ± 2
Experiment 2		
Infected (n=6)	106 ± 16	27 ± 4 †
Control (n=6)	0	38 ± 2

* Mean ± S.E.

† Infected significantly different from control ($P < 0.05$).

Data from Forsum *et al.*, « Parasitology », *83*, 497-512 (1981).

Furthermore, dietary intake can be dramatically influenced by socioeconomic factors, which can also affect rates of parasitism. Since these factors were not controlled in their study, it is impossible to assign causal importance to the presence of worms. It is clear that more work is required to quantify the effects of ascariasis on the dietary intake of human populations. Nevertheless, the weight of evidence from the available experimental studies suggests that a slight depression in voluntary dietary consumption may accompany heavy ascaris infections.

Intestinal Digestion and Absorption

General reviews of the intestinal pathophysiology of enteric parasitic infections are available [15-18]. Alterations in intestinal morphology and digestive and absorptive functions have been described during ascariasis. Martin *et al.* [19] have recently presented a series of elegant scanning electron micrographs of the intestinal mucosal surface of protein-deficient animals infected with *Ascaris suum*. There were subtle disruptions of the villus architecture of the infected animals, including flattening of the villus surface and fusion of adjacent villi. These changes were patchy in distribution and were sometimes observed in segments of intestine

where no worms were present. Mucosal damage tended to be more severe in anterior than posterior segments of the small intestine. At higher magnification, small craters of uncertain significance were identified on the micro-villi of the enterocyte surface. The authors speculated that these lesions might be related to the malabsorption of lactose that has been reported to occur during ascariasis since lactase activity is located in the brush border. The findings from this study are compatible with the evidence of villous deformation, crypt elongation, and cellular infiltration of the lamina propria that had been reported previously by light microscopy [20].

Pancreatic enzymes and bile salts are required for hydrolysis of macronutrients, solubilization of fats and consequent maximal assimilation of these nutrients. Inhibitors of pancreatic proteases have been isolated from *Ascaris lumbricoides* [21-22], but inhibitors of other pancreatic enzymes have not been identified. Specific studies of bile salt metabolism during ascariasis are lacking, with the exception of the complete absence of bile secretion observed clinically during mechanical obstruction of the biliary tree. Additional information in this area would be of interest since relative malabsorption of fat has been associated with ascariasis, as described below.

Other intraluminal events that might deprive the host of ingested nutrients include direct competition by the roundworms and secondary small intestinal bacterial colonization conditioned by them. Quantitative empirical studies of these hypothetical events have not yet been completed, however.

Several experimental studies have examined the impact of intestinal ascariasis on intestinal absorption. The previously cited studies by Stephenson et al. [12] reported slightly reduced apparent nitrogen absorption (70.8% vs 75.5%) and retention (42.4% vs 48.4%) by their infected, low protein dietary group compared with controls during the early stage of infection. These differences — derived from only three infected pigs — were not statistically significant. By contrast, the apparent absorption of fat was significantly reduced in the infected, low protein group during week eight of the infection (74.4% vs 82.3%, p < 0.10). The average daily increment in body weight (0.13 kg vs 0.16 kg/d) was less in the infected group (P < 0.05) and the efficiency of feed utilization (6.87 vs 3.32 kg feed/kg gain) was reduced (P < 0.10).

During the two sets of experiments by Forsum et al. [13], reduced true digestibility of nitrogen was found in one experiment (80.9% vs

85.2%, P < 0.05) and reduced biological value of dietary protein was noted in the other (69.7% vs 78.5%, P < 0.05). The fat digestibility of infected pigs was lower during both experiments (Table 3). Differences in weight gain between infected and uninfected pigs appeared during the second month following infection. These differences were exaggerated in animals receiving low protein diets and in those with greater worm burdens. These authors also reported that lactase levels in the mucosal scrapings decreased by more than 50% in the ascaris infected groups on both diets (Table 4) and lactose tolerance (blood glucose rise following lactose ingestion) was significantly reduced. These findings are consistent with recent reports of lactose malabsorption by ascaris-infected children [23].

Impact of Ascariasis on Children's Nutrient Absorption and Growth

More than 30 years ago Venkatachalam and Patwardhan [24] showed that children with relatively heavy ascaris loads excreted significantly less fecal nitrogen after pharmacological elimination of the worms. Tripathy and coworkers [25] similarly found improved nitrogen absorption following successful treatment for ascariasis and additionally showed an improvement in the absorption of fat and d-xylose in their patients. More recent studies from Bangladesh have confirmed the adverse

TABLE 3 - *Mean (± S.E.) digestibility and biological value of dietary protein and apparent digestibility of fat by protein-deficient, ascaris-infected young pigs and controls.*

| | Experiment 1 | | Experiment 2 | |
	Infected (n=5)	Control (n=6)	Infected (n=6)	Control (n=6)
True N Digestibility (%)	81 ± 2[a]	85 ± 1	79 ± 2	78 ± 1
Biological Value (%)	73 ± 2	73 ± 2	70 ± 3[a]	78 ± 2
Fat Digestibility	71 ± 2	77 ± 2	62 ± 1[b]	71 ± 2

[a] Infected vs control, P < 0.05.
[b] Infected vs control, P < 0.01.
Data from Forsum *et al.*, « Parasitology », *83*, 497-512 (1981).

TABLE 4 - *Mean (± S.E.) lactase activity * from small intestinal mucosal scrapings of ascaris-infected and control pigs receiving low and normal protein diets.*

Intestinal Segment	Low Protein Diet		Normal Protein Diet	
	Infected (n=16)	Control (n=6)	Infected (n=11)	Control (n=4)
Upper small intestine	37 ± 5[a]	69 ± 3	27 ± 9[b]	52 ± 2
Mid-small intestine	6 ± 1[a]	16 ± 3	5 ± 1[b]	14 ± 3
Lower small intestine	2 ± 0	3 ± 1	1 ± 0	3 ± 1

* Expressed as mole glucose liberated/min/g mucosal protein.

[a] Infected vs control, $P < 0.01$.

[b] Infected vs control, $P < 0.05$.

Data from Forsum et al., « Parasitology », 83, 497-512 (1981).

effect of ascariasis on nitrogen and fat absorption; but, notably, found these effects only in children with relatively heavy infections [26]. Absorption of nitrogen and fat was significantly less in children with heavy infections (> 10 worms) than in children with light infections before therapy, and improved significantly following therapy only in the heavily infected group (Table 5). Furthermore, there was a positive linear relationship between the number of worms present initially and the degree of change in the percentage of dietary nitrogen absorbed after therapy. Xylose absorption improved slightly in both groups, but the differences were not statistically significant.

Despite the similar conclusions of these three papers, other authors have not found significant positive effects of ascaris therapy on intestinal absorption [27-29]. These latter studies were compromised, however, by small numbers of patients, a failure to report worm burdens, unsuccessful elimination of all worms and/or failure to maintain the patient's dietary intake constant before and after therapy (Table 6). It seems fair to conclude, therefore, that severe intestinal ascariasis does indeed interfere with normal nutrient absorption.

Although this review focuses on the absorption of macronutrients, it is worthwhile to note two studies of vitamin A absorption by ascaris-infected children since the pathway for retinol absorption is similar to that

TABLE 5 - *Absorption of nitrogen and fat before and after therapy for ascariasis by severity of infection.*

Severity of Infection	Nitrogen Absorption (% Intake)		Fat Absorption (% Intake)	
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx
Heavy (n=8)	57.2*	65.9	93.4	96.6
	± 6.2	± 3.4	± 5.2	± 1.5
	P < 0.02		P < 0.05	
Light (n=5)	64.1*	65.8	96.0	96.5
	± 5.3	± 2.9	± 0.8	± 0.8
		N.S.		N.S.

* Difference between heavy and light infections before therapy: $0:05 < P < 0.10$.
Data from Brown *et al.*, « Am. J. Clin. Nutr. », *33*, 1975-1982 (1980).

for dietary triglycerides. In each of these studies, mean vitamin A absorption — as detected by radioisotopic tracers [30] or by vitamin A tolerance tests [31] — was impaired during infection and improved following therapy.

In addition to these clinical studies, cross-sectional (case-control) and longitudinal treatment studies have been conducted in the field to enhance our understanding of the nutritional cost of ascariasis. One such cross-sectional study completed in rural Louisiana found that ascaris-infected children had lower serum albumin levels than non-infected controls of similar socio-economic and dietary status [32]. These results are especially intriguing in view of the previously mentioned effects of ascaris on nitrogen absorption.

Although the forementioned studies suggest that eradication of ascariasis in a community might be expected to yield an observable nutritional benefit, presently available field trials offer conflicting results (Table 7). Unfortunately, it is often difficult or impossible in the field setting to control for all of the potentially confounding variables such as socio-economic status, dietary intake, worm burdens, other parasitic and non-parasitic infections, ineffective antihelmenthic therapy, rapid reinfection, self-treatment, etc. These considerations make interpretation of such field studies much more problematic. It is not entirely surprising,

TABLE 6 - *Comparison of six clinical studies of intestinal absorption in relation to ascaris infection.*

Author/Year/Ref	No. of Subjects	Controlled Dietary Intake	Worm Loads Reported	Success of Ascaris Therapy Documented	Control Group	Improvement in Intestinal Absorption		
						N	Fat	Xylose
Venkatachalam (1953) [24]	9	Yes	Yes	Yes	Before vs After rx	Yes	ND	ND
Tripathy (1971) [25]	12	Yes	Yes	Yes	Before vs After rx	Yes	Yes	Yes
Brown (1980) [26]	13	Yes	Yes (8 heavy inf; 5 light inf)	Yes	Before vs After rx Heavy vs light infec	Yes	Yes	± *
Bray (1953) [27]	4	Yes	Yes	No	Before vs After rx	No	ND	ND
Teotia (1969) [28]	5	Yes	No	No	Uninfected Children	ND	No	ND
Freij (1979) [29]	13 (6 piperazine; 7 placebo)	No	Yes	?	Before vs after rx; Rx vs placebo	No	No	± **

ND: Study not done.   *: Not statistically significant.   **: Improvement seen in both treatment and placebo groups.

TABLE 7 - *Comparison of five field studies of increments in nutritional status following treatment of ascariasis in children.*

Author/Date (country) (ref)*	Type of Therapy	Control Group	Length of Follow-Up of Nutritional Status	Analysis by Worm Load	Nutritional Status Outcome
Gupta/1979 (India) [53]	Tetramisole one daily dose two days, every four months	Assigned to rx or placebo by village	1 Year	No	Greater proportion of treated children showed improved nutritional status
Willet/1979 (Tanzania) [33]	Levamisole, 3 monthly	Matched ascaris-infected & non-infected control (placebo)	1 Year	No	Greater weight gain in levamisole-treated, ascaris-infected group than in matched controls
Stephenson/1980 (Kenya) [34]	Levamisole, single-dose	Uninfected children	14 weeks before rx, 14 weeks after rx	No	Poorer increments of triceps fatfold in infected group before rx & better increment of triceps fatfold & weight in infected group after therapy
Greenberg/1981 (Bangladesh) [35]	Piperazine 2 doses within 2 week period	Random assignment to placebo	11 Months	Yes	No effect of therapy (Although incomplete cure rates & rapid reinfection were noted, no nutritional effect was observed even when only cured patients were considered)
Kloetzel/1982 (Brazil) [54]	Mebendazole 2 doses x 3 d	Random assignment to placebo	10 Months	No	No effect of therapy on nutritional status even when only cured patients were considered

* Refers to reference number in bibliography.

then, that the few controlled treatment studies that are available have arrived at different conclusions.

Three of the most extensive community-based treatment studies are presented in some detail; other relevant studies are noted in Table 7. In 1979 Willett [33] reported the results of three-monthly levamisole therapy (or placebo) on the annual weight gain of matched groups of both ascaris-infected and non-infected Tanzanian children. He reported a significantly greater weight gain in the levamisole-treated group, particularly among those known to be infected with ascaris at the outset of the study. Since egg counts were completed for the infected children, it would have been interesting to know whether heavier infections were associated with smaller increments of weight during the study period, but these results were not reported.

The following year Stephenson and coworkers [34] reported their findings from a single dose trial of levamisole in ascaris-infected Kenyan children. They treated all infected children so there was no untreated control group. Instead, they compared the increments of weight and triceps fatfold thickness during 14-week periods before and after therapy in infected and non-infected children. The choice of control groups is unfortunate since inherent differences in children who are or are not infected potentially bias the interpretation of the anthropometric findings. The results showed a significantly greater increment of triceps fatfold among non-infected than infected children before therapy and a greater increment in both weight and fatfolds among the infected children after therapy. Although the authors concluded that there was a beneficial effect of levamisole therapy, it is difficult to explain their observation that the uninfected children gained relatively less weight following therapy (compared with the infected group). The negative increment in triceps fatfold of the control group following therapy is also a puzzling finding.

A third study reported by Greenberg et al. [35] compared changes in nutritional status among ascaris-infected and non-infected Bangladeshi village children randomly assigned to a single course of piperazine therapy or placebo at the beginning of eleven months of observation. Their carefully controlled study found no difference in nutritional status between treatment groups during the period of observation. These negative findings persisted even after controlling for the initial worm burden and for the outcome of therapy for the initial infection. Notably, incomplete elimination of worms (especially among heavily infected children) and

rapid reinfection were common. Detectable effects of treatment on worm burdens persisted only for five months.

One additional thought-provoking study deserves consideration in this section. Cerf and coworkers [36] examined the nutritional status of Balinese village children by their intensity of ascaris infections. Although the villages were of similar socioeconomic status in terms of per capita income and educational levels, the inhabitants of the central village had better access to health services and consumed significantly greater amounts of dietary energy and protein. Whereas there was no relationship between ascaris infection and nutritional status in the central village, the intensity of infection was negatively related to nutritional status in the outlying villages, explaining 18% of the variability in the percentage of expected weight for age. The authors concluded the relationship between ascariasis and malnutrition was detectable only in the face of heavy infections and was conditioned by multiple factors such as dietary intake and access to health services.

STRONGYLOIDIASIS

This second helminth selected for more detailed discussion was chosen because of the wealth of experimental data on nutritional aspects of *Nippostrongylus brasiliensis* infections in rats. Detailed studies of the dietary intake and intestinal function of infected animals have been reported. On the other hand, relatively little has been written about the nutritional effects of *Strongyloides stercoralis* infections in humans.

Dietary Intake

A series of elegant studies of the dietary intake of rats infected with *Nippostrongylus brasiliensis* have been completed at the Molteno Institute [37-39]. In the first paper cited, food intake and body weight of infected rats fed low or high protein diets were compared with those of non-infected, ad libitum fed and with non-infected, pair-fed controls [37]. The food intake declined in all rats following the introduction of the low protein diet, but the degree of reduction by infected rats was generally significantly greater than by uninfected controls. No significant differences were detected by infection status in the high protein dietary group. Both pair-fed, non-infected rats and the infected animals lost weight on the low protein diet,

but, interestingly, the infected group lost significantly more than their pair-fed controls. Subsequent studies demonstrated that the decline in dietary intake was dose-related and followed a specific day-to-day pattern that included two discrete dips in intake [39]. The relationship between these decrements in food consumption and specific phases of the infection was not clear, however. In another intriguing series of experiments, it was demonstrated that infection with *N. brasiliensis* produced a specific taste aversion to the diets that the rats were receiving at the time of the induction of the infection [38].

Intestinal Digestion and Absorption

As previously described with regard to experimental *Ascaris suum* infections, *Nippostrongylus brasiliensis* produced morphological changes in the intestines of infected rats studied with scanning electron microscopy [40]. The changes were dose-related and included shortening and flattening of the villi, villus fusion and increased number and activity of goblet cells.

Scofield had previously studied the effect of the level of infection with *N. brasiliensis* on absorption of hexoses [41]. Significant reductions in some transfer parameters occurred with as few as 100 larvae. These findings were confirmed by recent studies of Nolla *et al.* [42], who found changes in net intestinal glucose uptake beginning on the fourth day post-infection. Parasite-induced water secretion was also detected after day four, but disappeared by days 13 to 19, when worm expulsion had already begun. A further set of studies by Cheema and Scofield [40] examined the effects of continuous, daily challenges with *N. brasiliensis* larvae on glucose absorption. Unlike the results following single, acute infections, no specific effects of infection on intestinal function could be identified. These results are noteworthy, since chronic exposure may be more common in natural settings.

Although few, well-controlled clinical studies of the effects of strongyloidiasis in humans are available, one study by Garcia *et al.* [43] deserves mention. Malnourished, infected adults were treated either with thiabendazole and a low protein diet or with a high protein diet and no antihelminthic drug. The malnourished patients of both treatment groups had reduced xylose excretion and fat absorption compared with infected, but better nourished, control patients. The malnourished patients who received drug therapy showed delayed recovery of intestinal absorptive

function, whereas those who received dietary therapy demonstrated improvement despite persistence of the infection. The authors concluded that malabsorption was secondary to the malnourished state of the host and not to the parasitic infection *per se*. These findings have been cited to stress the complexity of the relationship of acute and chronic helminthic infections, nutritional status, diet and intestinal function. Our understanding of these complicated and inter-related events is still limited.

Other Helminthic Infections

Adverse nutritional effects have been attributed to a number of other intestinal helminths including hookworm [44-45], heavy infections with *Trichuris trichiura* [46], *Fasciolopsis buski* (Gilman, unpublished), and several cestodes [47-48]. *Trichinella spiralis* has been used in animal models to study the effects of nematode infections on dietary intake [49], gastric secretion [50], intestinal motility [51] and intestinal absorption [52]. Discussion of the details of all these studies is beyond the scope of the present review.

CONCLUSIONS

The bulk of evidence from both clinical and experimental studies suggests that, in general, subtle reductions in dietary intake and intestinal absorption occur during some phases of acute helminthic infections. Studies of the nutritional effects of chronic infections, however, have yielded more variable results. In both cases, there is a clearcut relationship between the number of worms and the magnitude of the nutritional effects. It makes little sense to discuss the presence or absence of infection; rather it is important to quantify the severity of the infections that are present in order to judge their potential nutritional importance.

Another general conclusion to be derived from the available evidence is that the diet and nutritional status of the host will modulate the nutritional impact of a given infection. When unlimited amounts of a high quality diet are available, the nutritional consequences of infection are often negligible. The same degree of infection in an undernourished individual receiving a marginal diet will result in more severe nutritional complications.

The programmatic implications of these observations are still uncer-

tain.   Although this review has focused specifically on the nutritional effects of enteric helminths, programmatic decisions must also take into account the obstructive complications of roundworms and the potential importance of worm therapy from the perspective of the "felt needs" of the community. If a community believes strongly in the value of anti-helminthic therapy, this might be a useful means to encourage participation in primary health care programs.   Thus, parasite eradication programs may have secondary advantages even if a positive nutritional impact is not demonstrable. Although some nutritional advantage might be expected from treatment of children with heavy worm burdens, practical questions that must still be addressed are: (1) Is it cost-effective to identify children with heavy worm burdens and target treatment accordingly, or is it more economical to treat all individuals in a community regardless of their infection status?   (2) Since heavy infections are most resistant to treatment, will a single round of periodic therapy eradicate the infection in those heavily infected individuals who are most likely to benefit from successful therapy? (3) If appetite is not severely depressed by infection, would it be more economical to provide supplementary feedings to overcome the effect of malabsorption, or would it be more advantageous to provide antihelminthic therapy? (4) Most importantly, will a clear and functionally important nutritional advantage be obtained from antihelminthic therapy under the practical constraints and real conditions of individual communities?

Additional research will be required to address these issues. Ideally, future prospective treatment studies should simultaneouly evaluate the dietary intake, initial nutritional status and worm burdens of infected populations. Appropriate untreated comparison groups must be included and sufficient effort must be devoted to control potentially confounding variables such as socioeconomic status, rates of non-parasitic infections, success of therapy, unscheduled therapy, reinfection, and so on.   These studies will be difficult to carry out, but not impossible; the results obtained would permit rational decisions on whether to commit the necessary resources to eradication programs and to what extent might nutritional benefits be expected.

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NUTRITION IN PARASITIC DISEASES:
SCHISTOSOMIASIS AND CHAGAS' DISEASE (*)

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Introduction

Similarly to other infectious and parasitic disease, a complex inter-relationship appears to link *T. cruzi* infection and schistosomiasis to the nutritional status of the host and function of the immune system. Although infections in humans have often been shown to be worsened by pre-existing malnutrition, and then to contribute to an increase in coexisting nutritional deficiencies, this has not been always the case. In animals, equivocal findings were reported in protein deficient mice infected with *S. Mansoni*, and, in rats, *Trypanosome gambiensis* infection was less severe in protein deficient animals [1].

In humans, demonstration of a cause-and-effect relationship between degree of malnutrition and severity of most parasitic infections is still lacking. The number of uncontrollable variables in studies designed to tackle this problem have been too large. This is well exemplified in the variables associated with study of *T. cruzi* and schistosome infections:

1. These parasitic infections rarely occur as isolated events. Other parasitic and infectious diseases are prevalent in areas where they are endemic.

2. Infecting doses of these parasites in humans are usually not measurable, exposures are continually occurring, and the diseases are chronic. Since clinical pictures are widely variable, it becomes particlarly difficult in such a dynamic setting and throughout many years of natural evolution of these diseases, to define clearly the inter-relationship with nutritional deficiencies.

3. In addition, nutritional deficiencies in humans are complex in terms of their severity, nature and multiplicity of involved nutrients, duration, and the impact of coexisting infectious and other diseases. They are also chronic, and may show seasonal variations and exhibit great variability among different regions.

4. Finally, Chagas' disease and schistosomiasis are clearly related to poor socio-economic conditions as well as malnutrition and many other infectious diseases. Determinants of malnutrition also favour the prevalence and incidence of these conditions.

Schistosomiasis: Diversity of Clinical Presentations

There has been great progress in the understanding of schistosomiasis in recent years, mainly as a result of experimental studies of the immunopathogenesis of this disease and field studies evaluating the morbidity and the effects of therapeutic interventions. The disease affects around 300 million people and is an important cause of morbidity and mortality in endemic areas [2].

The biology of schistosomiasis suggests that malnutrition could affect the parasite, the host and the interaction between them. Consideration of the host-pathogen biology allows characterization of schistosomiasis as an immunologic disease in response to the deposition of ova in tissues [3].

There are distinct clinical phases in schistosome infection: a) *the acute phase,* or Katayama fever, which occurs 30 to 60 days after infection by *S. japonicum* or *S. mansoni.* It is characterized by fever, abdominal pain, diarrhea, arthralgia, and occasionally skin eruptions, usually subsiding within three to six weeks; b) *the chronic phase* covering the subsequent course of this parasitic infection. Most patients in an endemic area remain as "egg passers", without well defined clinical manifestations; others due to fibrosis around eggs develop increasing portal fibrosis (*S. mansoni* or *S. japonicum*) or urinary bladder fibrosis (*S. hoematobium*). This phase may result in hepatosplenomegaly, portal hypertension with consequent

esophageal varices (*S. mansoni* or *S. japonicum*) or lower urinary tract obstruction with resulting hydronephrosis (*S. hoematobium*). In a few heavily infected individuals, an extensive intestinal inflammatory reaction may give rise to colonic polyposis or pseudotumor formation; in others, extensive pulmonary deposition of eggs and interstitial fibrosis lead to pulmonary hypertension with "cor pulmonale". Finally, as a result of the immunological derangement observed in this disease, a few patients develop an immune-complex glomerulopathy which can evolve to chronic renal failure.

The complexity of the clinical picture and the variability of the disease from country to country make it easy to understand the difficulties encountered in correlating schistosomiasis with malnutrition.

Nutritional Implications in Human Schistosomiasis

The nutritional implications of schistosomiasis have been recently reviewed by Akpon [4]. The difficulties in answering basic questions related to this problem are compounded in humans, where studies are meager or lacking. DeWitt *et al.* [5] compared the influences of nutrition in a group of undernourished prisoner volunteers infected with *S. mansoni*. One group received an enriched diet for nine months and responded with an overall improvement in nutritional status, as compared to the other. Treatment with Stibophen of both groups was equally effective however and there was no detectable effect of the feeding program on the schistosomiasis.

The association of heavy schistosome infection with isolated nutritional deficiencies has been sporadically reported in the literature (Tables 1 and 2). In Egyptians with *S. mansoni* infection an increased fecal blood loss has been documented [6]. The chronic loss of blood (and iron), however, is greater in cases of *S. hematobium*. Protein losing enteropathy has also been described in patients with polyposis as well as the loss of vitamins and albumin-bound trace elements [6]. Heavy infection has also been responsible for fat malabsorption [7], glucose intolerance [8] low D-xylose absorption [6] and subnormal levels of serum carnitine [9]. Coutinho [10] compared nutritional status and weight-for-height in patients with and without *S. mansoni* infection in two endemic areas in Pernambuco, Brazil. Signs of malnutrition and subnormal weight-for-height were more common in the *S. mansoni* infected group. Also, symptoms atributable to schistosomiasis were exacerbated in malnourished patients. No cor-

TABLE 1 - *Schistosoma infections: nutritional implications in human clinical studies.*

Clinical findings	Infections	Reference
Improvement in nutritional status following enriched diet with no effect on parasite infection.	*S. mansoni*	De Witt *et al.*, Am. J. Trop. Med. Hyg., *13*, 25-33, 1964.
Signs of malnutrition and subnormal weight for height in infected group.	*S. mansoni*	Coutinho - Thesis, Recife, 1976.
No effect in standard weight, height and skin fold thickness (group aged 5-18 years).	*S. mansoni*	Lehman *et al.*, Am. J. Trop. Med. Hyg., *25*, 285-294, 1976.
Weight gain after successful treatment.	*S. hoematobium*	Latham *et al.*, Trans. Roy. Soc. Trop. Med. Hyg., *77*, 41-48, 1983.

TABLE 2 - *Schistosoma infections: nutritional implications in human clinical studies.*

Clinical findings	Infections	Reference
Blood loss from gastrointestinal tract.	*S. mansoni* *S. hoematobium*	Waslien *et al.*, South Med. J., *66*, 47-50, 1973.
Protein losing enteropathy.	*S. mansoni*	Waslien *et al.*, South Med. J., *66*, 47-50, 1973.
Low D-xylose excretion.	*S. mansoni*	Waslien *et al.*, South Med. J., *66*, 47-50, 1973.
Fat malasorption.	*S. mansoni*	El Rooby *et al.*, J. Egypt. Med. Ass., *46*, 777-782, 1963.
Glucose intolerance.	*S. mansoni*	Ghanem *et al.*, J. Trop. Med. Hyg., *74*, 189-194, 1971.
Low levels of serum carnitine.	*S. mansoni*	Mikhail & Mansour, Clin. Chim. Acta., *71*, 207-214, 1976.

Adapted from Akpon C.A., Rev. Infect. Dis., *4*, 776-782, 1982.

relation was found between low serum albumin and anemia with *S. mansoni* infection, but there was a correlation with malnutrition. A similar lack of association between anemia and severity of *S. mansoni* infection was documented by Lehman *et al.* [11]. The authors found, however, blood in feces more frequently associated with increasing egg excretion. No deleterious effect of schistosomiasis was apparent in patients aged 5 to 18 years when percent of standard weight, height and skin fold thickness was plotted against egg counts. The lack of alteration in patterns of growth was similar to results noted by Cook *et al.* [12] in St. Lucia and Walker *et al.* [13] in South Africa.

Latham *et al.* [14] studied the prevalence of anemia in hookworm, malaria and *S. hematobium* infected roadworkers in Kenya, to evaluate the feasibility and effectiveness of field treatment of the worms and chloroquine prophylaxis. It was a surprise to the authors when successful treatment of urinary schistosomiasis with Metrifonate was associated with weight gain. In fact, successful therapy of urinary schistosomiasis was associated with increased weight gain and improved nutritional status, particularly in men with relatively high initial egg counts. For ethical reasons it was decided not to have untreated control groups. Changes in weight between the baseline and the final examination were used as a means of evaluating the results of therapy. It is of interest that 31% of patients included in this study were markedly underweight, with a weight for height below 80% of the expected value, and only 21% of men had a weight for height above 90% of the expected value. The number of patients studied was small, however, and they had relatively low egg counts in the urine.

A survey on the nutritional consequences of *S. mansoni* infection, hookworm and giardiasis was undertaken in the Malumfushi area of north Nigeria [15]. There was a low prevalence of *S. mansoni* in the area (4% in children aged 5-15 years). Anthropometric data suggested a high incidence of protein-energy malnutrition. The authors correlated the greater wasting with poor water supply. Giardiasis was considered a possible factor for impaired nutrition in pre-school children in this area. No correlation could be drawn regarding *S. mansoni* infection.

In Jacobina, Brazil, a small town in the interior of the State of Bahia (40,000 inhabitants), a prospective survey of the cumulative prevalence of several parasitic diseases has been in progress in recent years (Figure 1). This survey was part of a study to detect relevant factors contributing to the occurrence of visceral leishmaniasis. The town is
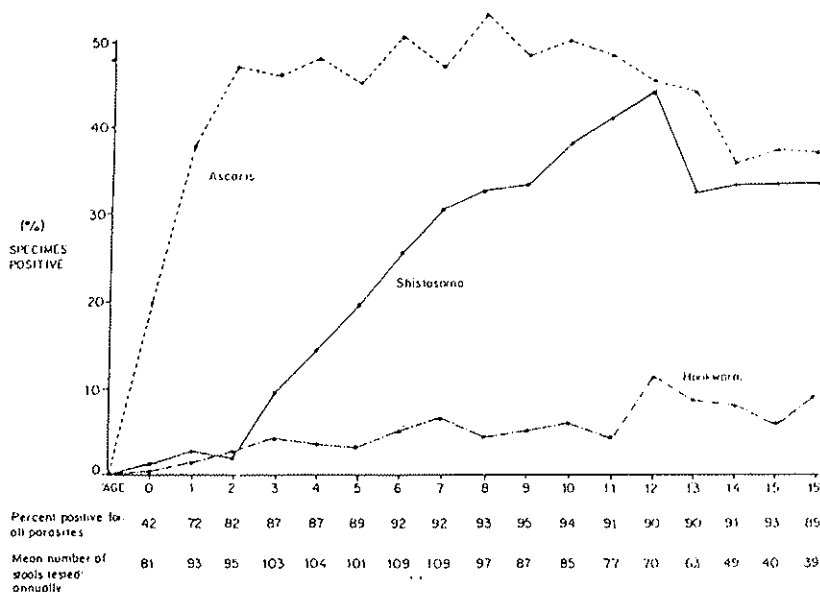
FIG. 1. Occurrence of some parasitic infections in children 0-15 years in Jacobina (Bahia).

endemic for several parasitic diseases including visceral leishmaniasis and schistosomiasis. A health post for care of all clinical illness has been properly staffed and an annual survey has been done of a mean annual population of children under age 15 years in 636 families for the past 5 years. Parasitologic stool examination used the method of Faust. A survey of weight-for-age and height-for-age was used to evaluate relationship with malnutrition. As compared to a group of patients with no detectable parasitic infection, patients with schistosomiasis showed a highly significant ($p < 0.0005$) abnormality in weight for age (713/988 abnormal in the latter vs. 286/501 in the uninfected) (Table 3).

Comparison of the group with schistosomiasis (and other parasitic infections) with the group without schistosomiasis (but with other parasitic infections), clearly demonstrates that the additional burden of schistosomiasis results in a highly significant degree of abnormality in weight-for-age ($p < 0.005$). A similar comparison undertaken in patients with and without *Ascaris lumbricoides* (65% abnormal compared to 64%, respectively) did not show any difference ($p < .6$). The presence of schistosome eggs in stool was also correlated with more severe malnutrition (Table 4).

The difference in severe reduction in weight-for-age was observed in age groups 5 to 9 and 10-15 years, but not 0-4 years (before significant schistosome infection occurs in Jacobina) (see Figure 1). When all grades of weight-for-age were analysed (Gomez I-III) schistosome infection contributed to reduced growth at all ages (Table 5). In this study, no quantitative stool egg counts were done and correlation with severity of schistosomiasis with degrees of malnutrition was not possible. However, the data are highly suggestive that *S. mansoni* infection contributes to malnutrition in such an endemic area.

Chagas' Disease: *Pertinent Clinical Findings*

Chagas' disease is one of the major public health problems of South America and nearly 10 million people suffer from it in Latin America. This disease was discovered by Carlos Chagas in 1909 [16] who described the etiology, pathology and clinical picture in extraordinary detail and impressive perception [17]. The disease exhibits three distinct clinical phases: an acute phase, characterized by intense parasitism easily demon-

TABLE 3 - *Association between weight for age abnormality and parasitism in children in Jacobina, Bahia* (Bahia-Cornell project).

Group	Nº Studied	Abnormal weight/age	% abnormal	p. value
1. No parasites	507	286	56	
2. Two or more +	1008	708	70	< .0005*
3. *S. mansoni*	998	713	71	< .0005*
4. No *S. mansoni*	3143	1943	62	< .03* < .0005**
5. *A. lumbricoides*	1990	1288	65	< .0005*
6. No *A. lumbricoides*	2151	1368	64	< .0004* < .6***

+ (Including *S. mansoni, A. duodenale, E. histolytica, A. lumbricoides*).

* Comparison with Group 1.

** Comparison with Group 3.

*** Comparison with Group 5.

TABLE 4 - *Severe malnutrition in patients with* S. mansoni *in Jacobina.*

Group	(Age)	Number and percent of children within Gomez criteria II or III in weight for age							
		0-4 yrs		5-9 yrs		10-15 yrs		All yrs	
		No	%	No	%	No	%	No	%
No intestinal parasites		32/413*	10	10/101	10	27/92	29	69/507	14
S. mansoni		5/124	4	77/454	17	153/420	36	235/998	24
No S. mansoni		134/1356	10	158/1066	15	249/725	33	541/3143	17

* Number abnormal over number studied.

TABLE 5 - *Abnormality* (%) *in weight for age in children in Jacobina (Bahia) related to* S. mansoni *infection.*

Group	(Age)	No and abnormal (Gomez criteria I to III)							
		0-4 yrs		5-9 yrs		10-15 yrs		0-15 yrs	
		No	%	No	%	No	%	No	%
S. mansoni		67/124	54	317/454	70	329/420	78	413/998	71
No S. mansoni		694/1356	51	694/1066	65	555/721	77	1943/3143	62
No parasite		160/314	51	62/101	62	65/92	70	92/507	56

strated in the circulation and some tissues of the affected host; an indeterminate or latent phase, characterized by the absence of clinical symptoms and positive serology extending for several years or some decades following the original infection; and a chronic phase characterized by cardiac or digestive tract involvement.

Most patients with Chagas' disease in endemic areas demonstrate only positive serology. A minority develop evidence of chronic disease, however factors contributing to progression of the disease are still unknown. Some of the probable factors are listed in Table 6. It is likely that the outcome of the indeterminate phase is primarily dependent on the initial infection, even though reinfection, stress and other factors probably play additional roles. The importance of host factors has been stressed in several publications, and the role of nutrition in this setting has been

TABLE 6 - *Factors in the evolution of Chagas' disease.*

T. cruzi intraspecific variations
Nature of inflammatory process
Immune pathological mechanisms
Reinfections
Host factors:
age, sex, race
Nutritional status
Intercurrent diseases

mentioned by Prata [23], Marsden [24] and Pereira *et al.* [25]. However, no specific study on nutritional status and Chagas' disease in man has been undertaken.

Chagas' disease is distinctly related to poor social and economic conditions. Its highest prevalence occurs in the poorest rural areas, where we also find malnutrition and high infant mortality. Despite a wealth of data concerning experimental models, pathogenesis and clinical aspects of this disease gathered in recent years, the interaction of *T. cruzi* infection and nutrition of the host has not attracted great interest.

Nutritional Studies in Experimental T. cruzi Infection

As can be seen in Table 7, a series of experiments were done in rats subjected to specific deficiencies and challenged with *T. cruzi* [18-22]. In general, deficient animals exhibited an increase in severity of the experimental infection and they demonstrated more cardiac lesions, including thiamine [18], pantothenate [20] and pyridoxine [21] deficiencies [20] but not riboflavin deficiency [19]. Vitamin A deficient animals did not exhibit increased susceptibility to *T. cruzi* infection after a short period of deprivation (4 weeks), but lesions were seen after 13 weeks of deficiency [22].

Nutritional Factors and Human Chagas' Disease

Very little is known in humans about the interaction of nutritional status of the host and *T. cruzi* infection, even though there is frequent

TABLE 7 - *Effect of specific deficiencies on susceptibility of rats to T. cruzi infection.*

Reference	Animal	Vitamin deficiency	T. cruzi infection
YAGER & MILLER Exp. Parasitology, 9, 215-222, 1960	Rats	Thiamine	↑ parasitemia ↑ cardiac lesions
YAGER & MILLER Exp. Parasitology, 10, 227-231, 1960	Rats	Riboflavin	No increase in susceptibility ? ↑ severity of infection
YAGER & MILLER Exp. Parasitology, 10, 232-237, 1960	Rats	Pantothenate	↑ severity of infection ↑ parasitemia ↑ cardiac lesion
YAGER & MILLER Exp. Parasitology, 10, 238-244, 1960	Rats	Piridoxine	↑ susceptibility ↑ parasitemia ↑ cardiac lesion
YAGER & MILLER Exp. Parasitology, 14, 9-14, 1963	Rats	Vitamin A	04 weeks - no effect on susceptibility 13 weeks - ↑ susceptibility

mention of nutrition as an important pathogenetic factor in this condition [21-23]. In fact, the major factors involved in the evolution of Chagas' disease are likely to be influenced by the nutritional status of the host. In the acute phase of Chagas' disease, a few findings suggest a possible role of malnourishment in the outcome of this process. Children up to 2 years of age are more vulnerable to malnutrition and in an endemic area such as Bambui, in Minas Gerais, mortality of acute Chagas was significantly higher in the same age group [26]. Unfortunately, the nutritional status of the patients was not analysed and other factors such as genetic determinants and immunological alterations could play an important role in this setting.

In the chronic phase, very few studies have been reported. In an isolated community located 32 Km north of Brasília, and endemic for both Chagas' disease and malnutrition, Pereira *et al.* [25] studied the serum albumin levels in patients with positive serology for *T. cruzi* compared to a seronegative control group. Diagnosis of *T. cruzi* infection was determined by fluorescent antibody, indirect hemaglutination and complement fixation tests. Levels of serum albumin and serum globulins

were compared in 41 patients who had all three tests positive and 107 who were seronegative. Serum albumin was similarly low in both groups (2.94g% ± 0.74 in patients with *T. cruzi* compared to 3.04g% ± 0.61 in controls). Serum globulins were slightly, but not significantly, higher in the seropositive group (1.91g% ± 0.40 as compared to 1.75g% ± 0.41). Similar findings have been reported by Edozien *et al.* [27] on African children living in a community plagued by endemic malaria and malnutrition. Food consumption of people in this small Brazilian village was surveyed in 93 families, and was considered deficient. However, no characterization was done in patients and controls of this study. Also, the low albumin could have been related to a high incidence of intestinal parasitic infection in the community (87.4%), with 76.7% of patients showing hookworm.

More recently, studies in endemic areas of Bahia [28] and Goiás [29] noted prevalence rates of 8.6% and 6.7% respectively of digestive involvement in chronic Chagas' disease. Symptoms of dysphagia occurred 2.5 times more frequently among seropositive individuals compared to seronegative individuals [28]. Symptoms increased with age, with a peak prevalence of 23% in the age group 45-60 years of age [30]. The morbidity produced by esophageal lesions in Chagas' disease includes weight loss, pulmonary infection (related to regurgitation) and impaired esophageal emptying. Patients with megaesophagus rapidly become undernourished, with frequent cachexia. Cardiopathy, as defined by EKG alterations, has been documented in 50% of patients with megaesophagus and megacolon.

Finally, malabsorption of glucose and galactose has been documented in some patients [30]. This has been explained by the intestinal dysmotility resulting from the intestinal denervation observed in this disease, but, so far, clinical relevance is uncertain except that the hyperabsorption of gluocse explains the rapid hyperglycemia observed in some cases during an oral glucose tolerance test [30].

In Chagas' disease, besides the deleterious effect of parasite multiplication within cells of the host, most of the long-term damage is related to immunopathogenic mechanisms, many of them already documented [31, 32]. Theoretically, at least, several of these mechanisms could be influenced by malnutrition, and this interaction should be evaluated in well conducted studies.

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III.

STRATEGIES FOR CONTROL
OF PARASITIC DISEASE

PERSPECTIVES ON MALARIA CONTROL

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In terms of severity of illness and involvement of the largest numbers of people, malaria is clearly the most important infectious disease. Not surprisingly, then, the motivation to control malaria had its roots even centuries before the causative agent — *Plasmodium* — was identified by Laveran in 1880. The strategies for malaria control have evolved under influences of philosophical, scientific, technological, sociological and economic factors. Each important innovation in disease control generally has been met with overwhelming optimism and hope that the malarial panacea was finally at hand. The full impact of some control measures has been restricted by biological developments such as resistance in both pathogen and vectors, by changing political priorities and economic realities, and even by emergence of environmentalist philosophies. The recent remarkable scientific discoveries that ushered in the age of bio-technology have provided for vaccination against malaria as the latest in a historic succession of potential control strategies. The prospects for control of this dreaded disease through vaccination are viewed with no less (and perhaps much more) optimism than that enjoyed by earlier control modalities. While we shall soon learn of the potential clinical efficacy of the first candidate malaria vaccine, and while other candidate malaria vaccines can be expected to also eventually reach at least early phase II trials, we cannot predict the impact of vaccination on malaria control. History would advise *cautious* optimism for this newest of antimalarial strategies. The unpredictability of certain biological aspects of mosquitoes and *Plasmodia,* and of human priorities and endeavors has in the past, and might also in the future, limit the utility of control strategies that today seem hopeful.

Vector Control

It is befitting this meeting that we should recall that malaria derives from the Italian "mal aria", coined at a time when periodic fevers (incidentally, also known as Roman fevers) were believed to be due to corruption of one of the Aristotelian elements, air. Undoubtedly this concept was espoused along with the philosophy that the corrupting element originated in swamps. Empirical observation had provided for the association between residing near swamps and acquiring malaria. Although the true explanation for this association was not forthcoming until the late 19th century when mosquitoes were recognized as the vectors, the earlier efforts to drain swamps must have influenced disease transmission. This earliest of malaria control practices, along with other methods to reduce mosquito breeding sites (source reduction), remains today an important modality in antimalarial campaigns.

It was only with Ross's and Grazzi's discovery in the 1880's that mosquitoes transmit malaria that a rational approach to disease control could be formulated. Naturally, Ross championed the idea that malaria could be reduced if not altogether eliminated by destroying vector breeding sites. He advocated a principle of "sanitary anarchy", the deatils of which included highly disciplined and collaborative efforts on the part of the populations to be protected. The infantry in this battle was to be organized in what he called "Mosquito Brigades". He was influenced in his design of control measures by the successful application of larval oiling in a small field trial carried out in the Catskills, New York [1]. Interestingly, a broad-based strategy for mosquito control has been articulated in a thesis written already a decade before Ross's discovery. Carrie Aaron, the thesis author, proposed a plan for mosquito suppression through the combined use of source reduction (i.e., water control), chemicals, larvivorous fish, and repellants and predators against the adults. Although her theoretical contribution is rarely acknowledged [2], the multifaceted attack on mosquitoes that she proposed characterized much of the antimalaria effort that ensued.

Application of control measures even before the development of DDT were very successful in malaria control in certain regions such as the South Pacific. The triumphs of early control efforts spearheaded by Chagas in Brazil and Gorgas in Panama are also noteworthy. Unquestionably, the introduction of DDT truly revolutionized vector control. The Rockefeller Foundation's costly campaign in Brazil between the 1930's and

1940's virtually eliminated the introduced vector, *A. gambiae*. A massive Rockefeller effort in Sardinia nearly eradicated malaria there as well, and similar successes were achieved elsewhere in the Mediterranean littoral. As a result of DDT's success in these early efforts, the World Health Organization launched its worldwide Malaria Eradication Program in the mid 1950's. The goal of the project was the cessation of malaria transmission and elimination of infective cases that serve as disease reservoirs. Tropical Africa was excluded from this program because of a lack of the health infrastructure deemed essential for the success of an intensive, time-limited campaign. In many areas where vector suppression and treatment of cases were achieved, malaria was controlled even when repopulation of the vector subsequently occurred. Experience in the United States serves as an example of this principle. Endemic malaria was eliminated more than 40 years ago. The vectors *A. quadrimaculatus* and *A. freeborni* continue to breed with exuberance, however, and their vectorial capacity is confirmed on rare occasions by small outbreaks of malaria transmission in the U.S. following disease importation.

The resounding success of the W.H.O. program can be summarized by the claim that DDT contributed to saving the lives of 15 million people that would otherwise have succumbed to malaria [3]. By 1967 more than one billion people were living in areas from which malaria transmission had been markedly reduced or entirely interrupted. Unfortunately, the emergence and dissemination of vectors resistant to DDT and to alternative insecticides, as well as detrimental administrative, political, and economic developments in participating countries so profoundly undermined W.H.O.'s eradication effort that the Program was abandoned in the 1970's. In its place, the World Health Assembly recommended the institution of a less ambitious scheme of locally-administered efforts to contain the disease at levels commensurate with countries' individual economic and administrative capabilities. The W.H.O., in collaboration with UNDP and The World Bank, also instituted an extensive research and training program (W.H.O. Special Program for Tropical Disease Research and Training) that targeted malaria and five other tropical diseases for what is largely disease control-oriented scientific investigation.

The "premature" withdrawal of the W.H.O. Malaria Eradication Program from the Indian subcontinent had devastating effects. In Sri Lanka, where the W.H.O.-based malaria control campaign had reduced the incidence to about 17 cases *per annum* by the mid-1960's, there were again over 1 million cases within 5 years. Local political developments that eroded

the control program's infrastructure contributed to this epidemic. The epidemic had a counterpart in India. Mauritius, declared malaria-free in 1973, had over 650 cases by 1982 due to a combination of unfortunate factors including a hurricane [4]. Malaria once more was on the rise worldwide.

Growing philosophical sentiments imbued in large part by Rachel Carson complicated the petrodollar economic realities of the early 1970's with respect to vector control strategies. Fears of a "Silent Spring" brought about by perturbations in the ecological homeostasis made DDT and other — particularly chlorinated hydrocarbon — insecticides repugnant to environmentalists and their sympathizers. Effective alternatives to DDT that could be produced from petroleum became hugely expensive as a result of the sharply rising cost of crude oil. The need to apply these alternative agents more frequently than was required with DDT and their greater potential health hazard to spray personnel provided additional financial and ethical constraints. In some areas, administrative philosophies reminiscent of Ross's "Mosquito Brigade" and "sanitary anarchy" have become social anathemas. Villagers in some cases have been unwilling to cooperate with efforts they perceive as infringements on their basic rights. This includes the right to privacy breached by the entry of insecticide sprayers into their home [2].

Alternative vector control methods are being considered that are perhaps less intrusive ecologically, are socially more acceptable, and are ones to which mosquitoes can be expected to retain susceptibility [5]. Prominent among the alternatives is biological control, including the use of natural insecticides (*Bacillus thuringiensis* var. *israelensis*), mosquito pathogens (*Nosema algerae*; gastromermis), and larvivorous fish (*Gambusia affinis*; *Poecilia retuculata*). None have as yet been applied on a sufficiently large scale to assess their potential efficacy. Clearly, specific breeding behavior of local vectors and the nature of water sources will influence the outcome of biological vector control. For example, anopheles (*A. balentor*) that breed in water that collects in the tops of bromeliads or in water-filled hoof-prints of cattle (*A. gambiae*) are clearly not targets of such biological control.

While release of millions of chemosterilized male anopheles successfully but transiently reduced the vector population along the shores of Lake Apastapeque in El Salvador, this approach is impractical on a large scale. Similarly, no practical fruits have been borne of the once well-

supported application of mosquito genetics research to the problem of malaria; little work in this area is presently on-going.

The complexities of vector control escalated at what would seem to be a particularly impropitious time. As reported in at least one study [6], there appears to be a significant contribution of the application of "green revolution" technology to malarial resurgence. Irrigation ditches provide new mosquito breeding sites, and extensive pesticide use (needed to maximize crop yields) selects for insecticide-resistant anopheles. It would be encouraging to believe that coordination of agrarian development and malaria control programs might provide some solutions. Conflicting priorites undoubtedly will pose substantial challenges to establishing such coordination.

There are no "easy" solutions to vector control on the horizon. Conventional (and even "classical") methods continue to be applied to largely prevent an increase in transmission, and to buy time until an attack with novel armamentarium can be launched that might substantially reduce or eliminate transmission altogether. Just how effective the present modalities themselves might be in significantly reducing transmission seems to be a matter of conjecture. In a careful analysis, Laird [2] recently argued that a vastly more aggressive application of existing measures (but at a huge cost) could be effective. He states:

> "... I cannot envisage any malaria situation, anywhere, that could not be resolved *now* through an integrated vector control methodology...".

Pondering the questions of who is to pay for such efforts and who will establish the priorities where these controls could be instituted can certainly dampen one's enthusiasm for his argument, however.

Chemoprophylaxis and Chemotherapy in Control

Control strategies directed at the human host take into consideration not only the fact that inhibition of parasite development abrogates disease in the individual, but also that man serves as the only known natural reservoir for the *Plasmodia* species that commonly cause human malaria. Since gametocytes (the sexual forms ingested by mosquitoes during a blood meal) are the biological basis for continued transmission, interference with gametocytogenesis in the human host or with the sporogonic cycle in the mosquito provides for theoretical strategies in malaria control.

Chloroquine and folate antimetabolites (sulfonamides and pyrimeth-amine) are presently the most widely used prophylactic compounds. The presence in *P. falciparum* strains of resistance to chloroquine was first recognized in Thailand and Colombia in the early 1960's. Since then, dissemination of choroquine-resistant strains in Asia, Latin America, Oceania and East Africa have occurred at a surprising rate. Fortunately, other species causing malaria in man remain susceptible to the drug. A fixed-dose combination of a long-acting sulfonamide (sulfadoxine) and pyrimethamine (marketed in the U.S. and elsewhere under the trade name Fansidar) became commercially available in the late 1970's and proved highly effective in prevention and treatment of falciparum malaria including chloroquine-resistant strains [7]. Reports of severe reactions to Fansidar (primarily hypersensitivity-type, including Stevens-Johnson syndrome) and repeated identification of strains of Fansidar-resistant *P. falciparum* in some localities must raise concerns about the long-range safety and efficacy of the new agent. Mefloquine, a representative of a new class of antimalarial compounds, recently emerged from the four decade-old, and costly U.S. Army anti-malarial drug-screening program. The drug is effective both therapeutically and prophylactically against multi-drug resistant strains of *P. falciparum*. However, since resistance to this agent can develop, efforts are under way to restrict its worldwide use to chemotherapy in the hopes of delaying dissemination of resistant strains that might be selected by mefloquine chemoprophylaxis. A fixed-dose combination of mefloquine and Fansidar is being used in Thailand for therapy, and may eventually also be marketed for prophylaxis. It is hoped that the drug combination might delay emergence of resistance to the constituent agents.

The goals of chemoprophylaxis for short-term travellers to endemic areas seem clear enough, and do not require consideration here. On the other hand, the goals for protection of residents of areas with endemic malaria are perhaps less clear-cut. At least two benefits of chemoprophylaxis can be expected in this population. The recipients of chemoprophylaxis are personally protected and also the total reservoir for transmission may be quantifiably reduced. Indeed, the integration of chemoprophylaxis programs with vector control campaigns were important in achieving eradication or reduction of malaria in many geographic regions during the days of the W.H.O. Malaria Eradication Program. Nonetheless, controversies surround the large-scale use of chemoprophylaxis in endemic areas. It is argued that use of antimalarials in this way favors selection of drug

resistance in *Plasmodia,* an argument supported by well-documented field experience. Since these agents then become useless, the burden placed on constantly developing new antimalarials becomes immense. Another argument against chemoprophylaxis is that its use in children may simply delay their natural development of protective immunity and clinical tolerance to severe *P. falciparum* infections. Although this concept has not yet been documented, efforts are under way to test the hypothesis in West Africa. Individuals protected from acute infection with chemoprophylactic agents such as chloroquine develop certain immune responses to plasmodial antigens nonetheless [8]. It is therefore conceivable that protective immunity might after all develop in the children receiving chemoprophylaxis. Since the relationship between all measurable immune responses and protection is uncertain, the results of such tests cannot as yet be used to predict clinical outcome.

One has to consider the beneficial impact of early-age malaria protection in the broad context of all the infectious onslaughts of children in the Third World. Malaria very likely plays a major role in reducing host-defense mechanisms against the respiratory and gastrointestinal pathogens that repeatedly plague these children. There is an impression among tropical doctors that certain other ailments such as measles, meningitis, diarrhea and pneumonia frequently accompany acute malaria in young children. It has been proposed that the basis for these clinical associations is induction of widespread immunosuppression by acute malaria [9]. One could well imagine that malaria chemoprophylaxis used in the first 5 years of life might therefore reduce overall morbidity and mortality due to other infections. Documentation of this principle would certainly influence public health policies and hopefully will be forthcoming.

Some blood schizonticides (agents that act against the intraerythrocytic asexual stages) such as chloroquine and quinine also are gametocytocidal against *P. vivax* and *P. malariae* but unfortunately not against *P. falciparum.* This means that individuals treated with these agents may remain as potential reservoirs for transmission if they have developed circulating infective gametocytes even after their acute illness is cured. Primaquine (used clinically to prevent relapses due to *P. vivax* and *P. ovale*) and chloroquanide are sporonticides. That is, they can interfere with the sporogony in the mosquito. Their widespread use in transmission control is unacceptable because of toxicity, however. There is no question that from the viewpoint of transmission control, new antimalarial agents that can inhibit the sexual cycle of *Plasmodia* are needed. In response to this

need, researchers have become increasingly interested in the molecular aspects of gametocytogenesis, a process that can now be studied *in vitro*.

Irrespective of the stage of the target in the parasite's life cyle, new antimalarial agents are critically needed. The exciting finding that a traditional Chinese treatment for malaria may provide an important new class of antimalarials, suggests that natural products in addition to quinine are potential sources [10]. Cinchona alkaloids and quassinoids from *Simaroubaceae* plants are among those presently being investigated. New knowledge about plasmodial metabolism could also lead to the rational design of drugs. Financial resources and development of antimalarials are insufficient to expect appropriately rapid responses to the worldwide dissemination of multi-drug resistant strains. Considering the potential market, pharmaceutical companies cannot expect an attractive margin of return on their investments. Efforts to deal with this situation through development of an industrial consortium are being considered. The risk that drug resistance will outrun development of new antimalarials is substantial and one of the greatest concerns regarding the present worldwide malaria situation.

Vaccines

In the last few years, optimism that malaria might be controlled by vaccination reached unprecedented heights. The development of methods for production of monoclonal antibodies permitted the identification of antigens that are important targets of specific protective mechanisms. Recombinant DNA technology permitted cloning the genes for these antigens, inserting the genes into *E. coli,* and producing the quantities of antigen that are needed for huge numbers of vaccine doses. Establishment of the principle that protection against the infective stage sporozoite was possible, and important insights into the molecular aspects of protective sporozoite antigens derived from work of the Nussenzweig's and their colleagues at New York University. Their seminal work brought many others into the vaccine effort. Phase I trials of a recombinant sporozoite vaccine have begun. Many other candidate antigens, including stage-specific ones of merozoites, schizont-infected erythrocytes, and gametes are being analyzed but none are presently in the advanced stages of development awaiting clinical trial (for review, see 11).

Only large long-range efficacy trials in residents of malarious areas

will indicate whether the sporozoite vaccine (or vaccine against any other stage) is likely to have an important impact in malaria control. Conjecture supported by rational arguments has been posed on both sides. The optimists point out that since the target antigens that permit irradiated sporozoites to induce protection are also the ones used in the recombinant vaccine, and since humans have been protected with inoculation of ir- radiated sporozoites, humans should also be protected with the recombinant DNA vaccine. Other, rather less direct experiential support is also mustered in the defense. The less optimistic arguments focus largely on the probability that if even only one infecting sporozoite evades the vac- cine-induced defense, malaria infection will ensue. In rebuttal, the opti- mists point out that reduction in the number of sporozoites that progress to intrahepatic development might itself sufficiently reduce the severity of illness as to be of great clinical value. This counter argument is based on only limited documentation that a reduced sporozoite "load" might attenuate clinical malaria. From a biological perspective one would anticipate that once the intraerythrocytic cycle is initiated, sporozoite number would not influence the replicative potential of schizonts. Since the speculations should soon be resolved by direct investigation, the arguments pro and con are becoming moot.

Research in identifying target antigens on other plasmodia stages has expanded virtually at a logarithmic rate in the last few years. Certain biological considerations have directed much of this work. For example, it is widely perceived that only the extracellular stages — sporozoites, merozoites, gametes and the other vector-borne stages (zygote, ookinete) — are reasonable targets of immune attack. The extracellular stages of this obligate intracellular parasite that are present in the human hosts exist only briefly in the extracellular milieu. The intracellular residence is largely viewed as a haven protective of immune recognition and host defense. This consideration may serve to explain why numerous acute malaria infections experienced over a few years are required to develop protection naturally. Under natural conditions, the target antigens are presumably presented to the immune system in an inefficient manner. The goal of vaccines against these extracellular stages is to present the target antigens to the immune system artificially in a manner that would be more efficient in leading to protective mechanisms than occurs naturally.

Certain obstacles stand in the way of developing vaccines against asexual stages. Marked stage-specific antigenic heterogeneity exists among

isolates from different geographic regions and even those from within the same region. Furthermore, within the mammalian host *Plasmodia* can undergo certain phenotypic (somatic) changes that lead to antigenic variation. Worse yet, immune responses to variant-specific antigens can trigger emergence of new antigenically distinct variants. Surprisingly, this can occur even after vaccination with a purified, defined target antigen [12]. To circumvent this complication, scientists are searching for conserved target antigens that are invariant. This search is frustrated by the concern that the *in vitro* techniques used to identify target antigens (*in vitro* blockade of red cell invasion by merozoites, for example) may not suitably represent relevant *in vivo* defenses.

If we change our focus from the complexities involved in basic malaria vaccine research to more general consideration, other potential problems come to view. Concerns about the economics of vaccine production and sale, challenges to cold-chain technology, worries about duration of vaccine efficacy, and social sensitivities regarding population compliance all confront us. If vaccine supplies and delivery personnel are limited, the issue of setting priorities regarding the recipient population becomes pressing. The goal of the vaccine must also be defined in public health terms. If the malaria vaccine proves to be as effective and long-lasting as that for smallpox, for example, the goal can be more easily defined. Failing such success, one would assume that the goals would be similar to those reflected in options articulated by the W.H.O. Expert Committee on Malaria regarding malaria control short of eradication. These include: 1) reducing and preventing mortality, 2) reducing morbidity in the most vulnerable age groups, and 3) reducing malaria prevalence.

Reducing the mortality of malaria without also reducing morbidity could be a mixed blessing. If, for example, immunized children were to experience a prolonged but non-lethal illness the tragedy of malaria would still be substantial. Family- and community-based resources in caring for these patients might be so reduced as to stress the social and economic development of the community. The pathophysiological consequences of chronic symptomatic malaria, perhaps including protein-calorie malnutrition and reduced resistance to other infectious agents might pose a second set of medical problems. Even if the acute morbidity of malaria could be reduced by vaccination without also favorably influencing the course of secondary complications (e.g., intercurrent viral infections), malaria would still be problematic. Establishing goals and monitoring

vaccine impact will therefore require tremendous human resources, even once the efficacy of a vaccine is established in the initial clinical trials. The potential long-range success of vaccines in malaria will undoubtedly depend on the combined creative efforts of individuals in disciplines as remote as molecular biology, public health, economics, and medical anthropology. The greatest challenge to a successful malaria vaccine may not ultimately prove to be identification of the correct target antigen; mustering all the additional necessary human resources may require that the 21st century counterpart of Ross's 19th century "Malaria Brigade" be a veritable "Malaria Vaccination Army".

Relation of Primary Health Care Delivery to Malaria Control

Prevention of mortality due to malaria and reduction of morbidity in the most vulnerable age groups are goals toward which primary health care can most readily contribute. The primary health care worker must assume that a febrile patient or the patient who has had recent febrile attacks has malaria and must treat accordingly. Parasitological documentation is usually impractical under most field conditions and the direct therapeutic algorithm seems reasonable. Since most adults living in malarious areas have acquired clinical tolerance to severe disease, whereas children under 5 are more prone to the lethal complications of *P. falciparum* infection, fever as an imperative for antimalarial chemotherapy is most compelling in the pediatric age group. Presently, malaria case-fatality in the pediatric age group is estimated to be in the range of 10% [14]. Attacks of acute malaria may occur six or more times during the rainy season in children and 1-3 times in adults. A conservative chemotherapeutic regimen administered by primary health care workers (using, for example, chloroquine) would cost, in aggregate for all related expenses, about $1 *per capita* population. In countries of Africa, only about $0.05 per person per year is allocated for *all* drugs [14]. The economic burden increases when drug resistance dictates the use of more expensive and potentially more toxic agents.

Targeting reduction of morbidity to the most vulnerable age groups is another activity in which primary health care workers are appropriately involved. Children under 5 and pregnant women comprise the bulk of this population. Integration of a malarial chemoprophylaxis program with maternal health care programs is an obvious mechanism for achieving this goal. An estimated cost of $2 per protected person per year using chloroquine to achieve this goal has been published [14]. Again, alter-

native drugs increase cost and may enhance the risk of toxic effects on the fetus and growing child. Monitoring the efficacy and benefits of a preventive program of this sort is essential but adds expense and extra demands on manpower.

The complexities of integration of malaria control programs into primary health care are obviously substantial. Yet the success of such programs focused as they are on a single disease of the tropics, can be expected to succeed only if they are integrated in comprehensive primary health services. The substantial cost of an integrated approach suggests that success of such an antimalaria program will depend heavily on the socioeconomic advances of the population and the health priorities of their administrators.

Summary and Conclusion

The enormous impact malaria continues to have on human suffering provides a compelling motivation for devising and instituting new control strategies. For several reasons, presently-available strategies for vector control are unlikely to contribute in the near future to substantial further reduction of worldwide malaria. Application of existing strategies will hopefully help prevent further deterioration of the malaria situation. The impact of chemotherapy and chemoprophylaxis as isolated control regimens are difficult to assess in endemic regions but certainly contribute to a multifaceted control program. The consequences of chemoprophylaxis of children on their general health and growth, and the impact on their development of antimalarial immunity is just being evaluated. Increasing problems of drug resistance in *P. falciparum* has created a virtual crisis situation to which research and development institutions must respond more vigorously. The first malaria vaccine should be available for field testing in the next few years. While viewed by many with resounding optimism, cogent arguments can be made for why a malaria vaccine might have limited applicability and not provide the long dreamed-of panacea. It would thus seem a responsible course to retain an attitude of restrained optimism regarding malaria vaccination. Over-selling the idea that a panacea is in sight could add to the tragedy of malaria if vaccination proved not to be the solution to this age-old scourge. Similarly, agencies funding malaria research need to continue supporting broad-based basic research in addition to narrowly-focused goal-oriented studies. Increasing our fund of basic knowledge about malaria now may be essential for developing novel strategies for disease control in the future.

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NUTRITION OF THE PARASITE VERSUS NUTRITION OF HOST

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This brief presentation relates chiefly to malaria parasites and the effect of malnutrition of the host.

Malaria parasites are animals, and as such are dependent upon food, as are their hosts, e.g., man. If man is starved, he will lose vitality; the parasite will suffer also. Malnutrition of the host will quickly be followed by a lowering of density of malaria parasitaemia. Of course, the equation is not so simple as this; the food requirements of each are not exactly similar. Yesterday Kenneth Brown compared briefly the metabolism of host and parasite.

Observations on a population, under conditions of famine and exposed to malaria, sometimes show that the incidence of the disease is reduced, and such an effect is confirmed by experiments on laboratory animals.

Unfortunately, the older records of the effect of famine on malaria in tropical countries are based on random observations. In contrast to intestinal diseases, like dysentery or cholera, in which epidemics are well known to accompany famine in the population, there is little or no precise knowledge about the effect of the disaster on malaria. There is either complete silence, or sometimes a fall in numbers of acute cases of malaria is reported, but there is no enhancement of virulence of chronic infections — the one ray of sunshine in the otherwise grim picture. George Edington (1967) referred to the absence of cases of pernicious malaria in famine-stricken areas of Ghana.

An obvious explanation of the paradox is that conditions of famine are usually associated with the failure of the rains: the absence of water means that the mosquitoes have nowhere to breed and the transmission of malaria is interrupted. This is an important factor, but would not affect the severity of chronic infections. A careful assessment of all aspects of the epidemiology has to be made, and this may be quite impracticable, when so much has to be done to relieve the cruel effects of the disaster. It is most unlikely that "controls" could be established.

Perhaps a scientific approach has been made in some of the disaster areas today in tropical Africa, and it may be that some of our colleagues here have some concrete information.

Laboratory Investigations

The use of animals in malaria research provides opportunities for the study of the effect of restriction of food infections in a variety of malaria-infected hosts. They include chimpanzees, the best model of the human disease, and monkeys, while malaria in rodents or birds offers a less comparable approach.

Workers on monkey malaria are familiar with the poor or abnormal results which accompany the use of debilitated animals or those in a bad condition, perhaps from inadequate diet, or from fretting or maybe from the onset of some unsuspected disease, such as tuberculosis. It is unnecessary to emphasize here the importance of keeping all experimental animals under optimum conditions. The first thing that a parasitologist looks for in new premises is the state of the Animal House.

The early Indian investigators on simian malaria demonstrated that the course of *Plasmodium cynomolgi* infections could be profoundly depressed if the diet of the animals was restricted. Jaswant Singh (1956) noted that infections of *P. inui* and *P. knowlesi* in rhesus monkeys were much less intense in tuberculous than in non-tuberculous monkeys. Quentin Geiman (1948) told me that when he starved his monkeys for 1 or 2 days, they almost lost their malaria parasites; he went a step further by showing that administration of para-aminobenzoic acid (PABA) quickly caused the infection to resume its normal course.

The best examples of the influence of diet deficiency on the growth of malaria parasites are provided by the well-known experiments in which infected animals were placed on a milk diet (*in vivo*; *in vitro* culture should give more precise results). Maegraith (1952) discovered that if

the food of the rodents was limited to milk, an infection of *P. berghei* could be suppressed; the parasites were not completely eliminated, but a fatal disease was converted into an inapparent infection. Hawking (1953) in the following year demonstrated that a lack of PABA in the diet was responsible, and that if this substance was added to the milk, the rats usually regained their full susceptibility to the parasite.

About the same time (1953) Bray and I studied these phenomena in rhesus monkeys infected with *P. cynomolgi*. Their food was limited to milk and the erythrocytic cycle was almost abolished. We next inoculated 2 monkeys with sporozoites from the salivary glands of mosquitoes, and two days later the animals were placed on a milk diet. In one monkey, parasites appeared in the blood on the typical eight days later, but the infection remained low and there was no increase of parasitaemia until day 23, when a relapse occurred (relapses are now known to occur after such an interval by early activation of hypnozoites in this strain, Krotoski *et al.* 1982). The second monkey received a larger dose of sporozoites, parasites appeared in the blood on the characteristic 8th day and were so numerous that the milk factor was unable to control them until 2 days later, when the number of asexual parasites fell dramatically.

Mosquitoes (*Anopheles atroparvus*) were fed on the latter monkey on the 12th day, when gametocytes were present in its blood. Ookinetes were found in the gut of the insect, oocysts developed and sporozoites entered the salivary glands on the 10th day. Thus sporogony was unaffected by exposure of gametocytes to the milk factor.

We assumed from the above observations that the milk diet had the following effect on malaria parasites:

1. No action on the sporozoite, as the pre-erythrocytic stages developed normally in the liver;

2. Pre-erythrocytic schizonts in the parenchyma cells were unaffected as they grew and matured at the natural rate (i.e., 8 days);

3. Merozoites developed in these schizonts and were able to invade the red blood cells, but the majority failed to grow;

4. These immature parasites suffered most from the "milk factor" because they were at the stage when nuclear division takes place, i.e., when the presence of DNA is essential;

5. Gametocytes are apparently not harmed by the inhibitory milk factor, as their immediate progeny in the mosquito undergo normal sporogony.

These results were confirmed by many, but not all, investigators. Parisian workers in the Pasteur Institute had negative results in rodent malaria and Colbourne (1956) showed that West African children still had heavy infections of *P. falciparum* when their diet was restricted to milk. Unless experiments are carefully controlled (practically impossible under West African conditions), it is difficult to guarantee that the children were not receiving the odd titbit containing PABA.

More recent work by Edirisinghe, Targett and co-workers (1981) and the Murrays (1977) has clarified the nature of the deficient elements in suppression experiments in rodent malaria. There is competition between the host and the malaria parasites for essential amino acids, particularly threinine, isoleucine and valine.

Effect of Competition in Multiple Infections and Genetic Factors

The natural cycle of the malaria parasite in the human host may be changed by factors other than malnutrition.

The presence of other organisms in the blood may have an adverse effect on the malaria parasite by competition over the food supply. I mention this point only because it is often ignored or goes unrecognised both in clinical medicine and in laboratory research. Some of the most interesting work was done by Professors W. Peters (1970) and F. E. G. Cox (1975) on the concomitant effect of *Haemobartonella* and *Eperythrozoon,* and the protozoa *Babesia* and *Anthemosoma* on malaria. The last two organisms may influence the malaria infection by the operation of cross-immunity, rather than by depletion of the food supply.

Three other factors reduce the severity of human malaria; they are unconnected with nutrition and are genetic in origin. They relate to: 1) the presence of sickle-cell haemoglobin (HbS) (Alison, A. C. 1963), 2) a deficiency of the enzyme, glucose-6-phosphate dehydrogenase (G6PD), and 3) the absence in West African blacks of the "Duffy locus" on the cell membrane of erythrocytes — essential for invasion by *P. vivax* (Miller *et al.*, 1976). The first two factors inhibit to a considerable degree the development of *P. falciparum.*

The effect of all these factors, including malnutrition, is thus seen to be only on the blood phase of the malaria parasite; the sporogonic and tissue stages are apparently unharmed. Presumably, the dormant stages (hypnozoites) are doubly resistant to the effect of famine because of the genetic dormancy itself and the persistence of hypnozoites (Kro-

toski *ed al.*, 1982), for months in certain species of *Plasmodium,* e.g., *P. vivax* and *P. ovale.* I wonder, for instance, how relapses are affected in famines in Ethiopia or possibly in North India, where *P. vivax* is common.

Much less is known about adverse factors in regard to the intestinal parasites. It would be interesting to know if those protozoa, which live chiefly on the surface of the intestinal mucosa, such as *Cryptosporidium* and *Giardia,* are affected by the lack of food in the lumen of the small intestine and duodenum in the malnourished host, in contrast to those which inhabit the deeper tissues of the viscera, such as *Entamoeba histolytica* or most coccidia..

Wright and Tomkins (1977) relate the effect of giardiasis on malabsorption.

The intestinal flora of a bacterial nature seem to flourish under conditions of starvation, when epidemics of bacillary dysentery and cholera are frequent.

An iron-deficient diet also depresses the multiplication of malaria parasites in the blood and *E. histolytica* in the intestine (Diamond *et al.*, 1978). On the other hand, these diseases and others may be enhanced in virulence if they are accompanied by a general immuno-depression. Such opposing forces complicate the picture, and Kasprzak (1968), the Polish parasitologist and Targett (1980), discussed these biological factors in detail. Each response needs individual interpretation.

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STRATEGIES FOR THE CONTROL OF VISCERAL, CUTANEOUS AND MUCOCUTANEOUS LEISHMANIASIS

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Abstract

Control of leishmaniasis poses a difficult problem because of the diversity of the leishmanias, variations in the ecology of their vectors, the wide range of reservoirs and the complexity of the parasites' interactions with human host defense mechanisms. At present there is no universally effective means of vector or reservoir control, but suppression of peridomestic or domestic sandfly vectors by residual insecticide spraying, elimination of reservoir animals, or mass treatment of patients where humans are the principal reservoir may help to limit transmission in some areas. Prospects for the future depend on several factors. A comprehensive understanding of the epidemiology of the various forms of leishmaniasis is necessary. The ecology and biology of sandfly vectors and animal reservoirs must be better characterized. New chemotherapeutic agents are needed to treat drug resistant strains, to simplify administration and to obviate the need for hospitalization. Finally, priority must be given to better understanding of the immunobiology of disease. The optimal means of controlling leishmaniasis would appear to be immunization, and experience with humans and animal models suggests that this approach may ultimately succeed.

Introduction

Leishmania species are found on every continent with the exception of Australia. They are estimated to cause 1.2 million new cases of leishmaniasis yearly in approximately 80 countries [1]. Although questions remain about the precise taxonomy of the leishmanias, the organisms can be divided into four *Leishmania* species complexes. Members of the *L. donovani* complex are responsible for visceral leishmaniasis (kala-azar) as well as post-kala-azar dermal leishmaniasis; members of the *L. tropica* complex produce cutaneous leishmaniasis in the Old World; members of the *L. mexicana* complex are responsible for localized and diffuse cutaneous disease in the New World; and members of the *L. braziliensis* complex produce cutaneous and mucocutaneous leishmaniasis throughout Central and South America [2, 3]. Each species complex is composed of multiple subspecies which produce variants of the major syndromes and often differ in their immunobiology and susceptibility to chemotherapeutic agents. The ecological systems maintaining the different *Leishmania* species also vary from place to place. Transmission to humans is by sandflies of the genera *Lutzomyia* or *Psychodopygus* in the New World or *Phlebotomus* in the Old World, usually from non-human reservoirs, but in certain instances such as visceral leishmaniasis in India, man is the principal reservoir. The animal reservoirs differ from one geographic area to another and include canines such as dogs, wolves and foxes, and many species of wild rodents.

Attempts at controlling the leishmanias have been complicated by the many diversities among parasite strains, vectors and reservoirs [4]. To be successful strategies for control must take into account the infecting *Leishmania* species, the spatial distribution and number of human cases, the behavior and feeding preferences of the sandfly vectors, the nature and habits of animal reservoirs, the immune capacities of the human host, the efficacy and toxicity of chemotherapeutic agents, and the geography of the endemic area. Control strategies have included: a) elimination of sandfly vectors by residual insecticide spraying, b) control of reservoir animals, c) early identification and treatment of humans, and d) vaccination. A combination of one or more of these methods may be appropriate in any locale. However, control measures which are successful in one geographic area may not be appropriate in others. Marsden [5], Marinkelle [4] and Greenblatt [6] have recently reviewed various aspects of control programs.

The Parasite

Precise identification of infecting leishmanial species is important for several reasons [7, 8]. First, from an epidemiologic and disease control perspective it is necessary to know whether the isolate causing disease is the same biotype as that found in local sandflies or in putative animal reservoirs. Second, in the case of cutaneous disease in Latin America the nature of the cutaneous lesion at the onset of disease does not necessarily indicate its final outcome. For example, the cutaneous lesions caused by *L. mexicana* species and *L. braziliensis braziliensis* may be clinically indistinguishable, but only the latter is commonly associated with the subsequent development of mucocutaneous disease. Third, treatment and subsequent follow-up is to some extent determined by the species of the infecting organism. Finally, different vaccines may ultimately be required for protection against different *Leishmania* species.

There are currently three major techniques used for identification of *leishmania* species: isoenzyme electrophoresis, species-specific monoclonal antibodies and kinetoplast DNA (kDNA) hybridization. Species identification is available through three WHO reference centers. It is important to characterize the causative leishmanial isolates in endemic or epidemic areas in order to devise appropriate control strategies.

Control of Sandflies

Leishmanias are transmitted by sandflies of the *Phlebotomus* genus in the Old World and by *Lutzomyia* or *Psychodopygus* genera in the New World. Sandflies require humid but not wet conditions for breeding and live on a wide range of organic materials. They are generally found only in areas having a mean temperature of 20^0 C for at least one month of the year. The females usually require a blood meal for development. Sandflies are short-lived, tiny insects with a limited flight range. They fly in a series of short hops, rarely gaining much altitude [5].

Control of domestic or peridomestic sandflies has proven partially effective in some areas. Sandflies are usually quite susceptible to insecticides such as DDT or dieldrin although resistance has been reported from a few areas [4]. Insecticide spraying in Brazil has been shown to be useful in the control of peridomestic *Lutzomyia longipalpis,* which is responsible for transmitting *L. donovani chagasi* from dogs to humans [9]. The widespread use of DDT for malaria control on the Indian

subcontinent, where *L. donovani* is transmitted from human-to-human by peridomestic *Phlebotomus* species, was accompanied by a dramatic reduction in the incidence of visceral leishmaniasis. Unfortunately, discontinuation of residual insecticide use for malaria control was followed by major epidemics of visceral leishmaniasis in India [10, 11].

Residual insecticides are reported to have played a role in the control of anthroponotic *L. tropica* infection in the USSR [4]. In Uzbekistan eradication of cutaneous leishmaniasis was the result of a campaign against malaria, and in Askabad City, eradication was related to a campaign to control sandfly fever [4]. Elimination of *L. tropica* infection from the cities of Kirovad and Barda in Azerbaijan was apparently the result of a planned program to detect and treat all human cases of cutaneous leishmaniasis along with DDT spraying in homes of people with lesions [4]. In Iran the cessation of antimalarial spraying was associated with the reestablishment of cutaneous leishmaniasis [12].

There are limitations to the use of insecticides as a control measure. The identity and ecology of sandfly vectors remain unknown or unproven in many leishmania-endemic sites. Proper application of insecticides is dependent on the seasonality and longevity of the vector, the duration of its life cycle, the number of bloodmeals it takes, its human biting frequency, its ecology in relation to houses and breeding sites, and other factors. Except in those instances where domestic or peridomestic transmission is dominant, large scale sandfly control is impractical. Insecticide fogging of towns, desert areas, and forest should not be carried out because of potential ecological damage and lack of proven efficacy [13]. Even when transmission of leishmaniasis is by domestic or peridomestic sandflies and good control is accomplished by residual insecticides, dramatic reemergence of leishmaniasis may occur when spraying is discontinued as happened in India [10, 11]. In addition, the use of residual insecticides is costly and may have adverse effects on the environment, and emergence of resistance among sandflies remains a potential problem [4]. Nonetheless, residual insecticides will continue to play an important role in areas of high transmission where peridomestic sandflies are responsible.

Marinkelle [4] has recommended application of DDT, dieldrin or diazinone solution to a height of 1.5 meters from the floor. DDT at a dose of 3.2 gm/m² of surface provides several months of protection against most sandflies. Other recommendations appear in the literature depending on the sandfly behavior and susceptibility. As previously noted, DDT application to houses has been useful in control of *Lutzomyia longipalpis*

in Brazil [9]. A control program in Kenya involved spraying the ventilation shafts of termite hills where leishmania-infected sandflies were found. In Greece and Italy, phlebotomine sandflies were eradicated from buildings as a result of the malaria control program. In Southern France and Peru it was necessary to spray stone walls as well as the interiors of buildings to achieve control of sandflies [5]. Repair of cracks in mud walls and removal of rubbish from around houses may be helpful by reducing the number of breeding sites.

Insect repellents, long-sleeved clothing, fine mesh netting and avoidance of sandfly-infected areas during the evening and at night may provide partial protection for transient visitors but are not practical for residents of endemic areas. Mosquito nets impregnated with insecticide offer some degree of protection. In a recent study of troops undergoing jungle training N, N-diethyl-m-toluamide (DEET)-impregnated net jackets and repellent cream on the face provided good protection against sandflies [14]. The risk of sandfly bites among groups of people may be decreased if they camp in cleared areas on high ground with a wind [5]. Living in high-rise apartments probably reduces the risk of urban *L. tropica* infection. Unfortunately, very little attention has yet been paid to potential biological methods of sandfly control, an area that is worthy of study.

Control of Wild and Domestic Reservoir Hosts

The dog is an important reservoir of both visceral and cutaneous leishmaniasis in many parts of the world [2, 3]. In the dog visceral infection is associated with emaciation and peeling, erythematous skin. *Leishmania* species that produce cutaneous disease in humans and dogs often produce lesions on the dog's ears or mask that resemble lesions in humans. In hyraxes in Ethiopia, *L. aethiopica* is frequently recovered from the tip of the nose [5].

In northeastern Brazil [9] and the Mediterranean [3], where domestic dogs are the reservoir of *L. donovani chagasi* or *L. donovani infantum* respectively, reductions in the incidence of visceral leishmaniasis have followed extermination of infected animals. Serological tests such as the indirect immunofluorescence assay (IFA) or enzyme-linked immunosorbant assay (ELISA) are used to identify infected domestic dogs, which are then killed. Unfortunately destruction of an infected dog is not always permitted by the owner, and control of wild canines is virtually

impossible.   In northeastern Brazil, foxes serve as a wild reservoir from which domestic dogs become infected resulting in reemergence of visceral leishmaniasis even after successful eradication of infected dogs.

In a few areas where desert rodents serve as the reservoir for *L. tropica,* control has been possible. One approach used in the USSR has been to close animal burrows with dirt [4]. Those that are found to be reopened have occupants.   Poison is inserted and burrows are closed repeatedly until no longer reopened. Animals burrows have also been treated with in-secticide to combat sandflies.   Alternatively, DDT-inpregnated pieces of cloth have been left close to the burrows of gerbils, which carry them into their nests. Deep plowing (0.5 meters) or land leveling in combina-tion with appropriate changes in the agricultural system have also been successful.   Effective reservoir control is dependent on identification of critical reservoir species and an understanding of their ecology. Although this approach has been effective in certain isolated situations, reservoir control is not practical in many other settings. For example, the *L. bra-ziliensis* complex and *L. mexicana* complex are transmitted in or near forests and sylvatic mammals (porcupines, sloths, anteaters, etc.) constitute the reservoirs [15]. Although a program for selective trapping of these animals has been proposed, it is unlikely to be effective. Similarly, eradica-tion of hyraxes that are reservoirs of *L. aethiopica* in parts of Africa is not possible.

Control of Human Leishmaniasis

There is circumstantial evidence to suggest that malnutrition is a contributing factor to the development of visceral leishmaniasis in humans [16] and animal data to suggest that it worsens cutaneous disease [17, 18]. Every effort should be made to ensure adequate nutrition among people living in endemic areas.

Identification and early treatment of human leishmaniasis is of obvious importance to the patient and can limit transmission in areas where the disease is anthroponotic as is the case with visceral leishmaniasis in India and *L. tropica* in some areas of central Asia and the Middle East. As previously discussed, treatment of human cases in concert with vector control has proven effective in controlling urban, anthroponotic *L. tropica* infection in some areas of the USSR.

There are, however, limitations to case identification and treatment in endemic areas. For example, visceral leishmaniasis is often an indolent

disease and patients may be symptomatic and probably infective for sand-flies for months before seeking medical attention. In addition, patients with post-kala-azar dermal leishmaniasis following therapy in India or Africa may serve as reservoirs. Although highly desirable for infected individuals, early identification and treatment of human cases alone have not been effective in eradicating leishmaniasis in any area where disease is anthroponotic. Futhermore, in the majority of areas, leishmaniasis is a zoonosis.

There are also limitations with the available forms of chemotherapy. Pentavalent antimonials remain the treatment of choice for most forms of leishmaniasis [19]. Two compounds are available: sodium stibogluconate (Pentostam) is used in the Old World and meglumine antimonate (Glucantime) in the New World. These drugs are chemically similar and are thought to have the same toxicities and efficacy in relation to their content of pentavalent antimony (Sb^v). Both drugs require parenteral administration over prolonged periods of time (e.g., the recommended minimum duration of therapy for visceral leishmaniasis is 20 days), are variably effective, and particularly at high doses, potentially toxic. Side effects, which are usually transient and mild [20] include nausea, vomiting, malaise, headache, lethargy and electrocardiographic (ECG) changes. Pentavalent antimony failure is not infrequent among patients with *L tropica* and *L. aethiopica* infection, and in patients with mucocutaneous and diffuse cutaneous leishmaniasis. In addition, antimony failure has been reported in some patients with visceral leishmaniasis in East Africa and India.

The currently accepted alternative drugs to pentavalent antimonials are amphotericin B and pentamidine isethionate [19]. Both of these are associated with potentially severe side effects. Pentamidine can produce life-threatening hypotension, hypoglycemia, or paradoxically, hyperglycemia and occasionally insulin-dependent diabetes mellitus [21]. Amphotericin B has multiple toxic effects including dose-related renal failure. The lack of an effective, non-toxic oral drug has tempered enthusiasm for intensive screening programs to identify cutaneous leishmaniasis due to the *L. tropica* complex and the *L. mexicana* complex since these are usually self-healing conditions. The need for new, effective compounds for oral administration is clearly evident.

The leishmanias have been shown to possess a purine salvage pathway whereas mammalian cells depend primarily on *de novo* purine synthesis [22]. This finding led to the discovery that allopurinol, a compound

widely used to prevent attacks of gout, and related purine analogues have antileishmanial activity. Subsequent studies on nucleotide metabolism in the leishmanias have led to the development of allopurinol riboside, a nucleic acid analogue now undergoing limited clinical trials [7], and other potentially effective compounds. More fundamental approaches to the development of new drugs may arise from the search for parasite-specific metabolic pathways or enzymes such as the leishmanias' 3′- and 5′-nucleotidase [23] and membrane-associated acid phosphatase [24], which might serve as chemotherapeutic targets.

Vaccination

The optimal means of controlling leishmaniasis would appear to be by immunization, and clinical experience with humans and animal models suggests that this approach may eventually succeed. Cutaneous leishmaniasis is a chronic, self-limited disease during which there is development of apparently life-long, cell-mediated immunity [25]. A second episode of cutaneous Old World leishmaniasis following spontaneous cure of naturally acquired disease is very rare [26]. For centuries residents of the Middle East exposed the bare bottoms of their infants to the bites of sandflies while covering the rest of the infants' bodies. Typical leishmanial lesions followed. This practice successfully prevented later acquisition of cutaneous leishmaniasis on exposed areas. Alternatively, material was taken from active human lesions and inoculated into recipients by excoriating the skin of the arm or thigh [5].

As culture techniques developed, workers in Russia and Israel produced local disease and subsequent immunity by injecting cultured promastigotes at inconspicuous sites. Greenblatt [6] estimated that as of 1980 more than 20,000 people had been vaccinated in the USSR while at least 5,000 had been immunized in Israel. It is believed that if a typical leishmanial ulcer forms, the recipient is protected for life against infection by the homologous *Leishmania* strain. There is also evidence of partial cross protection within the *L. tropica* complex [27, 28]. Infection with *L. major* is thought to protect against exposure to *L. tropica,* but protection in the reverse direction is incomplete. It is generally agreed that vaccination with *L. tropica* does not protect against *L. donovani,* the causative agent of visceral leishmaniasis [29]. Cross immunity between the *L. mexicana* complex and the *L. braziliensis* complex has not been fully assessed, but Lainson and co-workers have reported some evidence to suggest that it might occur [30].

Despite the success of promastigote-induced infection in preventing natural infection, the method has important limitations [6]. Laboratory strains of leishmania have varied in their ability to produce cutaneous lesions and thus to elicit protection. Even the more virulent strains have tended to lose potency over time. Conversely, some recipients have developed large lesions at the site of promastigote injection, some of which have taken 4 or 5 months or longer to heal. Others have developed secondary bacterial or fungal infections of their lesions which have required antimicrobial therapy. There is also concern that viable amastigotes may persist even after an ulcer heals and that disease may reactivate in the setting of immunosuppression years later. Futhermore, patients who have previously suffered from cutaneous leishmaniasis may develop local immediate or delayed hypersensitivity reactions in response to immunization. There are also some data to suggest that immune responses in children may be suppressed for periods up to 6 months following live promastigote immunization potentially interfering with diphtheria-pertussis-tetanus or other vaccines [4]. Finally, some Israeli physicians believe that leishmanial immunization may be associated with recrudescence or initial activation of latent psoriasis. These considerations have limited the use of live promastigote vaccines.

There have been several studies over the years which suggest that dead promastigotes might be effective immunogens. Mayrink and coworkers [31] reported success in the use of a dead promastigote vaccine, composed of material from five leishmanial strains, in producing delayed cutaneous hypersensitivity and lymphocyte responsiveness (assessed by inhibition of leukocyte migration in response to leishmanial antigens) among Brazilians. Unfortunately, in field studies of efficacy, cutaneous leishmaniasis, which was prevalent in the area prior to the study, did not occur in either the control or experimental groups. Subsequent use of the vaccine as an emergency measure to control an epidemic of dermal leishmaniasis in Brazil suggested that the vaccine might be partially protective, but the program was not conducted as a randomized clinical trail [32]. Earlier studies in the late 1930's and early 1940's using dead promastigote preparations also appeared to show partial protection against natural infection [32]. Despite these encouraging results a number of investigators have failed in attempts to protect mice or hamsters using dead promastigote vaccines [6], and there has been a general lack of enthusiasm for this approach. Further studies are needed to disprove or validate the efficacy of vaccination with dead promastigotes.

A third approach to vaccination has been the use of live, attenuated promastigotes. Attempts to elicit protective immunity with actinomycin-treated or multiply passaged promastigotes have generally failed [6]. However, recent studies by Liew, Howard, and Hale [33] indicate that immunization with irradiated *L. tropica* promastigotes given intravenously results in protection against reinfection in a murine model of cutaneous leishmaniasis. Avirulent leishmania promastigote clones have also shown immunization potential in a mouse model but only when promastigotes were given intravenously or intraperitoneally in high doses [34]. These findings raise the possibility that irradiated promastigotes or genetically or chemically altered parasites may eventually prove to be effective vaccines if administered in the correct manner.

Finally, the advent of molecular biology and monoclonal antibody techniques may lead to the isolation, purification and characterization of leishmanial antigens against which protective immune responses can be elicited in humans. Enthusiasm for this approach is engendered by the recent advances in the development of a malaria vaccine, and the strides which have been made toward understanding the immunology and immunogenetics of leishmaniasis [35]. It is beyond the scope of this article to review in a comprehensive manner what is known about the immuno-biology of the various leishmanias. A few of the more recent advances will be discussed as they relate to vaccine development.

The preponderance of human and animal model data suggests that resolution of leishmaniasis is dependent on cell-mediated immune mechanisms [35, 36]. Great excitement has been generated by recent studies using T cell culture and cloning techniques [37-39]. Sheppard, Scott and Dwyer [37] have successfully isolated T cell clones using *L. donovani* as an immunogen. Their clones exhibited a high degree of cross-reactivity toward other *Leishmania* species. The findings suggested that leishmanial antigens capable of eliciting protective cell-mediated responses might soon be identified. Titus *et al.* [39] have isolated T cell populations with helper/inducer phenotype that are specific for antigens of *L. major*. These T cell populations have been shown *in vitro* to mount antigen-specific proliferative responses, to provide specific helper activity for antibody responses and to activate parasitized macrophages resulting in *L. major* destruction, but paradoxically, transfer of these cells to syngeneic animals has resulted in development of larger skin lesions after challenge with live amastigotes. There is clearly a critical need to better define the immunology of leishmaniasis as a prerequisite to vaccine development. It

would be tragic to immunize humans with a component vaccine that produces an antigen-specific T helper/inducer response as measured by *in vitro* assays but increases the severity of disease.

Equally intriguing is the recent work of McMann-Pratt and coworkers [40] who found that exposure of promastigotes to species-specific monoclonal antibodies provided protection to mice challenged with *L. mexicana.* Earlier studies of passively transferred immune serum failed to show any protective role for antibody [35]. Prior to McMann-Pratt *et al.*'s studies, control of leishmanial infection was assumed to be by cell-mediated immune mechanisms in all instances. Although a great deal more needs to be learned about the immunology of leishmaniasis as indicated by these paradoxical findings, immunoprophylaxis would seem to hold the greatest potential for controlling leishmaniasis in the future.

Current Strategies for Controlling Visceral and Cutaneous Leishmaniasis

Visceral leishmaniasis: Visceral leishmaniasis is usually a sporadic disease in endemic areas of South America, the Mediterranean, and East Africa. In Latin America, the Mediterranean, and probably China, dogs are the principal reservoirs of *L. donovani.* Extermination of infected dogs and control of peridomestic or domestic sandflies have reduced the incidence of disease in some regions. However, foxes serve as a wild reservoir in areas such as Brazil and are probably responsible for reemergence of visceral leishmaniasis.

A thorough understanding of the epidemiology of disease is necessary to optimize the effects of vector and reservoir control. For example, Lainson and coworkers [41, 42] recently found large numbers of sandflies, some leishmania-infected, in chicken houses during an outbreak of visceral leishmaniasis in Para State, Brazil. The chicken is an ideal maintenance host for sandflies. Peridomestic sandflies were thought to have fed on leishmania-infected foxes, which were attracted to chicken houses, and sandflies subsequently transmitted *L. donovani chagasi* to domestic dogs or humans. Residual insecticide spraying of patient houses alone is unlikely to be successful in such a setting. Attention must be directed to chicken houses as well. These observations illustrate the critical need for a thorough understanding of vector and reservoir ecology in devising control strategies.

In Kenya and Sudan transmission of *L. donovani* to humans is thought to occur near termite hills in the evening. Humans are believed to be an important reservoir. Epidemics of visceral leishmaniasis have occurred in East Africa among troops passing through uninhabited areas indicating that a sylvatic reservoir also exists. Although insecticide spraying of termite hills has been attempted and early identification and treatment of human cases is indicated, these measures are not likely to eradicate transmission of the disease. Aerial fogging of endemic areas with insecticides has failed [13].

In India, where humans are the only identified reservoir of *L. donovani,* great epidemics of visceral leishmaniasis have occurred [10]. Circulating parasites are frequently found in the blood stream of Indian kala-azar patients, and patients with post-kala-azar dermal leishmaniasis are thought to provide another reservoir for infection of sandflies. Identification and treatment of human cases as well as the use of residual insecticides to eliminate peridomestic sandflies are the best available approaches to control in the Indian subcontinent. Obviously, safe, effective vaccines would greatly facilitate control of visceral leishmaniasis in India and throughout the world.

Cutaneous leishmaniasis of the Old World: Anthroponotic *L. tropica* infection in the USSR has reportedly been controlled by residual insecticide spraying in conjunction with mass treatment of infected humans [4]. Extermination of infected dogs is important in areas where they serve as reservoirs for *L. tropica. L. major* occurs in rural areas of Israel, Jordan, the USSR and West Africa. Environmental changes including deep plowing and the poisoning of rodents such as the gerbil have proven effective in the USSR [4]. In other locales such as Ethiopia, where rock hyraxes are the animal reservoirs for *L. aethiopica,* reservoir and vector control are impractical or impossible. Live promastigote vaccines have been widely used in the USSR and Israel as previously discussed, but they have major limitations.

Cutaneous leishmaniasis of the New World: Members of the *L. mexicana* complex and the *L. braziliensis* complex are acquired by entering the forest. The epidemiologic cycles are extremely complex and involve many different sandfly vectors and wild animal reservoirs [15, 42]. Wide scale vector and reservoir control are virtually impossible under these conditions. Currently, protection of individuals who penetrate the forest

is limited to the use of insect repellents, protective clothing or netting and avoidance of danger areas. None of these are particularly effective [42] for residents of the area. In hot, humid conditions the efficacy of insect repellents is quickly neutralized by sweating. Long-sleeved protective clothing is totally impractical. Prevention of sylvatic leishmaniasis among gangs of laborers, topographers, forestry workers, or soldiers can be effected on a limited scale by placing men in forest encampments in areas that are adequately cleared, spraying the bases of larger trees with insecticides, and prohibiting night hunting or other activities in the forest [41]. More research is needed on the forest leishmanias of the Americas. In particular, there is an urgent need to map the distribution of the predominant *Leishmania* species that infect humans in Latin America because treatment schedules differ for the various types of American cutaneous infection [5]. If a vaccine can be developed, it will be of great utility.

Priorities for the Future

Control of the leishmanias poses a difficult problem because of the diversity of the parasites, variations in the ecology of their vectors, the wide range of reservoirs, and the complexity of the parasites' interactions with human host defense mechanisms. Until vaccines become available, partial control of leishmaniasis in some areas can be accomplished by focusing on vectors and reservoirs. The ecology and biology of sandflies need to be better characterized in many locales to facilitate this approach. The development of biological methods for sandfly control is worthy of study. New chemotherapeutic agents are needed to deal with drug resistant strains, to simplify administration and to obviate the need for hospitalization. Finally, priority must be given to achieving a better understanding of the immunobiology of disease and to vaccine development.

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CONTROL OF INTESTINAL PROTOZOAL INFECTIONS: REALITIES AND OPPORTUNITIES

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Introduction

Of the numerous protozoa that may be found in the human gastro-intestinal tract, only a few are both pathogenic and frequently encountered. This select list includes *Entamoeba histolytica, Giardia lamblia,* and the recently recognized common pathogen of both immunocompromised and normal hosts, *Cryptosporidium* [1, 2]. The nature of the interaction of these parasitic infections with nutritional state of the host is described in other papers in this symposium. These nutritional effects, combined with the direct morbidity and mortality the organisms cause and their high prevalence, are sufficient reason to make control of infection a highly desirable public health goal.

To increase the likelihood of success, control strategies should be based on a knowledge of the life cycle of the parasite, its epidemiology with an emphasis on transmission, and the behavior of people which affects their risk of infection. At the present time, there is relatively little known about these aspects of *Cryptosporidium,* and it seems prudent to focus attention on amebiasis and giardiasis in the hope that general principles will be apparent which may be applied equally to *Cryptosporidium* in the future. This paper will, therefore, describe the life cycle and epidemiology of *Entamoeba histolytica* (Eh) and *Giardia lamblia* (Gl) and the present and potential future control strategies which are based on this information.

Life Cycle

Both Eh and Gl have similar and simple life cycles, involving just two developmental forms and no intermediate host [3, 4]. In the human, both infection and illness are due to the motile, multiplying trophozoite stage, while transmission of Eh and Gl results from passage of thick walled cysts in the stool, which are able to survive in the environment. Infection is initiated when cysts are ingested by mouth and following excystation, trophozoites are released in the gut lumen. The life cycle then depends on encystation, excretion of cysts in the stool, and ingestion by a susceptible host. While Eh is a strict human pathogen, it is now apparent that Gl can infect several other mammalian species and be transmitted as a zooinosis. This has been reasonably well documented in a few water-borne outbreaks of giardiasis in which contamination of water by infected beavers has been found [5, 6]. It remains to be seen how common zooinotic transmission actually is.

Once viable cysts are ingested, excystation is initated (at least for Gl) by contact with gastric acid [7]. By the time excystation is accomplished, the trophozoites must exit the stomach, for they cannot survive the low pH [3, 4]. The particulars of Eh and Gl infection differ from this stage until cysts reach the colon. Gl lives in the small intestine, primarily in the duodenum and proximal portion of the jejunum. Site predilection for Gl may be the result of two properties of the organism. First of all, *Giardia* are unable to produce the phospholipids necessary for membrane synthesis, which is an obvious prerequisite for multiplication. Instead, Gl utilizes preformed phospholipid [8] and requires bile salts for its efficient uptake [9, 10]. The presence of dilute bile in the proximal small intestine provides for both of these needs, and appears to be biologically advantageous for the organism. Bile salts also seem to promote growth of Gl in a fashion independent of enhanced phospholipid uptake, and thus may be the more critical determinant of giardial localization [10]. A second factor of importance may be a recently discovered sugar-specific carbohydrate binding protein (lectin) in the plasma membrane of the organism which is activated by limited tryptic digestion [11]. The lectin can also be activated by small bowel juice, which contains trypsin, and the activation is inhibited by addition of soybean trypsin inhibitor. Its relevance is at this time suggested only by *in vitro* studies which show that the lectin can recognize receptors on small intestinal epithelial cells and result in their agglutination. It is at least a plausible hypothesis that the lectin provides a mechanism of adherence to the gut mucosa for a

pathogen which appears to require the biochemical milieu of the small bowel for growth.

In contrast, Eh trophozoites live in the large bowel. The reason for this preferential colonization is not clear. Eh trophozoites utilize anaerobic energy pathways, and of course, appropriate conditions are present in the colon. This alone cannot explain site preference, for Gl which grow so nicely in small intestine are also anaerobes. Although both organisms seem to need L-cysteine for growth *in vitro*, it is not certain that this is simply for effects on oxidation-reduction potential, since other reducing agents do not substitute well [12]. Eh is, in fact, somewhat aerotolerant, as evidenced by its ability to grow in the presence of 5% oxygen whereas Gl are rapidly killed in low oxygen in the absence of cysteine [13]. Lectins have also been described in Eh trophozoites with specificity for either N-acetyl-D-glucosamine or N-acetyl-D-galactosamine in different studies [14, 15]. Neither lectin has been demonstrated to be necessary for colonization, nor has specificity for gut cells been clearly shown, but the latter is speculated to play a role in the contact cytolethal properties of the organism [15].

The life cycles are completed with transformation of trophozoites to the cyst form, which is then excreted in the stool. The trigger for initiation of this event is not known, but it is necessary for survival of both parasites outside of the body, for trophozoites are very susceptible to environmental conditions and rapidly die. The cyst wall of both Gl and Eh is primarily made of chitin, a linear polymer of $\beta 1 \rightarrow 4$ linked N-acetyl-D-glucosamine [16, 17].

Epidemiology

The critical determinants of the epidemiology of giardiasis and amebiasis are dictated by the biological constraints of the life cycle. Transmission is anal-oral, almost exclusively via the cyst form, and perhaps on occasion via the direct transmission of trophozoites during anal-oral sexual practices. In amebiasis, the transmission is always from human to human, because of the rigid host-adaptation of *E. histolytica*. The same conceptual restriction used to apply to *G. lambia,* since it was believed that this organism was also a strict human parasite, and many recent texts still indicate this. Indeed, in the past *Giardia* were named for the host species they were recovered from, as if all were distinctive host-adapted organisms [18]. However, it has proven to be difficult to distinguish among these

so-called "species", and instead cross-infection among animals appears to be common [19]. On morphological grounds, three *Giardia* types can be separated, based mainly on the shape of the trophozoite and the median bodies within them: *G. agilis,* found in amphibians; *G. muris,* present in a variety of rodents; *G. lamblia* (sometimes known as *G. intestinalis*), the parasite of humans and a number of other mammals [20]. Whether or not better criteria would confirm these "species" designations or establish others, and whether or not there are distinctive strains of *G. lamblia* with different pathogenic potential remains to be determined [19]. Recent attempts have been made to analyze antigens, isoenzymes, and DNA relatedness to determine the degree of homogeneity among various "lamblia" isolates [21-24]. However, the "chemotaxonomy" of *Giardia lamblia* remains a complex, but promising, technique for the future, and we are currently unable to clearly distinguish one isolate from another.

In contrast, considerable progress has been achieved in the classification of pathogenic and non-pathogenic strains of *Entamoeba histolytica* by means of isoenzyme analysis [25-27]. Epidemiologic studies in several areas of the world have shown that certain zymodeme patterns are associated with virulence, while others are "non-pathogenic" and appear to result in harmless carriage alone. This provides a potential explanation for the calculations of Brumpt, who estimated that 1 in 5 infected individuals in tropical countries with a high incidence of invasive amebiasis will have infection and disease, whereas in temperate climates only 1 per million of those infected will experience clinical manifestations [28]. The biological correlates of the virulent zymodemes are not known. Recent studies indicate that close to 100% of individuals harboring such zymodemes, whether clinically ill or asymptomatic, demonstrate a high-titer serum antibody response to the organism [29], whereas much lower titers are found in only 20% of those carrying avirulent zymodemes, suggesting the inherent invasiveness of the virulent strains and a lack of this property in avirulent strains. In one study, pathogenic zymodemes were found in 14/1381 (1%) healthy individuals, 2 of whom subsequently developed symptoms of amebic colitis. The diagnosis was confirmed by sigmoidoscopy and demonstration of amebic trophozoites in stool in one [30].

Both organisms are widespread in the world. Good estimates of prevalence are difficult to obtain. Walsh has pointed out some of the problems [31], including survey of non-representative populations, failure

to distinguish pathogenic from non-pathogenic Eh zymodemes in most studies, reliance on only microscopy examination of single stool samples for diagnosis, the problem of intermittent excretion of organisms, and the intrinsic limitation of point prevalence surveys which cannot account for seasonal transmission and give no picture of the cumulative incidence of infection over time. Walsh calculates that in Mexico, approximately 5% of the population acquires antibody to *E. histolytica* per year, and that nearly 10% have amebic disease each year. The majority of cases are watery diarrhea, lasting for 5-7 days but severe enough to lead to visits to a health care worker.. She also estimates that as many as 30,000 deaths may occur on an annual basis due to severe invasive amebiasis, predominantly due to liver abscess in males in the third and fourth decade of life and to a lesser extent in pregnant and post-partum women. A best guess global extrapolation of available data for the year 1981 suggests that there are 480 million infections, with 36 million cases of amebic colitis or liver abscess, and at least 40,000 deaths annually.

It is equally difficult to assess the global impact of *Giardia* infection. Diagnosis is even more problematic than for Eh, since serological tests are of uncertain relevance and specificity [4, 32, 33], and sensitivity of diagnosis by stool microscopy examination is considered to be no better than 50%, even in symptomatic patients [34, 35]. Cyst excretion is highly variable from day to day, and therefore 3-4 negative stool examinations over 7-10 days are often recommended to rule out giardiasis in symptomatic cases [36]. Even so, some experts suggest empiric treatment of clinically suspicious cases with negative stools [34]. In developing countries, 40-50% of children under 10 may be carrying *Giardia* in stool, and nearly 100% will become infected at some time if they are followed sequentially [37, 38]. Analysis of prospective data suggests that approximately 50% of initial infections are associated with symptoms [39]. Extrapolation of survey data to the world's population suggests perhaps 200 million infections per year, resulting in about 500,000 clinical cases [40], with very few deaths but a definite impact on child growth and development (see M.J.G. Farthing in this symposium).

As far as can be determined, the routes of transmission of Eh and Gl are the same, differing only in the order of importance as determined in the more affluent countries: food, direct contact, and water for Eh, and water, direct contact, and food for Gl. However, the data are inadequate to determine the actual mechanics of transmission under natural conditions in endemic areas, where poverty, overcrowding, poor housing and sanitation

facilities, lack of water of good quality, ignorance and inadequate education may increase the relative importance of direct contact transmission for the two organisms. In the United States, *Giardia lamblia* is now the most common intestinal parasite and the leading cause of water-borne diarrheal disease. Contamination of the drinking water in the U.S. with cysts has been observed under several sets of circumstances. In some, direct cross-contamination of sewage and water pipes has occurred, sometimes associated with malfunctioning of water treatment plants. Smaller communities often rely on ground water supplies that pass through natural habitats of animals such as beavers that may act as reservoirs of *Giardia lamblia*. Instances of community outbreaks of giardiasis have *occurred* when water supplies have been exposed to infected beavers [6, 41-43], although as noted by Navin *et al.* [6], direct evidence of animal to human transmission is lacking. The occurrence of outbreaks of giardiasis among day care school children has indicated that direct contact may be a frequent means of transmission in developed countries for certain populations [44, 45]. Novel routes of transmission have also been suggested; for example, transmission to users of a swimming pool after infant swim classes resulted in fecal contamination of the pool water, in spite of chlorination [46].

The key to transmission of either Eh or Gl is the ingestion of viable cysts. The central question is whether or not it is possible to prevent the entry of cysts into the water or food supply, or to remove or kill them when prevention is not possible. Cysts are considered to be extremely hardy, but this is not to say that they are indestructible. Resistance to physical and chemical factors can vary markedly with small changes in the environment of the cyst. For example, Eh cysts may persist in feces, damp soil, or water for weeks or longer, but they are quite sensitive to dessication [3]. They are killed within 10 minutes of deposition on skin due to drying [47], but will persist for at least an hour in fecal material present under the fingernails [48]. Sunshine and drying inactivate cysts, and three days of dry weather will kill cysts deposited on the surface of vegetables by fertilization or watering with contaminated materials [49]. The process is hastened by high environmental temperature, as cysts are heat sensitive. Killing depends on the height of the temperature and the length of time it is maintained [50]. Thus, cysts may survive for 1 month at 20^0 C but will not survive beyond 1 day at 40^0 C and are rapidly killed at 68^0 C or above. Cysts are susceptible to chlorination if concentrations of 3 mg/1 are provided, the pH lowered, the water warmed and prolonged contact maintained [51, 52]. However, water containing this

level of chlorine must be dechlorinated before use [3]. Bacteria are more sensitive to chlorination, and water considered safe by conventional testing can certainly contain viable cysts. As a practical measure, the only method of sterilization of drinking water considered to be completely safe is boiling for 10 minutes [53].

It has also been a prevailing concept that Gl is extremely resistant to disinfection [54]. The available data, however, suggest that cysts of Gl, like those of Eh, will vary in susceptibility to chlorination in municipal water systems depending on the free residual chlorine concentration attained, water pH and temperature, and duration of exposure [55, 56]. For example, at a level of 1.5 mg/1 of free residual chlorine, total inactivation of cysts is obtained after 10 minutes of exposure at 25^0 C at pH values from 6 to 8. However, reducing the temperature to 15^0 C requires an increase in the chlorine concentration to 2.5 mg/1 for 60 minutes in order to kill all cysts when the pH is 7-8. At 5^0 C, 1 mg/1 of residual chlorine, a concentration commonly attained in water systems, fails to eradicate viable cysts after 60 minutes of exposure, even at pH 6. Thus, it is certainly possible that cysts will survive in many water systems, especially at the low water temperatures during the winter and in some areas during the summer months as well. In contrast, in smaller volumes of water appropriate for individuals or groups, complete destruction of cysts can be readily accomplished with chlorination [57].

Water treatment to physically remove cysts of Eh or Gl is feasible and is the only way to insure that municipal water is safe [58]. Various methods are used in sequence, such as coagulation, flocculation, or sedimentation to pretreat water prior to perculation through matrices designed by engineers to achieve specific filtration goals. Whereas there has been considerable work published concerning conditions for removal of Eh cysts, few data are available for Gl, presumably because it was not considered a pathogen until relatively recently. Of interest, effective removal of cysts by filtration does not correlate with reduction of turbidity, since the cyst is so much larger than clays and bacteria which contribute to turbidity. Both granular media and diatomaceous earth filtration methods appear to be useful to remove Gl cysts under proper operating conditions at the water treatment plant.

Control Measures

The life cycle and epidemiology of *Entamoeba histolytica* and *Giardia lamblia* indicate that control measures need to be designed to 1) prevent the contamination of food or water with cysts, 2) kill or remove cysts which manage to reach water or food, 3) reduce the number of clinically asymptomatic chronic cyst passers, and 4) improve personal hygiene to minimize the risks of person to person contact spread.

1) Prevention of contamination of food or water with cysts depends on the availability and use of safe fecal waste disposal systems, the treatment of human feces used as fertilizer to kill cysts, and protection of the sources of drinking water from contamination with infected material, whether derived from humans or potential animal reservoirs. In the long run, this approach in developing nations has the potential to significantly reduce morbidity and mortality due to diarrheal disease of all etiologies. Hence, there need be no specific focus on protozoal illness to justify national investments in environmental sanitation projects. Similarly, supply of sufficient quantities of safe water for washing and for human consumption can reduce the risk of both Eh and Gl infection, as well as other diarrheal diseases. Therefore, access to water should be considered to be a basic precondition for the achievement of good health for all.

Many different water and waste management systems are available, depending on economic resources and demography [58, 59]. It is difficult to put a cost figure on environmental sanitation and water projects, since the technical requirements (and hence, cost) differ in rural and urban settings. Simple methods designed for smaller numbers of users can provide benefits that approach those of more expensive, sophisticated systems for larger municipal usage. However, even the simple methods must be appropriately used to be effective, while the more complicated systems demand recurring costs in maintenance in order to work as designed [58]. Given the limited resources generally available or committed to health projects by governments, decisions to improve environmental sanitation facilities quickly become issues of priorities and the assignment of the necessary resources. However, with enough political will (which often can be stiffened by demands from the local populations) or self-help projects of individuals or communities, improvements are possible, particularly if enough time is allotted to see the benefits. These will not necessarily come in a short time period, but may be noted only after years of consistent performance and the additive effects of other health improvement

measures [53]. Since chronic asymptomatic Eh cyst excreters can pass nearly 50 million cysts per day [3], there are many opportunities for transmission other than via contaminated sewage and water systems, such as the real possibility of direct transmission within the household [19, 44, 60-63]. It should also be pointed out that installation of sewage and water systems does not insure safe excreta disposal or pure water for the consumer. In too many places in the world, including industrialized nations such as the U.S. and U.S.S.R., antique sewage and water systems have deteriorated to the point of establishing direct communications, particularly in older systems using cast iron pipes which become leaky with age. The result is continuous contamination of water with a constant high risk of infection, best demonstrated by the incidence of *Giardia lamblia* infection in visitors to affected cities [64-66]. Evaluation of published studies on the impact of sanitation improvements on the incidence of amebiasis reveals no consistent results, but this strategy promises the most benefits [53].

2) Removal of cysts in water supplies can be accomplished by adequate filtration systems, but these can be complex and expensive to construct. The problem of killing cysts in water has been discussed already, as current methods of chlorination will not work on a large scale. Boiling water is effective, however in the third world the cost of fuel is a major limiting factor in the use of this otherwise simple method of water purification.

3) Any strategy to reduce transmission of Eh and Gl infection must also deal with those individuals already infected [3, 4]. There are two distinct issues, first the treatment of those with clinical illness, and second, eradication of the cyst carrier state. The first, case control, depends on diagnosis and the availability of effective treatment. Neither is entirely satisfactory at the present time. Only rarely are drugs inexpensive.

There has been considerable improvement in drug therapy of invasive amebiasis with the introduction of metronidazole, and a resulting decrease in the mortality rate. But not all patients who need treatment will get it, and not all patients who receive it will respond. Drug therapy of the cyst passer is possible with either diiodohydroxyquin or diloxanide furoate, however the treatment is prolonged. With the high prevalence of the infection, mass chemotherapy of large populations would be needed as well as surveillance to detect treatment failures (and or reinfections) in need of repeat courses.

Three drugs are effective in treatment of clinical Gl infection, includ-

ing quinacrine, metronidazole, and furazolidone. A recent literature review of treatment studies of giardiasis, concludes that quinacrine and metronidazole are superior to furazolidone [67], but that quinacrine results in more side effects than metronidazole. However, the latter is carcinogenic in rodents and caution is recommended in its use. Thus, furazolidone may be selected by some physicians, especially for children because it comes in a liquid dosage form. Tinidazole and ornidazole, other imidazole drugs with less carcinogenic potential, have been tested and found to be very effective for Gl in a single dose regimen [68, 69]. However, the same limitations for mass chemotherapy described for Eh apply to Gl infection as well. Treatment regimens for asymptomatic cyst passers still need to be defined.

4) Improved personal hygiene is a matter of education and opportunity. While many of the measures seem to be plain common sense, they are so only when the rationale for recommending the measure is clearly understood. The concepts of causality at the village level are often very different from those established by scientific investigation, and may lead to behaviors considered to be inappropriate from the latter point of view. Health benefits can come from better preparation and storage of food and water, hand washing, and control of insects which may become contaminated with infected human stool and secondarily contaminate food or water in the household. Using shigellosis as a marker of a contact spread disease with a small infectious inoculum, it has been shown that reductions of 14 to 48% in incidence may result from improved personal and domestic hygiene [70]. The efficacy of education as a tool to reduce transmission of Eh and Gl is unknown. Without greater availability of water for washing and better housing, it is unlikely that education alone will have a major impact. On the other hand, without education it is equally unlikely that improved sanitation and water systems will affect disease rates.

Future Strategies

It is the hope that current studies of pathogenesis of amebiasis and giardiasis and of the host response to these organisms will lead to the development of effective prophylactic vaccines. For both diseases, this goal is a long way from reaching fruition. The immunology of amebiasis is far better understood than for giardiasis and the chances of ultimate

success appear much greater for a vaccine for Eh at the present time [71].

Understanding the biology of the organisms may lead to new epidemiological strategies. For example, if it were possible to prevent cyst formation by some means then the transmission of disease might be interrupted. The finding that chitin is a major component of the cyst wall of both Eh and Gl [16, 17] presents the opportunity to accomplish this goal with chemotherapy. Thus, Avron and colleagues have recently studied the effects of the chitin synthesis inhibitors, nikkomycin and polyoxin D (which are structural analogues of UDP-N-acetyl-D-glucosamine, the building block for biosynthesis of chitin), to inhibit *in vitro* cyst formation by *Entamoeba invadens* trophozoites [72]. It remains to be shown that the same effect occurs with Eh (which cannot yet be induced to make cysts *in vitro*), or that the drug will work *in vivo*. For Gl, there is also no *in vitro* encystation system, however an *in vivo* model is available using *G. muris* infection in mice. Indeed, this infection results in a large output of cysts which are used for serial transmission of infection to new susceptibles.

Continued research on drug therapy, based on metabolic studies of the two protozoa, may yield new compounds, effective in a single dose, without the toxicity of presently available agents, and inexpensive for mass use. In combination with other strategies, mass therapy may even allow eradication of the human adapted Eh in some places, and a sharp reduction in prevalence of Gl.

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CONTROL OF INTESTINAL HELMINTHIASES

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Summary

Intestinal infections constitute a heterogeneous group of infections, which cannot be controlled by one method. The objectives of control measures should be disease-oriented or disease and infection-oriented. A horizontal approach is the preferable control strategy but the control of some intestinal helminthiases may require vertical intervention. Optimal control tactics should be area-specific and based on chemotherapy and sanitation supplemented by health education. The area specificity depends on the local health importance of intestinal helminthiases, other health priorities and the feasibility of successful action. Basic strategies for controlling major intestinal infections have been elaborated. Diagnostic and therapeutic tools are available. Practical implementation of the control measures fits well into the Primary Health Care system. Parasite control, with its important social impact, is a good partner for other programmes promoting health.

Introduction

The problems related to the control of human intestinal helminthiases can be presented and discussed by considering the aims and objectives of control, by defining the tactics and the target groups, by evaluating the health priorities and the feasibility of control activities, by monitoring their linkage with Primary Health Care (PHC) and other public health programmes and finally by learning the lessons that come from previous experience and reviewing the present situation.

Aims of control

There are more than 34 species of nematodes, cestodes and trematodes that can invade the human intestine [1]. However, only 10 intestinal helminthiases [ascariasis, hookworm infections (two species), strongyloidiasis (two species), trichuriasis, enterobiasis, taeniasis (two species) and hymenolepiasis] have a wide distribution and/or serious pathology; among them ascariasis, hookworm anaemia and *T. solium* taeniasis are the most important on the global scale.

Depending on the local health priorities, the control measures may be limited to one particular infection (e.g. ascariasis) or disease (e.g. hookworm anaemia) or may be extended to a group of infections characterized by a similar mode of transmission, which may be soil-borne, zoonotic or person-to-person by faecal contamination. In other words, intestinal helminthiases constitute a heterogeneous group of infections in respect of their clinical expression, susceptibility to different anthelmintics, epidemiological patterns and appropriate control measures. It would be a mistake to think that all intestinal helminthiases can be controlled in the same way.

The decision as to which intestinal helminthiases or group of helminthiases have to be controlled depends much on the local public health priorities and policies and on the local feasibility of the control measures.

Objectives of control measures

Although some intestinal helminthiases have been eradicated in certain countries (ascariasis in Japan and Israel, *T. solium* infections in West Europe) eradication is not a very realistic goal except in highly organized and developed societies or in isolated areas (e.g. islands). The reduction of the prevalence and intensity of infection to a level of insignificant public health importance is a far more practicable goal. The criteria for low public health significance are both quantitative and qualitative, e.g. disappearance of hookworm anaemia as a prevalent disease [2]; only sporadic incidence of *T. solium* taeniasis and neurocysticercosis [2, 3]; a low intensity of ascariasis, that will not interfere with the growth and weight of children and cause parasitic intestinal obstructions [2]; a low fatality ratio in infants with strongyloidiasis, etc. In other words the control measures may be focused on disease only (hookworm anaemia) or on both disease and infection (taeniasis, ascariasis).

The definition of objectives of control measures can only be based on the results of a local survey and in comparison with other health service priorities.

Tactics of control

The control of common intestinal helminthiases requires a more horizontal approach based on the activities of the existing peripheral health services infrastructure (e.g. PHC); this approach will ensure the continuity of control measures, their wider coverage, better coordination with other health programmes and more direct community involvement in prevention and control schemes.

However, in certain local situations, vertical interventions by special teams may be justified. More direct interventions are needed in arresting the epidemic spread of ascariasis by agricultural use of sewage, in lowering high prevalences of taeniasis/cysticercosis in endemic foci, and in preventing easy transmission of hookworm infections in tea, coffee, rubber or jasmin plantations.

Theoretically, intestinal parasitic infections can all be effectively prevented and controlled by proper sanitation, but in practice this is a process which could take decades and require comprehensive social, economic and educational development in order to be successful. Depending on the aims of control, in addition to improved general sanitation, the hygiene measures should be focused on excreta disposal in the case of soil-transmitted helminthiases; on personal and domestic hygiene in the case of faecally transmitted infections; and on the control of zoonotic reservoirs and food hygiene, including meat inspection, in the case of zoonoses.

Where the organizational facilities and economic standards are adequate, community-oriented chemotherapy is a potent tool and offers more immediate and sometimes even spectacular results. Community-oriented chemotherapy may be based on mass-treatment, selective or targeted therapy.

Costly individual treatment (e.g. in Kenya, 55% of anthelmintics for ascariasis are used for uncoordinated self-medication) is of little help for control purposes; cost-effectiveness would be much improved if community-oriented chemotherapy replaces individual treatment.

Individual-oriented chemotherapy may contribute towards controlling certain intestinal helminthiases only through standard case management. For example, standard treatment of hookworm anaemia, when widely and continuously offered for some time to all anaemic individuals, may lower the prevalence of hookworm infection in the population; easily available and free treatment of taeniasis can reduce effectively the transmission of *Taenia spp.*

Therefore, optimal control tactics should be based both on chemotherapy and sanitation supplemented by health education. The most appropriate proportion of the measures should be determined for each infection and area separately, depending much on the local situation.

Targets for control activities

The distribution of several helminthiases paralleling their transmission patterns is concentrated in the same age, sex or professional groups. Targeting of the therapeutic interventions on these specific population groups may increase their effectiveness and lower the costs [4]. The efficacy of targeted chemotherapy has been confirmed in ascariasis [5].

In those areas where indiscriminate defaecation prevails, ascariasis occurs most often in preschool and primary school-children [6].

Adults working in mines or plantations are most exposed to hookworm infection. Targeted treatment of those workers or individuals who are anaemic because of a heavy hookworm load should effectively reduce, not only the morbidity, but also the total prevalence rates of hookworm infection in a given area.

In the case of *Strongyloides fulleborni*-like infections in Papua New Guinea, the chemotherapy probably should be targeted on mothers and infants, the latter showing the highest mortality rate [7]. In hymenolepiasis, the targeted groups are preschool and school-children, especially those who are living in children's institutions or crowded homes.

Taeniasis more frequently occurs in adulthood, when raw meat is more likely to be eaten. However, as the diagnosis of taeniasis still remains inadequate, difficult and uncertain while, on the other hand, treatment with taeniacides is safe and cheap, large-scale treatment of the whole adult population in areas hyperendemic for *T. solium* taeniasis/cysticercosis may give better results.

Intestinal helminthiases as health priorities

Some intestinal helminthiases are common and wide-spread (ascariasis, hookworm infections, trichuriasis). However the high prevalence rates do not in themselves determine the health priority, e.g. high prevalence rates for trichuriasis may be of little public health significance if the intensity of infection in general is low.

In several regions, where public health importance was measured by more objective morbidity and mortality criteria, the results were impressive; for example, in the early 1970's, the annual rate of intestinal obstructions due to *Ascaris* in the southern United States of America was approximately two per 1.000 infected children aged between 1-5 years [8]. The case mortality rate for intestinal obstructions due to *Ascaris* was 11% and for biliary ascariasis 9.4% in Brazilian hospitals [9].

In the Rangoon Children's Hospital from 1981-1983, three percent of all admissions and 57.6% of acute abdominal cases were due to ascariasis [10]. In Bangladesh, intestinal helminthiases, mainly ascariasis, are the sixth leading cause for hospitalization (4.9% of all inpatients) and the second leading cause of seeking medical help in health centres (11.1% of all outpatients) [11].

In 1976, in Kenya, 88,804 patients were hospitalized because of ascariasis, i.e. 2.6% of all hospital admissions [12]. In the Red Cross War Memorial Children's Hospital, Cape Town, South Africa, ascariasis is the most common cause of acute abdominal emergency in children [13]. In Acapulco, Mexico, intestinal obstructions due to *Ascaris* ranked fifth as a cause of pediatric admissions to the hospital [14].

In El Salvador, hookworm infection occurs in 35 to 40% of the general population; 0.5 to 1.0% of the population, i.e. 40,000 people, carried more than 100 hookworms and suffered from hookworm anaemia; among these, 4,000 people had less than 5.0g haemoglobin and 1,000 of them die annually either directly from hookworm anaemia or indirectly from concomitant infections [15].

The prevalence of neurocysticercosis in the Latin American countries was estimated as 0.1%, which means that 350,000 persons have *T. solium* larvae in the brain; the prevalence of taeniasis is about 1% in some Latin American countries [16].

Recently, a criterion, healthy life lost, based on annual incidence of disease, the disability caused by the disease and the case fatality rate has been introduced in order to estimate the public health importance of certain diseases [17]. The calculations made for Ghana in the late 1970's

have shown that hookworm infection causes 1,482 days of healthy life lost per 1,000 persons per year, and ascariasis, 1,222; both infections are not among the 25 most important diseases occurring in Ghana. There are no such estimations on intestinal parasitic infections from other countries as yet.

Public health importance is one of the important factors for setting up national health priorities. The other factors are political commitment, resource allocation, community involvement, health services infrastructure, including man-power available.

Intestinal helminthiases, especially ascariasis, are socially sensitive issues. The Integrated Health Project, practiced in South-East Asian countries for many years by the Japanese Organization for International Cooperation in Family Planning (JOICFP) has shown that parasite control can be successfully used as an entry point for a long-term strategy of community health development [18]. JOICFP practical experience which deserves more recognition has added a considerable amount of indirect social benefits to the calculations measuring the cost/benefit ratio in terms of money only [19].

Feasibility of the control projects

The basic strategies for controlling major intestinal helminthiases have been elaborated [2] and are now in the process of verification in practice through some operational research projects. Diagnostic and therapeutic tools are available.

Diagnosis of the most important intestinal helminthiases (taeniasis and some trematode infections excepted) is simple and inexpensive by current techniques [20]. These are Kato or Kato-Katz thick smears, simple decantation and sedimentation, Baermann's funnel or Harada-Mori's tubes for collecting or culturing nematode larvae. The techniques do not require much laboratory equipment in addition to the microscope. The preparation of slides and microscopical diagnosis need only basic training. The only difficulties in field examinations are that all these examinations are performed with faecal material, for which collection may not be easy.

There are highly effective, safe and relatively cheap anthelmintics available for all major intestinal infections [1]. The efficacy of a single dose treatment (with the exception of strongyloidiasis) is usually over 80% [21]. The cost of a single treatment varies from five to 35 US cents.

It has been shown that effective control of ascariasis in a hyper-endemic area needs treatment of a target group (children) every three to four months for at least three consecutive years. Mass-treatment executed every two months can control ascariasis within 28 months [22]. The control of hookworm disease and anaemia requires treatment of all anaemic individuals with iron and anthelmintics about once a year for some years [2]. Treatment of *T. solium* taeniasis in hyperendemic areas (over 1% of taeniasis, over 0.1% of neurocysticercosis in the local human population and over 5% of cysticercosis in pigs) may need large-scale chemotherapy but when the infection becomes less prevalent and focal in distribution, targeted treatment can be introduced in families rearing infected pigs; these can be diagnosed by meat inspection and traced back to their place of origin [3].

The constraints delaying a successful implementation of control programmes in many countries are inadequate epidemiological surveil-lance as a base for setting-up and monitoring the optimal interventions [23], inadequate operational research to confirm in practice the efficacy of different control variants [1], and lack of political will and govern-mental decision to include control projects into the national health pro-gramme [24]. The importance of a national epidemiological survey and surveillance of planning, monitoring and evaluation of the control project has been frequently emphasized [23, 25].

Links with Primary Health Care

Diagnosis, treatment, prevention and control of intestinal helmin-thiases fit well into a Primary Health Care system [2] both as standard case management and community-oriented actions are concerned.

Setting up a standard case management at health centre and hospital levels is important for lowering morbidity and mortality rates due to hookworm anaemia, and for preventing complications of ascariasis and strongyloidiasis, *T. solium* cysticercosis and other fatal intestinal infec-tions. It can indirectly limit the spread only of some helminthiases, such as hookworm infections and *T. solium* taeniasis in the population. The spread of the others, such as ascariasis, characterized by high egg production and their easy dissemination, is not usually much affected by casual treatment of individuals.

The major role of the PHC system is community-oriented preventive and control action [2]. The main activities of the

PHC worker are to improve the local level of sanitation and hygiene, carry out basic health education and link the communities with health services. All these activities are essential for antiparasitic community-oriented control programmes. In principle, health centres should be involved in any diagnostic and therapeutic actions. However, the District Health Office is the focal point for initiation, implementation and supervision of community-oriented chemotherapeutic and sanitary projects. At the top of the PHC infrastructure there should be a reference centre, which is responsible for national or area surveys, the technical expertise needed and training. The reference centre in this case is usually a Public Health Institute or an academic institution where a parasitologist is working.

The prevention and control of intestinal helminthiases should be one element in the whole package of preventive activities; however, sometimes it is the element easiest to start with because of a lively social interest in combating "worms".

Links with the other health programmes

Where a PHC infrastructure does not exist, the prevention and control of intestinal helminthiases may be an important partner of the other major health programmes.

Mass parasite control can well stimulate the community acceptance of environmental sanitation [19]. For this reason parasite control is attached to environmental hygiene and sanitation programmes in Nepal, Tanzania, Tuvalu, Tonga and Vietnam. In Singapore, it is part of the personal hygiene campaign.

Intestinal parasitic infections also provide highly appropriate subjects to start health education because people know about and dislike "worms".

Whether research confirms it or not, the majority of people do not have any doubts that the presence of intestinal parasites interferes with nutrition. In countries like India, Indonesia, Kiribati and Nepal, parasite control is strongly linked with nutritional programmes.

The common intestinal parasitoses create problems mainly in children, the most vulnerable segment of the population, and as such are in the sphere of Maternal and Child Health interest. The control of intestinal helminthiases is based on chemotherapy of school-children in some parts of India, the Dominican Republic and South Korea.

Workers' Health may be involved in the control of some intestinal

helminthiases such as hookworm anaemia among workers on plantations, or in mines as in Indonesia.

The control of intestinal helminthiases is also combined with several other major WHO programmes such as the Essential Drug Programme [26], the Diarrhoeal Diseases Control Programme [27], the Communicable Diseases Programme and the Zoonoses Control Programme [3].

In Brazil and the Philippines, deworming is organized in conjunction with schistosomiasis control; in Samoa, it is part of the filariasis control project.

The control of intestinal parasitoses fulfills well the criteria for an efficient partnership in promoting other health programmes which have been formulated as follows: (i) the problem has to be deeply related to the people's daily life in the community; (ii) the effects of control activities should be visible and the activities easily spread to other areas; and (iii) the control measures should not require highly sophisticated technology or a great deal of equipment and investment.

Both the parasite control campaign in Japan and the recent achievements of the Asian Parasite Control Organization (APCO) and JOICFP in promoting Integrated Health Programmes in South-East Asian countries have confirmed the usefulness of these criteria in practice.

Past and present control programmes

As early as 1913 the Rockefeller Foundation launched the first global programme for hookworm eradication, which started in the southern United States of America and was later extended to 52 countries. Although the hookworm campaign was not fully successful, it showed that chemotherapy should be used to control hookworm anaemia but hookworm infection should be controlled by sanitation [28]. This axiom has recently been rediscovered and is now included in WHO basic strategies [2].

In Japan, the control of ascariasis was initiated in 1931 by the Parasite Control Act, banning the use of human faecal material as a fertilizer. A nation-wide vertical control action, based on selective chemotherapy and improvement of sanitation started later on and brought down the prevalence of ascariasis from 62.9% in 1949 to 0.6% in 1973 [29].

In South Korea, a nation-wide selective chemotherapy programme

organized for school-children and students brought down the prevalence of ascariasis from 55.4% in 1969 to 10.2% in 1981 [22].

An epidemic spread of ascariasis caused by the consumption of wastewater-irrigated vegetables was successfully stopped in the Darmstadt area (Federal Republic of Germany) in the late 1940's [30] and in Jerusalem in the 1960's and 1970's [31].

Other control actions of a local or pilot character were organized in many other countries (e.g. Kenya, Philippines, Taiwan, Thailand, USSR). According to the report of the Asian Parasite Control Conference held in 1984 [32], major helminthiases control projects are being implemented in four rural areas in Bangladesh, two urban areas of Brazil, one urban and one rural area of China, among school-children, mine and plantations workers in Indonesia, in several areas in Nepal and the Philippines and some areas in Sri Lanka, Tanzania and Thailand.

The WHO Parasitic Diseases Programme is promoting the prevention and control of intestinal parasitoses by offering a technical service [24], supporting operational research (Brazil, Burma, Colombia, Ecuador, Jamaica, Malaysia, Mexico, Nigeria, Papua New Guinea, Philippines, St. Lucia, Thailand) and organizing training (Brazil, Cuba, Lesotho, Nigeria, Peru, Seychelles, Tanzania, Tunisia, 10 countries in the South Pacific and 9 countries in the Region of South-East Asia).

The WHO Regional Offices are at present involved in intestinal helminthiases control projects in Burma, China, Dominican Republic, Guatemala, South Korea and the South Pacific Islands.

The United Nations Children's Fund (UNICEF) is actively involved in parasite control in Vietnam and distributes large amounts of anthelmintics to the developing countries.

In conclusion, the above-mentioned activities in various countries demonstrate that the control of intestinal parasitic infections is becoming a more and more useful partner in the development of health programmes. For example, the control of ascariasis can help much in health education to change unhygienic life style, in adequate nutrition and water supply, in improving sanitation and mobilizing voluntary resources and people for prevention and control of locally endemic diseases in their communities. The setting-up of control projects is now more a matter of political determinations considering local health, social and economic priorities and of pushing appropriate decision mechanisms (who will carry out what actions, where, how will they be integrated and who will fund them) than a matter of technical support which is already available.

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CONTROL OF MALNUTRITION
IN THE DEVELOPING WORLD BY REDUCTION
OF INFANTILE AND CHILDHOOD INFECTIONS

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Introduction

Malnutrition has received considerable attention from major international organizations and foundations, bilateral aid programs, national governments and the general public. This concern for nutritional status is manifest in the Constitution of the World Health Organization which notes that adequate nutrition is a necessary common denominator for all WHO activities [1]. Yet there has been a continuing debate concerning the causes of malnutrition and the best approaches to deal with the problem, and in spite of all efforts the Director General of WHO, Dr. Halfdan Mahler, in 1984 stated that "the absolute number of malnourished children under the age of five in developing countries appears to have slightly increased over that of ten years ago" [1].

Following an extensive study, an expert group called together by the Food and Nutrition Board of the U.S. National Academy of Science [2], suggested four approaches to reduce malnutrition: increase food production, reduce poverty, stabilize food supplies, and control population growth. However, it is increasingly recognized that "malnutrition is by no means an inevitable consequence of an inadequate diet, even if a lack of food may obviously be a contributary cause. There are a number of other health and non-health factors which can interfere with energy flow, including an individual's ability to obtain full benefit from the

food that is consumed, whatever the amount. Infection and disease impair this process; when food is scarce the increased need for energy aggravates the effects of malnutrition, and the situation may deteriorate further with loss of appetite in the sick individual. The under-nourished are more susceptible to infection and disease, and thus a vicious cycle is formed" [2].

While some assert that food inadequacy is a consequence of maldistribution and not primarily a global production problem, there is little reason for optimism that this can be solved, at least in the short term, given the realities of political inaction and political and economic conflict [3]. In the meantime, a majority of the world's population will suffer, and millions, especially young children, will needlessly die. This chilling reality necessitates a different short term strategy. Until recently, little attention has been given to specific public health actions that are feasible for most countries and that collectively could significantly reduce the prevalence of malnutrition and its consequences. In particular, the role of infection in the causation of infantile and childhood malnutrition is often underemphasized, although there is reason to believe that infection is in fact a major factor in the etiology of malnutrition [4, 5].

Defining the Problem

Malnutrition has been defined as a disease state leading to "the deterioration of health status and/or social and productive performance of individuals arising from an intake of food either too low in quantity, or of the wrong kind, or both" [6]. WHO has further refined this definition by recognizing that "malnutrition represents a number of diseases, each with a specific etiology relating to the nutrient involved, and caused by a metabolic imbalance at the cellular level of the supply and demand of macro and micronutrients for maintenance, function and growth of the human body... It has clearly defined anthropometric, clinical and biochemical features" [7].

Infections cause many metabolic changes in the host that, uncorrected, can adversely affect nutritional status [8]. For example, fever can increase resting metabolic expenditures by 15-40% [9], while anorexia associated with infection results in reduced food intake [10]. Extensive changes occur in energy, protein, and mineral metabolism as well [8]. Amino acids are mobilized from skeletal muscle and serve as substrates for hepatic gluconeogenesis, aided by increased plasma concentrations of

insulin, glucagon and growth hormone. Since amino nitrogen derived from gluconeogenesis is excreted as urea while the carbon skeleton of the amino acid is converted to glucose, oxidized to CO_2 and lost via the lungs, infection leads to absolute losses of protein. In addition, new protein synthesis is diverted to pathways necessitated by immune responses to infection, including the biosynthesis of acute phase proteins, complement and immunoglobulin, production of lymphoid and phagocytic cells involved in host defenses, and repair of inflammatory tissue damage. The magnitude of these alterations in utilization of endogenous energy and protein, associated with anorexia and decreased food intake, can account for the weight loss during infection and, in children, cessation of linear growth.

Infection also results in changes in plasma levels and distribution of a number of minerals [8]. As an example, iron is sequestered in hepatic mononuclear phagocytes in a non-metabolic form as hemosiderin, leading to the iron deficiency anemia of chronic infection. Exogenous iron will not correct the anemia so long as the conditions that result in continued sequestration are present [8].

The mechanisms underlying fever and these metabolic responses during infection have been elucidated in part, and involve release of peptide mediators primarily from stimulated mononuclear cells, including interleukin-1 (IL-1) and cachectin. These are discussed in detail elsewhere in this symposium.

Prospective studies of growth and development of infants and children in developing countries have demonstrated the close association between infection, weight loss, and occurrence of severe forms of protein-energy malnutrition [4, 5, 10-12]. It is now well accepted that acute diarrheal disease is the most common immediate cause of severe malnutrition, and among the leading causes of death in young children [13]. The frequent transmission of infection is insured by crowding, poor sanitation and personal hygiene, poverty, and inadequate health care. Because malnutrition and infectious diseases are inextricably intermingled in the Third World [14, 15], the concept of a malnutrition-infection complex has grown as the starting point for new intervention strategies.

World Health Organization Strategy

The WHO program for nutrition for the period 1984-1989 is based on the identification of the several health and non-health factors which can underlie malnutrition [7]. These include:

— Decreased dietary availability of nutrients, due to any cause at the national level.

— Decreased dietary availability of nutrients, due to any cause at the family level.

— Decreased dietary availability of nutrients, due to decreased appetite, absorption, or utilization, or increased losses or requirements, at the individual level.

— Decreased dietary availability of nutrients for dependent infants and children, due to insufficient time, care or knowledge of caretakers.

WHO has recognized that many of these factors ultimately interact and operate at the cellular level. Furthermore, WHO has noted that the health sector cannot solve the nutrition problem by itself, although "primary health care with its potential for vastly increased coverage and an integrated health care delivery, offers the best opportunity to provide nutrition and nutrition-related health service to those who need them most" [7]. Several operational problems have been identified which impede effective national nutrition programs. These include:

— Insufficient availability or utilization of technical capability to develop, monitor or evaluate programs.

— Lack of nutrition training facilities.

— Inadequate inter-sectoral and inter-agency cooperation.

— Inadequate allocation of resources because of assignment of a low priority to nutrition activities.

Based on this assessment, WHO has specified three target goals to be achieved by 1989 [7]: 1. Implementation of programs to improve the nutritional status of mothers and children, 2. Implementation of programs to control specific nutritional deficiencies, if prevalent in a country, and 3. Initiation of programs to minimize the hazards of nutritional excess and imbalance. These goals are to be achieved by development of a competent national nutrition infrastructure, with technical and managerial support, by the incorporation of appropriate nutrition activities in the primary care system, and by the implementation of interventions to control at least one specific nutrient deficiency problem (e.g., iron, iodine, or vitamin A).

WHO has identified certain health related activities as action areas [1]. Thus, promotion of breast feeding and good weaning practices, attention to the health and social status of women, and improving access

of communities to understandable information on both health status and methods of improving it, are deserving of critical attention.

Specific Interventions

Keusch and Scrimshaw have recently suggested interventions to reduce the prevalence and/or impact of infection on nutritional status in infants and children, and they have set priorities for implementing these based on an assessment of costs and benefits [3]. These interventions can be classified under five headings: 1) control of infection, 2) nutritional support, 3) surveillance, 4) environmental sanitation, water and personal hygiene, and 5) education.

Under the heading of control of infection, Keusch and Scrimshaw suggest measures directed at reducing transmission, increasing resistance to specific diseases, or correcting nutrient-related acquired immunological defects (Table 1). They also note that while such interventions may be implemented as single measures, they are more likely to be effective

TABLE 1 - *Feasible Strategies to Interrupt the Infection-Malnutrition Cycle* *

A. *Enhance Host Defenses*

    a) Active Immunization
    b) Passive Immunization (Breast Milk)

B. *Improve Nutritional Status and Immune Function*

    a) Breast Feeding
    b) Selective Nutrient Fortification or Supplementation
    c) Education of Mothers or Other Child Caretakers

C. *Reduce Transmission and/or Impact of Diarrheal Disease*

    a) Improved Environmental Sanitation and Water Supply
    b) Improved Personal Hygiene Practices
    c) Oral Rehydration Therapy
    d) Breast feeding

* Adapted with permission from Keusch G.T. and Scrimshaw N.S., Reference 3.

when combined in a programmatic fashion for economy and efficiency, and for the possible enhanced benefit (synergism) that may ensue. Immunization is suggested as the first step to improve the nutrition and health of individuals since effective vaccines are available for some infections closely associated with malnutrition, such as pertussis and measles. The benefits to be realized are not insignificant but limited because good vaccines are as yet not generally available for diarrhea, dysentery, and malaria, and few have been released for respiratory diseases. However, significant progress is being made in developing vaccines for these problems, and whenever such vaccines become available they should be included in national immunization programs. Operational problems remain to be solved in the current expanded program for immunization (EPI) that is attempting to deliver DPT, live measles and polio vaccines, and BCG within the first year of life. Vaccine delivery is often spotty and vaccine efficacy may be less than optimal because of the failure to maintain vaccine potency or to complete the requisite series of immunizations [16]. Performance should be improved when more stable vaccines are available which induce a protective immune response with a single dose. This is a priority area for biomedical research. In spite of concern for the safety of pertussis vaccine [17, 18], Keusch and Scrimshaw [3] concluded that the benefits of DPT immunization far outweigh the risks in developing countries where pertussis is still highly endemic and where children with pertussis may require as long as 4-6 months to recover their pre-illness weight, even with optimal nutritional rehabilitation [4]. Thus, while a safer vaccine would be welcomed the present one should continue to be made available to all children.

Second on the list is the use of oral rehydration therapy (ORT) to prevent or reverse dehydration and acidosis during diarrheal episodes [19]. ORT is life saving for severely dehydrated individuals and capable of virtually eliminating case fatalities due to watery diarrhea [20]. ORT is simple, can be adapted to household administration, and may help in the early restoration of appetite [21] and successful feeding to minimize nutritional consequences of the illness [22]. Early breast feeding should certainly be promoted since this appears to continue unabated during diarrhea [23], demonstrating that anorexia for solid food does interfere with thirst promoting the ingestion of nutritious fluids [24]. There seems to be no intrinsic rationale for withholding food and the opposite is being advocated at the present time [24]. A potentially significant future development of ORT is the use of locally available rice (or other

cereal grain) powders in place of glucose or sucrose [25]; these products contain constituents which enhance absorption of sodium and water, long chain carbohydrates (dextrins, starch) which provide glucose at little osmotic cost, and other nutrients, such as protein, which can help to maintain nutritional state during the acute illness.

The next suggestion to control infection is promotion of breast feeding.   Feeding human milk not only provides nutrients, but also reduces contact with potentially contaminated food and utensils and confers a degree of protection against certain infections through its immune and non-immune factors [26, 27].

The second general strategy is nutritional interventions.   This heading includes all measures designed to minimize or reverse nutrient losses by appropriate feeding during and after infection [28, 29].   One important measure is to promote use of appropriate weaning food supplements to maintain growth and health [30].   While traditional feeding practices may be physiologically incorrect choices, acceptable mixes for weaning foods can often be prepared from locally available food stock.   This requires both the production and promotion of acceptable formulations. It is amply documented that achievement of good catch-up growth after infection can reduce the impact of subsequent episodes by restoring nutritional status before the next insult [28].   Where Vitamin A and iron deficiencies are of importance, they are amenable to control by specific interventions.

The third general category is surveillance, Because malnutrition develops over time and provides warning signals that indicate deteriorating nutritional status and heightened vulnerability to infection, surveillance may show which individuals require attention.   This is relatively easy to monitor in young children by serial height and weight measurements, since growth is influenced by nutritional adequacy and infectious disease morbidity, or by monitoring disease specific mortality rates for measles where immunization is not practiced.   Growth monitoring is the first element in the UNICEF child survival strategy [31] and may be carried out by illiterate mothers who can interpret a growth chart and recognize that failure to increase in weight means inadequate food or illness [32]. However, routine weighing is of no value unless the results are used to guide corrective actions.   This requires organization and an infrastructure to provide the necessary training and education.

The fourth heading is environmental sanitation, water and personal hygiene initiatives.   Transmission of diarrheal disease involves direct or

indirect contact with feces [33, 34], via contamination of food, water, and even nipples and other objects that enter the mouths of children. Several measures are needed to interrupt this transmission. These include improvement in quantity and quality of water, a costly but necessary investment [35, 36], and improved environmental hygiene, including sanitary fecal waste disposal and the proper storage of food. While simple in concept such measures can be difficult and costly to accomplish, for they require physical improvements and important behavioral changes [37].

The final heading for intervention measures is education. It is now clear that the effectiveness of the general education system is a major determinant of the effects of improvements in environmental sanitation and personal hygiene. Education is so basic a need that it seems unnecessary to point out. However, the greatest gains in health status may ultimately be realized by education [38]. For example, one study demonstrated that each additional year of maternal education is associated with a decrease in the mortality rate by 6 per 1000 [39]. Education of the father as well improves this figure to 9/1000.

Success of these various interventions depends on culture specific educational methods, since most cultures have developed their own concepts of causality and a rational approach to correction of the abnormal state based on these concepts [40]. The longevity of such traditions shows that they are not readily given up. At the same time, people are pragmatic and will adapt to what seems to work. What this means is that in teaching basic concepts of transmission of infection, the importance of hygiene, and the link between infection, malnutrition and child survival as the basis for specific interventions in communities with strong traditions, it is best to work within and essential to avoid denigrating the cultural norms.

Summary

To reduce malnutrition among infants and children in developing countries requires the introduction of national policies and infrastructure to implement and coordinate a broad range of interventions [41, 42]. The World Health Organization has addressed these needs and has published updated guidelines and recommendations for the next few years. An important recent development has been the recognition of the importance of infection, including parasitic diseases, in the causation of mal-

nutrition. As a consequence, a group of feasible, mutually reinforcing interventions of proven or likely effectivness has been identified. These interventions deal as much with reducing the burden of infection as they do with changes in food intake, and include immunization against a group of diseases of major significance for young children, the use of oral rehydration for moderate to severe diarrhea, promotion of breast feeding, continued feeding during and after infection, introduction of appropriate weaning foods, specific nutrient fortification, the use of growth charts to both identify those in need of intervention and to monitor their response, improved water supply and environmental sanitation to diminish diarrheal disease transmission, and education.

These interventions are not in a special category; they are an essential part of any program of primary health care. The first six measures can proceed without undue difficulty wherever and whenever there is political will and reasonable allocation of resources. Growth surveillance would be included in the same category if merely weighing children was the issue. However, to accomplish anything, growth monitoring requires use of the resulting growth curves to direct and monitor individual interventions. Unfortunately, this linkage between surveillance and intervention is not implicit, and it must be specifically encouraged. The remaining two measures, improved environmental sanitation and personal hygiene, and education, are in an entirely different category. This is because the time frame for implementation is indefinite and the potential costs cannot be supported except by amortizing them over many years. In addition, they will require behavioral changes of all segments of society and are unlikely to be accomplished over a single generation.

It is absolutely necessary that priorities are set which are consistent with the feasibility and cost of the program relative to the anticipated benefits. This paper advocates concentrating on preschool children because morbidity, mortality, and hence long term consequences for society, are the greatest for this group. Indeed, it can be argued that this is a necessary investment in the future of a nation.

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IV.

SUMMARY, RECOMMENDATIONS
AND CONCLUSIONS

POLICY IMPLICATIONS

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Considerable information, much of it new, has been reviewed during this conference concerning interactions of nutrition and parasitic infection, and there has been a lively discussion and debate. In turning attention now to the practical outcomes of the conference, let me begin by proposing a frame of reference for discussing the policy implications of the data presented. Let us suppose that we have the opportunity to make recommendations to high level officials of the ministries of finance and health in a poor developing country. Let us further suppose that the health budget per capita is $5 or less; that there is no hope of an increase in the health budget; that there are no major problems with resource allocation (no major bias to hospital beds and sophisticated medical equipment, for example); there is average commitment to primary health care; and that the Ministry of Health infrastructure reaches 30% of the population. What do we want to recommend to these officials?

Clearly, recommendations should be made mainly on the basis of what interventions will have the largest impact on mortality and morbidity at the least cost. Let us review the recommendations from the 1980 Bellagio conference on interactions of nutrition and parasitic infections [1]. The actions aimed at parasitic infections were to be added on to, or incorporated with, primary health care programs that included:

— nutritional surveillance and nutrition education;

— promotion of breast feeding and appropriate weaning practices;

— oral rehydration therapy; and

— immunization.

I believe that at least three more interventions should be added to this list:

— family planning, as another intervention that is both cost-effective and has a major health impact;

— antimicrobial therapy for severe acute respiratory disease; and

— improved prenatal and delivery care.

Turning now to parasitic disease, the 1980 conference gave first priority to malaria. The present conference has not altered that priority. The major recommendation here was for treatment of cases, giving priority to children, pregnant women and lactating mothers. Widespread vector control is usually too expensive to be feasible. The salutary impact of the wider availability of chloroquine on malaria in Africa has been discussed. In support of this, we should certainly recommend use of an essential drugs list, as well as support to community pharmacies, revolving funds for drugs, and other cost recovery schemes to stretch the health budget. People *will* pay for chloroquine, where they might not for immunizations. The World Bank is helping to finance several projects in which it is hoped that improved management of pharmaceuticals will generate savings sufficient to offset the incremental recurrent costs generated by the project investments.

Other recommendations from 1980 included targeted mass chemotherapy for schistosomiasis where the disease is prevalent. Dr. Pawlowski said that WHO will soon recommend targeting chemotherapy on individuals with high egg burdens. This is another way of stretching the health budget further.

Iron Supplementation for Hookworm Disease. I heard no argument on this intervention but it raises another question. With recent advances in technology, would we recommend iron fortification (of cereals, for example) to deal with the very high prevalence of iron deficiency anemia usually encountered? I assume the benefits to large numbers of women and children and men would outweigh the possibly deleterious effect on a much smaller number with malaria. This problem needs to be further addressed and resolved.

Periodic Antihelminthic Therapy. The 1980 conference [1] said "no" to this and Dr. Brown's review in the present conference gave no reason to change that recommendation. Unless we are sure of a major

impact at affordable cost, surely we should not recommend action. But Dr. Pawlowski raised the intriguing possibility of mass campaigns organized and paid for largely by the community. He ventured that this is an excellent way to mobilize communities for other health actions [2]. What then do we recommend? "No" to mass campaigns that would be costly and labor-intensive for the Ministry of Health, but "yes" if the communities can take much of the responsibility? Is this a good candidate for non-governmental organisations, or missions, or private sector activity — the social marketing of antihelminthic therapy? Parenthetically, it is absolutely clear in most poor countries that the ministry of health can not do all or even most of the job. It therefore behooves us to look constantly for candidates for action by NGO's and the private sector.

Health Education. This conference laid great stress on the need for behavioral change:

— in water use;

— in food preparation; and

— in safe disposal of feces.

Given the weak performance of the health sector in this area, we surely need to emphasize new approaches, learning from successes elsewhere — perhaps from the private sector (social marketing) and from agricultural extension.

Water and Sanitation Investments. This is the thorniest area and was one of the recommendations of the 1980 Bellagio meeting, although the question of how much to invest was not addressed. If the Ministry of Health is responsible for water and sanitation investments, about how much of the hypothetical $5 per capita should go to this area? Obviously, there is no simple answer but there are some guideposts and they may be clearer now than before. As we all know, many studies of water and sanitation investments have failed to show an impact on health. A recent review of 67 projects from 28 countries by Esray, Feachem and Hughes, however, reports median reductions in total mortality rates of 21% [3]. Other important reasons for investments in rural water supply are:

— communities want water and are willing to pay for it;

— the cost for rural water supply and sanitation is considerably less than for cities, and communities can maintain and pay for them;

— oral rehydration therapy (ORT) is surely only a temporary solution; and

— perhaps most important, studies show that locally available water saves women about two hours a day in time currently spent in hauling water. That time saving would surely be translated into better health for both the woman and her children if it were devoted to child care. We might also factor in the major time cost of administering ORT.

Is 20% of the health budget a reasonable amount to invest in improved water and sanitation, including, importantly, efforts to increase community involvement and strengthen management capacity?

Two Final Recommendations. Policy makers need two important pieces of information:

1. results of a review of the evidence regarding the impact and cost of the large number of mass deworming campaigns carried out during the last decade; and

2. cost data for interventions, which means that future community-based studies must routinely collect such information if they are to be of use in policy decisions.

With scarce resources for health, we cannot do everything at once. Each additional intervention has a price tag and an opportunity cost. The future does not look bright for additional resources in most of the poorest countries. This makes it crucial that ministries of finance and health be able to demonstrate impact at affordable cost in order for health to compete with other sectors for a fair share of resources.

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THE "MISSING LINK":
HUMAN BEHAVIORAL FACTORS IN
PARASITIC DISEASES AND NUTRITIONAL DISORDERS

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Introduction

Anthropologists have long tracked down "missing links" in their attempts to piece together the chain of human evolution. The "missing link" I am concerned with, however, is not the Austrolopithesis or *Homo erectus*: it is of a different order. It is the critical, yet often overlooked link between disease pathogens and the multitude of poor children who suffer daily parasitic infections and nutritional disorders. It is the human factor: the missing link in our full comprehension of parasitic and nutritional diseases.

Even the most sophisticated basic science runs the risk of being inaccurate if it excludes the way the people really approach illness. Serious limitations are imposed on our laboratory and clinical studies if we lose sight that behind every statistical mortality table lies the real life tragedy of unnecessary death and the anguish of parents who must cope. Behind every graph of disease attack rates lie its victims who struggle to survive against all odds. And behind every new laboratory technology to measure intestinal malabsorption or wasteful protein secretion lie starving children whose growth and development are severely retarded as a result.

The pressing task for scientists is not only to continue biomedical research on common health problems, but to translate the impressive *in vitro* discoveries described during this conference to *in vivo* realities.

Dr. Jon Rhode has so aptly stated this in his succinct fashion, "taking science to where the diarrhea (problem) is [1]". This transfer is a formidable task. It requires the consideration of human behavioral factors alongside of biomedical factors. Yet rarely does this happen. Laboratory studies of life-threatening parasitic diseases and nutritional disorders stand alone, stripped of their social significance. This may explain, in part, the medical community's relative indifference to such widespread health threats [2].

Given these problems, my purpose today is to discuss the role human behavioral factors play in these diseases. Specifically, I will first present evidence to support the inclusion of human or sociocultural factors in models of infectious and nutritional diseases. Next, I will present methods for eliciting key behavioral factors for analysis. Finally, I draw upon my Brazilian field experience to illustrate how the inclusion of a humanistic perspective has sharpened and enhanced our understanding of infectious diarrhea and malnutrition.

A Biobehavioral Approach to the Study of Parasitic Diseases and Nutritional Disorders

Adopting a biobehavioral approach to the study of parasitic and nutritional diseases is not a novel idea. As early as the late 1950's, such distinguished medical ecologists as Dubos [3, 4], May [5] and Audy [6] were arguing for a multifactorial appraisal of such diseases. They opposed the widely accepted "Doctrine of Specific Etiology" in favor of a model of disease causation which depended upon a complex interaction of many variables — only one of which is the disease pathogen. They maintained that other factors in this "causal network", as Dunn [7] has labelled it, include the host's general metabolic state, and immune response, the political and economic environment and the patient's cultural belief and practices, to name only a few. Hence, they maintained that exposure to a pathogen, while necessary, does not always result in infection, infection is not always sufficient to cause illness, and the impact that illness has on the overall health of the individual is not a constant [6]. Rather the multiple factors of "insults" mentioned above impinge directly on an individual. When one or more insults outweigh the coping ability of a person, disease results.

The strongest evidence to support the inclusion of human behavioral factors in biomedical models of infectious diseases are studies which demonstrate how specific cultural beliefs and practices expose people to

(or protect them from) the foci of disease transmission and directly contribute to (or inhibit) infection. Dietary customs, child-care patterns, religious practices, migration patterns, agricultural techniques and even medical practices have all been implicated as critical human behavioral links in infections and parasitic diseases. Fan [8] showed that the spread of the Oriental lung fluke, *Paragonimus westermani* was due to the Far Eastern dietary custom of eating "drunken crabs". Native recipes for this popular hors d'oeuvre call for fresh-water crabs and crayfish to be soaked in brine, vinegar, or wine, then consumed. But when improperly cooked, encysted metacercariae are ingested along with the crustaceans. Imperato *et al.* [9] have implicated traditional dishes of fermented pork prepared by migrants to New York as responsible for recent outbreaks of trichinosis. Glickman *et al.* [10] showed that children with appetites for eating dirt or clay are at higher risk for toxocariasis; children ages one to six, who eat feces, soil or grass were 20 times more likely to have elevated Toxocara antibody levels than controls. The most exotic dietary example comes from Nobel prize winner, Gajdusek [11], who demonstrated that the cannibalistic custom of South Fore women of New Guinea, who ritually eat the (often) partially-cooked brains of their deceased kinswomen, transmitted a slow virus, which resulted in "kuru", a degenerative neurological disease. Child care practices have been linked by Nelson [12] to the transmission of *Echinococcus granulosus* — hydatid disease — among the Turkana, nomadic pastoralists of Kenya. They train "dog nurses" to lick their children clean after defecation and vomiting and to provide warmth and protection by nuzzling the sleeping baby in their fur. During "nursing duties", infective eggs stuck around the dog's muzzle (due to licking its own anus) are transferred to and ingested by the child. The practice of washing before prayer among Muslims increases the exposure risk to bilhariasis; skin is exposed during cleaning to water infected with cercariae which penetrate and infect worshippers. Kochar *et al.* [13] has linked Hindu religious beliefs regarding defecation to increased hookworm infections in rural West Bengal. Migration patterns, specifically expansion of new trade routes, have been shown by Roundy [14] to be responsible for the spread of numerous infectious diseases including cholera, schistosomiasis, yellow fever and trypanosomiasis. Livingstone [15] linked such agricultural practices as the felling of forests, establishment of permanent settlements, cultivation of high-yield crops and associated multiplication of breeding sites for the *Anopheles gambiae* mosquito to a sharp rise in

the occurrence of malaria among the people of West Africa. Even medical practices thought to protect man from illness, have been implicated in the transmission of parasitic disease. A traditional brewed medicament made from proglottids of the pork tapeworm, *Taenia solium* is prepared for South African patients suffering from, ironically, tapeworm infection. Direct ingestion of the infectious *T. solium* eggs in the gravid proglottids is held responsible for the rare development of the cysticercosis stage in these patients [12].

Methods to Elicit and Analyze Human Behavioral Factors

The absence of sociocultural data in traditional studies of infectious diseases is not surprising given the longstanding separation of the social and biological sciences. This gulf is due in part to major methodological differences between the two. Yet, anthropology — dedicated to the study of social and cultural systems — can effectively bridge this gap. By observing and participating fully in the life of people being studied by medical scientists, the anthropologist is trained to elicit local attitudes, beliefs and values, to record the details of day-to-day events and family relations, and to take notice of larger socioeconomic forces which impinge on the community. Capturing people's own version of illness, known as an emic perspective by anthropologists (in contrast to an outsider's interpretation or etic view), requires total emersion in daily life: attending all-night voodoo healing ceremonies, washing clothes with mothers in the river, or, sadly, helping them bury their dead children. Taken together these insights into the culture enable the anthropologist to evaluate cognitive, social, and economic and political inputs in terms of their relative importance as determinants of disease transmission.

Cognitive factors — beliefs, attitudes, values, world-views — of local populations (or health professionals) about the infections and nutritional disorder in question, are best elicited using Kleinman's *et al.* [16, 17] technique. Their approach is to reconstruct the patient's "explanatory model" of his present illness. The task here is to capture the lay person's own version of the onset, etiology and pathophysiology of the illness along with self-treatment practices, resort to alternative health care providers and the patient's expectations from the clinic visit. Such open-ended questions as "What do you think caused your problems?", "How does it work in your body?", "Who else besides the doctor do you think can help with this problem?" are useful in both

piecing together the patient's cognitive model and zeroing in on key attitudinal factors.

For example, to explain why poor Brazilian women stop breast-feeding their infants when skin rashes appear, one must unravel the explanatory model of lactating mothers: certain foods are believed to pollute the mother's blood if eaten during her menstrual cycle, postpartum or lactation period. Because mother's milk is thought to be the same as her blood, these impurities pass to her milk and to the child's blood while suckling. While circulating in the child's body, the impurities escape through its pores, appearing as telltale impetigenous pustules.

Human behavioral factors — e.g. defecating patterns, infant feeding practices, water contact — are first uncovered with classic anthropological techniques of participant-observation and indepth interviews with key informants in the community. These are people such as traditional healers, lay midwives, mothers of sick children, etc. who have keen, front-line insights into the illness problem. These broad behavioral categories can be analyzed more closely by classifying them according to Dunn's schema [18]. Each behavior in question is classified according to three criteria: 1) it either enhances or undermines one's health; 2) it is a deliberate or non-deliberate health action; 3) it is influenced by the community or outside of it. Take the rapid decline in the initiation and duration of breastfeeding, for example. It is a behavior which definitely undermines children's health. Weaning is deliberate among many upper-class Brazilian women because nursing is thought to "age" the mother. Intimate pressure by husbands and status-conscious peers to maintain youthful breasts influences mothers' decisions as do impersonal advertisements for infant formulas by multinational corporations.

Human Behavioral Aspects of Infectious Diseases and Nutritional Disorders in Northeastern Brazil

In poor Northeastern Brazil death and illness from diarrheal diseases are among the highest in Latin America. It is estimated that 159 out of 1000 children born in urban centers die before their first birthday [19], with diarrhea as the primary or contributing cause of death in 54% of the cases [20]. Guerrant *et al.* [20] also report high morbidity rates in infants, ages seven to twelve months. In response to high infant mortality and morbidity, poor village parents have relied on their own healing ways from Dutch and Portuguese colonizers and the West African

slaves they captured and brought with them to Brazil. Other medical beliefs and practices evolved as direct responses to specific illnesses and environmental conditions found in the northeast.

Inclusion of the human behavioral aspects of illness has proven pivotal in our biomedical investigations of parasitic and nutritional diseases conducted by University of Virginia and University of Ceara Medical Schools since 1978 in at least four ways: in 1) detecting mortality; 2) assigning the most probable cause of death; 3) detecting morbidity; and 4) identifying potential risk factors [21]. Let's examine each.

1) *Detecting "Unreported" Infant Death*

Because mortality rates are the yardstick by which major health policy is guided, funds are allocated, and the effectiveness of many health interventions is measured, it is critical that deaths be detected and their cause assigned accurately. In developed nations, noting diseases that plague wealthy patients — cardiovascular diseases and carcinomas — is not an issue; patients are usually hospitalized, under doctor's care, tied to insurance and unemployment claims, and listed in tumor registries and the like. In contrast, in developing nations documenting deaths from widespread parasitic and nutritional diseases is problematic. Mortality reports from poor developing regions are routinely accompanied by the all-too-familiar disclaimer, "due to unrecorded early infant deaths, especially in rural areas, these rates may underrepresent actual childhood mortality". As of 1970, the World Health Organization estimates that reliable mortality statistics were available for only about 30% of the world's population [22]. As scientists dedicated to studying common illnesses of the poor, we cannot afford to let these events slip by unnoticed or undocumented. The truth is that in impoverished areas, "hidden" deaths often occur, are dealt with improperly, and, hence go undetected by health professionals or official registries. In the rural community, Guiauba in Northeast Brazil, for instance, McAuliffe et al. [23], found that only 14 of 49 (28%) or childhood deaths occurring during 1984 were recorded on the town's official death registry. Young victims often go unnamed and are simply referred to as "angelinhos", or little angels [21]. Because they have not yet sinned, they are believed innocent and not of this world; they are already in "God's keeping". Given this belief, burials are simple. "Angelinhos" are placed in a cardboard box, a crude wooden casket or their cloth hammock, carried to the cemetery by children and buried by the father. Properly registered

deaths are burdensome for poor families. Mothers must walk to town, pay a fee, and risk losing the child's government food ration. The death of a little angel remains "hidden" except of course to the traditional healers who were treating him, neighbors who lit votive candles as tributes, the local craftsman who built the crude wooden coffin, the school children who carried the open box in procession through the streets, the men and cemetery keeper who dug the grave and buried the angel. These are not the people who routinely report vital statistics to health bureaucracies.

Because as researchers we need accurate mortality data, it is critical to develop culturally sensitive mortality surveillance techniques. We have found networks of lay death reporters — traditional healers, mid-wives, grave diggers, coffin makers, etc. — keen observers of death in their communities. Using simple graphic forms adapted for illiterates [24], lay reporters can uncover and record deaths accurately as they occur.

2) *Determining the Most Probable Cause of Death*

In assigning a most probable cause of death, human factors also play a critical role. In industrialized nations establishing a most probable cause of death, while sometimes perplexing, is usually a straightforward task; hospital charts are reviewed, autopsies ordered, pathology findings considered, etc. In poor developing regions these clinical resources are lacking and in many cultures, dissecting the dead is strictly prohibited for religious reasons. Instead, researchers must rely on retrospective interviews or verbal autopsies alone [25], subject to much "human error". In January 1980 our University of Virginia project physician and epidemiologist reviewed the deaths of 43 project children with their parents. Taking a standard medical history, the physician established the majority of these deaths to be due to diarrhea and dehydration, followed by respiratory illnesses, measles, perinatal complications and others. Three months later anthropological interviews were conducted while informally visiting the same families. The causes of death voiced by parents were entirely different from the physician's. Those he labeled "diarrhea and dehydration" were called everything from "fright disease", "evil eye", "swollen belly", "wind in umbilical cord" to "contaminated milk" and "worms" by lay persons. Deaths the physicians believed were due to respiratory problems were popularly believed to be caused by "taking birth in nose", "white balls in throat" and "conditions of

hospital". The cited cause of death differed similarly in all 43 except two deaths due to "accidents". Only here did the medical and lay version agree exactly [26]. Our reconstructions of death are sharpened by first knowing the families' explanations of death, the symptoms associated with each folk illness and its correlation with biomedical diagnostic criteria.

3) *Detecting Real Morbidity Rates*

The standard procedure to assess the level of parasitic infections or nutritional status of a population is to conduct a prospective, house-to-house surveillance. Researchers armed with check lists of symptoms determine if each is present or absent. From these tallies, disease-specific attack rates are generated. These hold major policy implications for prioritizing diseases for selective public health interventions, among other things. Yet how accurate is survey data at capturing the actual occurrence of disease or undernutrition in households? Is there a sound method where villagers' perceptions of illnesses are based on an entirely different etiologic system? Potential inaccuracies have been pointed out by Bomgaars [27] who verified that the popularly recognized "runche" child (literally the crying one) in rural Nepal, who often escapes medical attention is also clinically undernourished.

The accuracy of frequencies of enteric pathogens detected at the onset by our own University of Virginia research group in Northeast Brazil likewise became suspect with the anthropological evidence that villagers know enteric infections by different names. These differed radically from our biomedical definitions. Villagers believed diarrhea to be a symptom of at least five folk illnesses — evil eye, fright diseases, spirit intrusion, illness of the child, and intestinal heat — each illness having its own social meaning, physical symptoms and even stool characteristics. The term "dehydration" was seldom spoken. In mother's language it is the folk illness, *moleira afunda* (sunken fontanelle), that alarms them to the serious condition.

In the early phases of our research in Pacatuba, it was not uncommon for mothers to report to our field epidemiologist, "no diarrhea today", only later to mention casually that she had taken her infant to the local *rezadeira* (praying healer) who treated it for *susto* (fright disease known by its green, foulsmelling liquid stool). Missing folk illnesses with diarrhea as symptoms resulted, I suspect, in underestimates of the true occurrence of enteric infections in the community. In other instances the

early administration of efficacious folk remedies — a fact not noted by our physicians — may have masked infections and skewed our pathogen and symptom frequency data. Infections by *Entamoeba histolytica*, for example, accounted for only 2.0% of the 150 enteric illnesses we cultured; this may lead to the mistaken conclusion that amebiasis is not a major problem here. Yet reports of "quintura" — intestinal heat — characterized by bloody, mucoid stools and fever are rampant in the village. Owing to the belief that "quintura" results from the build-up of excessive heat in the intestine, mothers counterbalance immediately with a cold remedy — the root of *ipecacuanha*. Its active ingredient, emetine, is a powerful amebicidal. Its use in mainstream medicine can be traced historically to the Tupi Indians of Northeast Brazil [21]. The prevalence of *E. histolytica* may be higher than 2.0%, but the early administration of an effective indigenous remedy makes detecting it difficult for the uniformed investigator. Grasping people's perceptions and practices related to diseases is fundamental in detecting parasitic and nutritional diseases in constructing accurate attack rates, and frequencies of responsible etiologic agents.

4) *Uncovering Key Human Behavioral Risk Factors*

The standard analytic approach to pinpointing causal factors in parasitic and nutritional diseases involves correlating a series of well-recognized factors such as income, education, nutritional status, maternal literacy, housing type or size, water source with mortality or morbidity rates. The numbers of factors examined can become quite complex with multiple regression analysis. My question is the following: are these standard factors, often selected by researchers writing protocols back at universities located thousands of miles away from the setting, the most sensible to examine? Are they the ones most closely tied to and responsible for the transmission of disease? I am going to argue that they are not always and that more powerful links can be documented between risk factors and nutritional and parasitic diseases when causal hypotheses are generated based on detailed anthropologic observations of people going about life as usual.

Suppose we wanted to clinically test the hypothesis that maternal antibodies in colostrum and early breastmilk confer immunological protection against infection by *Giardia lamblia* in newborns, as suggested by Hewlett *et al's* [28] *in vitro* experiment with suckling mice. In transferring this study to the field, we would likely measure the difference of

infection rates with *Giardia lamblia* in an experimental group of nursing newborns and a control group of non-breastfed newborns. Would we consider, without detailed anthropologic data, that nursing infants never drink their mother's antibody-rich colostrum; that women intentionally express, then discard their colostrum? We found this a widespread practice in rural Northeast Brazil where mothers consider yellowish colostrum "dirty or sour milk", unfit for consumption. They ritually discard it, placing it on the dampened dirt floor near the base of the clay water pot [21]. Omission of this critical fact can seriously underestimate the protective benefits of exclusive breastfeeding in preventing parasitic diseases and obscure colostrum withholding as a key behaviorial risk factor.

In generating hypotheses about transmission of such soil-borne parasites as *Toxocara canis, Ascaris lumbricoides* or *Strongyloides stercoralis*, would geophagia, or dirt eating, be considered in the initial protocol without first observing dietary custom? We never considered the practice in 1978 at the start of our Gastroenteritis Project. Only after observing children as they ate, played, and slept, did it become obvious that geophagia was a common practice among poor Brazilian children and pregnant women and that popular beliefs about the benefits of dirt-eating reinforced its hold. These behaviorial insights allowed us to integrate geophagia into our list of potential risk factors for chronic diarrhea and parasite carriage. Our only difficulty then was recruiting controls: children who did not routinely eat dirt. Discovery of these new human variables not only challenged us to rethink our model of the transmission of soil-borne parasites but it raised serious questions about the validity of our dietary intake histories.

Likewise, our initial hypothesis that the transmission of enteric pathogens such as enterotoxigenic *E. coli* and rotavirus was tied to the type of in-home toilet water of the patient, was suspect considering anthropological data. Children, those at greatest risk for diarrheal diseases, do not use the crude pit toilets dug into their backyards. Instead they defecate nearby on the ground. When heavy rains occur in December to March (the peak diarrhea season), children avoid the downpours, defecate on the back porch or the adjacent kitchen floor. Mothers, often interrupting their cooking duties, scoop up feces and fling them into the backyard. While toilet type can be statistically associated with enteric infections [20], this factor is probably a stand-in for general socio-economic conditions of the household. A stronger correlation might be documented, in this case, between the actual place children defecate

during the rainy season — an observation made by the anthropologist — and childhood diarrhea.

Finally, let's consider the hypothesis that widespread stunting and wasting of poor children in the developing world is due to insufficient protein intake in their daily diets. The standard approach to test this hypothesis would be to correlate anthropometric measurements with data on the daily dietary intake derived from a 24-hour dietary recall history elicited from an adult household member. Would the nutritionist's food check-list include such potential protein sources as rodents and insects or bone marrow or blood commonly eaten by the poor? Would the informant recall food scavenged from garbage dumps, begged from neighbors or picked directly from trees and eaten by children while at play? Nutritionist-Anthropologist Wilson maintains that knowledge of cultural dietary customs is essential and that only "child following" or accompanying children from the time they wake until they sleep will yield accurate dietary intake data. With dependable protein values, the likelihood of proving our hypothesis is far greater. My point is we can strengthen the association of risk factors to disease by building hypotheses from real-life observations of transmission pathways.

Conclusion

Translating *in vitro* discoveries to *in vivo* realities is a challenge that must be met in order to control serious parasitic or nutritional diseases. Because these diseases occur in the human context, it is in the behavioral realm that we, as scientists, must come to know them. Far too few biobehavioral studies of infectious diseases have been conducted; those that do exist, however, have been invaluable contributions to our understanding of the complex interactions of man and disease.

Anthropological studies of endemic communities and infected families or individuals are particularly insightful in capturing both cognitive and behavorial factors associated with these diseases. Beyond aiding in detecting mortality, assigning causes of death, defining morbidity and singling out risk factors, anthropological studies imbue life-threatening infectious diseases with their deserved social significance. If control strategies are designed that incorporate this critical human perspective, a community's acceptance of interventions to curb their health impact can be expected to improve dramatically.

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SUMMARY AND RECOMMENDATIONS

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The participants first addressed the definition of malnutrition in order to be certain at the outset that the meaning of the term was uniform and consistent in all presentations and discussions. A working group presented the following definition, which was later accepted by the conferees:

> Malnutrition refers to a deficiency or excess of nutrients which results in disorders within cells, tissues, or the whole body sufficient to interfere with an individual's health, genetic potential for growth, normal physiological functions, or with his/her ability to interact with other individuals or with the physical or social environment. When due to dietary inadequacy, malnutrition is considered primary; when due to anorexia, malabsorption, or metabolic alterations associated with infection or inflammation, it is considered secondary.

While there was no disagreement that reduction of parasitic disease and malnutrition to increase child survival were important priorities for national programs, it was also acknowledged that this goal might not be a high priority for certain governments, even for the Minister of Health, for whom the major concern might be health and nutrition in relation to work productivity of adults. A more balanced concern for health problems of both children and adults, and an emphasis of the value to the adult population of basic primary health care measures such as environmental sanitation and water projects, the EPI immunizations, primary school education, malaria control, iron supplements for hookworm, schistosomiasis control, antihelminthic treatment, etc., were therefore recommended. Since the Ministry of Health is often politically weaker

than other ministries in a government, the Minister of Health is in great need of information from the scientific community on outcomes of health strategies in order to do battle with other ministries for a larger share of the budget pie. It was suggested that the scientific community also begin to deal with other governmental agencies, for example the Ministry of Agriculture or Labor (or equivalent), to link health outcomes with improved performance of their sector responsibility. This is particularly important because of the many examples in which the Ministry of Agriculture supports food production destined for exportation to earn foreign currency rather than food produced for local consumption to correct nutrient deficiencies in the country.

In part, such problems are due to the tendency of the scientific community to deal with "hard" science and an accompanying inability (or unwillingness) to put disease in a social context. The dimensions of concern change when one realizes that a mortality graph of infant death rates is not simply a charting of numbers, but that each statistic represents a child's death and a family's grief. The task of adding the social dimension to science is one that the social scientist undertakes, all too often in isolation from the biomedical community. Since human behavior plays such an important role in determining nutritional status, and in determining the risk of parasitic infection, it is essential to bring together the social and biomedical science points of view. When this integration becomes a reality, studies on detection of disease, detection of death, identification of potential risk factors, and design and implementation of interventions are more easily performed with a much greater return in useful data. Not only is information generated, but when new interventions are planned on the basis of a clear understanding of behavioral factors, and the "bottom-up" rather than being centralized in a Ministry of Health far removed from the community in a "top-down" manner, the design and delivery of health care can be scientifically sound, culturally appropriate, and genuinely acceptable to the people it is intended to help. To succeed, this approach will require a reeducation of the physicians and scientists on the value of including social science concerns and expertise in projects and programs from the very first stage of planning.

It was noted that concomitant with the right of people to be healthy and to have access to a health care system it is their duty to become active partners in accomplishing these goals. In this sense, a major goal of primary health care programs is to promote community interest in improving the health of that community and of its individual members.

By means of highly visible programs, such as deworming, which alone may achieve little in the control of intestinal helminthiasis, community cooperation may be obtained for other health care initiatives. In some instances, delivery of antihelminthic treatment as an entry to the community has been useful for organization of the community itself, often with little or no governmental support. In other instances, assistance of non-governmental or private voluntary organizations has been used. In either case, the opening wedge, antihelminthic therapy, has resulted in other health-related activities with a real impact on the people. This also appears to tie in with the concept that development of good local services and involvement of local populations will lead to definition of local priorities and local action. This organizational schema has been used in small demonstration projects, where the needed labor-intensive effort can been mounted and maintained. It is still uncertain if this model can be scaled up to the national level. Other models also need to be studied, for example approaches which utilize village development committees working directly with health professionals who provide surveillance data and guidance. In this way a balance may be achieved between the ideal of community involvement and the need to use the knowledge and real data possessed by health professionals.

Another important general conclusion of the Study Week was that the emphasis given to the extensive overlap among "pure nutrition" interventions, "pure parasitic disease" interventions, and primary health care programs is both appropriate and highly desirable. When this is the working strategy it is more likely that one intervention will be added to another through the mechanism of primary health care. Without this emphasis, plans are usually implemented in isolation, thus restricting the benefits likely to ensue. Since allocation of scarce national resources is often dependent on the demonstration of results, an appropriate combination of interventions should increase the probability that an effect will occur or decrease the time interval between implementation and observation of benefits. This is the promise of synergy of effect from combinations of individual interventions.

It was reiterated many times during the Study Week that costs of programs have to be brought in line with the resources available. If this is not done, there is little chance that health programs will receive an appropriate share of the funding. Programs must also be carefully looked at for their impact in relation to the cost involved, so that the most appropriate choices will be made. There are enough examples of

developing countries assigning a major portion of the health budget to tertiary care facilities doing the most up-to-date transplantation surgery and providing other high technology care, but unable to successfully mount an EPI immunization program. Since the issue is priorities, it is important who is making the choices and what political power can be brought to bear on the choices. It is also reasonably clear that there may be some "pump priming" activities in the health sector, that is interventions which by themselves produce little apparent direct benefit in the measures that are usually looked at, i.e., morbidity or mortality rates, population growth etc., but which set the stage for other interventions to make a big impact and/or result in obvious synergy. Examples of these basic "pump priming" interventions are the attempts to increase female literacy or improve the quality of the broad range of health centered activities of mothers, which has been called maternal technology.

One practical way to accomplish some of these goals is for all of us in the health field to bring the messages of this meeting to the organizations responsible for health care planning at the international and national level, clearly and forcefully, whenever and wherever we can. It is necessary to emphasize our individual responsibility in this, with a goal to encouraging people with responsibility and resources to make decisions and to commit funding for projects. It is often the case that those in power in government are afraid to take a stand, to stand out, and thus to possibly fail because if this were to happen their career may be jeopardized. However, risk taking is a part of action, and accomplishment is severely limited without it. It will probably be necessary to find a select group of "historical figures" in the health field who will take these risks, and though they remain largely unknown will make significant contributions to improved human health. Finally, it was agreed that in addition to actions in practical primary health care, there must be a concomitant commitment of resources to epidemiology and surveillance systems, to improving diagnostic and laboratory services, and to research, without which we cannot know where we have been, where we are, or where we are going.

CONCLUSIONS

Malnutrition and parasitic diseases occur together in the same populations throughout the world. This is not a chance coexistence; rather it is the consequence of many diverse interactions between the parasite and the host that both affect and are modified by his/her nutritional status. These interactions may explain why, in spite of increases in world food production, the number of malnourished individuals has actually increased in the past decade.

This conference was called to focus attention on the interaction of parasitic diseases and nutrition and to consider the new information available from recent investigations.

We have reviewed the data on global food production and per capita energy availability and conclude that at the present time food production is not the limiting factor for adequate nutrition for most regions of the world, assuming limited population growth and sufficient economic resources to assure equitable food distribution. The more fundamental problem is that even when dietary intake meets minimal standards of adequacy, the frequency of infection results in nutritional deterioration. The mechanism for this, due to at least two small proteins called interleukin and cachectin, produced by certain host cells during infection, was described by two of the participants who have pioneered these investigations. We have discussed the clinical information available for eight parasitic infections: malaria, leishmaniasis, amebiasis, giardiasis, cryptosporidiosis, ascariasis, schistosomiasis and trypanosomiasis cruzi. We have carefully considered the evidence suggesting that undernutrition may protect the host against some of these infections and in general we find this inadequate to support this hypothesis. In the case of malaria, the data suggest that iron deficiency may inhibit the growth of malaria parasites and iron administration may increase the prevalence of parasitemia, but there is no indication of clinical deterioration and no reason to conclude that iron supplementation to treat iron deficiency anemia should be with held.

We have also reviewed the possible strategies for control of parasitic diseases and malnutrition and we conclude that development of primary health care programs, with the necessary infrastructure and funding, offers the best chance of success. These programs should include strong components of education, and they require strong commitments of governments and communities, including financing, for basic community development of water and environmental sanitation improvements.

Finally, we have reviewed the needs for clear interpretations of scientific data for prioritization of interventions, for selection of methodology and for identification of future research needs.

This requires a dialogue and interaction between scientists and policy makers. The role of social science and anthropology to translate policy decisions based on available information to language understandable by and acceptable to the populations concerned is critical. It is clear that success depends on developing an interdisciplinary integrated and comprehensive attack on the problems.