Global malnutrition

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SUMMARY

The four most important forms of malnutrition worldwide (protein-energy malnutrition, iron deficiency and anaemias (IDA), vitamin A deficiency (VAD), and iodine deficiency disorders (IDD)) are examined below in terms of their global and regional prevalences, the age and gender groups most affected, their clinical and public health consequences, and, especially, the recent progress in country and regional quantitation and control. Zinc deficiency, with its accompanying diminished host resistance and increased susceptibility to infections, is also reviewed. WHO estimates that malnutrition (underweight) was associated with over half of all child deaths in developing countries in 1995. The prevalence of stunting in developing countries is expected to decline from 36 % in 1995 to 32·5 % in 2000; the numbers of children affected (excluding China) are expected to decrease from 196·59 millions to 181·92 millions. Stunting affects 48 % of children in South Central Asia, 48 % in Eastern Africa, 38 % in South Eastern Asia, and 13–24 % in Latin America. IDA affects about 43 % of women and 34 % of men in developing countries and usually is most serious in pregnant women and children, though non-pregnant women, the elderly, and men in hookworm-endemic areas also comprise groups at risk. Clinical VAD affects at least 2·80 million preschool children in over 60 countries, and subclinical VAD is considered a problem for at least 251 millions; school-age children and pregnant women are also affected. Globally about 740 million people are affected by goitre, and over two billions are considered at risk of IDD. However, mandatory salt iodisation in the last decade in many regions has decreased dramatically the percentage of the population at risk. Two recent major advances in understanding the global importance of malnutrition are (1) the data of 53 countries that links protein-energy malnutrition (assessed by underweight) directly to increased child mortality rates, and (2) the outcome in 6 of 8 large vitamin A supplementation trials showing decreases of 20–50 % in child mortality.

Key words: Protein-energy malnutrition, iron deficiency anaemia, vitamin A deficiency, iodine deficiency diseases, zinc deficiency, malnutrition and infection.

Over half the children in South Asia and a third of those in Africa south of the Sahara and millions more around the world are malnourished, and because of that some six million young children die a year when they would be unlikely to do so if they were well nourished.

Stephen Lewis, former Deputy Executive Director, UNICEF in Keynote speech for conference on Malnutrition as a Human Rights Violation: Implications for United Nations-supported Programmes, Geneva, 12–13 April 1999

MALNUTRITION: THE NUTRIENT DEFICIENCIES AND THEIR CLINICAL CONSEQUENCES

The four most important forms of malnutrition globally are protein-energy malnutrition (PEM), iron deficiency anaemia (IDA), iodine deficiency disorders (IDD), and vitamin A deficiency (VAD) (Table 1).

Protein-energy malnutrition and stunting

PEM affects an unacceptably large proportion of the children under 5 years in developing countries:

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~ 27 % of under 5s are considered underweight (< -2 S.D. weight-for-age), about 32 % are stunted (height < -2 S.D. height-for-age), and about 9 % are wasted (< -2 S.D. weight-for-height), although prevalences vary greatly between areas and regions (see Tables 1–3). Stunting and underweight move in parallel, and both are most prevalent among South Asian children, followed by sub-Saharan African children (Table 2, South Central Asia and Eastern and Western Africa). The severe clinical manifestations of PEM are kwashiorkor, nutritional marasmus, and marasmic kwashiorkor. In most countries these are not highly prevalent but constitute the 'tip of the iceberg' of PEM. Mild and moderate PEM which cause poor growth are highly prevalent.

Low birthweight (< 2500 g) is now recognized as a major cause of stunting in childhood which will be present in an estimated 17·4 million infants (16·4 % of newborns) born in developing countries in 2000 (Table 4). Low birthweight is particularly common in South Central Asia, where 28·4 % of newborns are affected and is a major problem also in Middle and Western Africa (21·3 %, 17·2 % respectively).

Our knowledge about the geographical distribution of stunting and its sequelae has grown

Table 1. *Major forms of malnutrition in developing countries, 1995–2000*[1]

Form of malnutrition	Population group and % affected	Number (millions)
Protein-energy malnutrition		
Underweight in Children	27% of Under-5s (2000)	149·63
Stunting (chronic) – Children	32% of Under-5s (2000)	181·92
Wasting (acute) – Children	9% of Under-5s (1995)	50·59
Moderate Underweight-Adults		245
Severe Underweight-Adults		93
Anaemias	Pregnancy ∼ 56%	2000
	Under-5s ∼ 42%	
	Children 5–14 y ∼ 53%	
Iron Deficiencies	43% all women; 34% all men	3580
Iodine Deficiency Disorders		
Goitre	15% of world's population	834
Cretinoids (some mental impairment)	All ages	49·6
Cretinism	All ages	16·5
Vitamin A Deficiency		
Subclinical	42% of Under-5s globally	251
Xerophthalmia (clinical)	0·5% of Under-5s globally	2·85

[1] Mortality rates in children under 5 are 2·5 times higher in those moderately underweight, and 5 times higher in the severely underweight. About 50% of deaths among these children were associated with malnutrition, and for about 370 000 under-5 deaths in developing countries, malnutrition was the direct cause. (Source: *World Health Report* 1998 and *Fourth Report on the World Nutrition Situation*, ACC/SCN, 2000.)

Table 2. *Estimated prevalence (%) and estimated number (millions) of stunted and underweight children in developing countries by UN region and sub-region, 1995 and 2000.*

	Stunting				Underweight			
	1995	2000	1995	2000	1995	2000	1995	2000
UN Regions/Sub-regions	%	%	No.	No.	%	%	No.	No.
Africa	36·5	35·2	44·51	47·30	27·9	28·5	34·03	38·32
Eastern	47·7	48·1	19·28	22·03	33·2	35·9	13·42	16·47
Northern	23·3	20·2	4·90	4·44	14·8	14·0	3·11	3·08
Western	35·2	34·9	13·47	14·74	34·9	36·5	13·34	15·41
Asia	38·8	34·4	143·49	127·80	32·8	29·0	121·03	107·91
South Central	48·0	43·7	83·62	78·53	47·3	43·6	82·40	78·49
South-Eastern	37·7	32·8	21·51	18·94	32·6	28·9	18·56	16·68
Latin America and Caribbean	15·8	12·6	8·59	6·82	8·3	6·3	4·48	3·40
Caribbean	19·0	16·3	0·71	0·61	14·4	11·5	0·54	0·43
Central America	24·5	24·0	3·94	3·92	15·3	15·4	2·46	2·52
South America	13·2	9·3	4·55	3·16	5·7	3·2	1·96	1·08
Oceania				Data not available				
All developing countries	36·0	32·5	196·59	181·92	29·2	26·7	159·55	149·63

Adapted from *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Data source: WHO (1999).

enormously in the last decade; the consequences of stunting include increased morbidity and mortality, poor physical and mental development and school performance, and reduced adult body size and capacity for physical work – all of which may impact on economic productivity at the national level (WHO, 1995). Women of short stature are at greater risk of obstetric complications because of smaller pelvic size and are more likely to deliver an infant with low birth weight. Low birth weight infants tend to be smaller adults; thus, the negative consequences of stunting are passed on from one generation to the next; see Malnutrition and Parasitic Helminth Infections, this volume, for discussion of relationships between low birthweight and stunting and their sequelae in developing countries.

PEM also potentiates the effects of infection (Pelletier, Frongillo & Habicht, 1993). Malnourished children have more severe episodes of diarrhoea (measured by duration, risk of dehydration or hospital admission) and the associated growth faltering, and a higher risk of pneumonia. Such pre-

Table 3. *Prevalence and numbers (millions) of wasted preschool children in developing countries in 1995 by UN region and sub-region*

| UN regions and sub-regions | Wasting (< -2 s.d. weight/height) | | | |
	Countries[a] No./total	Population coverage (%)	%	Numbers affected (millions)
Africa	43/53	94·5	9·6	11·06
Eastern	16/17	95·8	7·0	2·74
Middle	5/9	84·6	8·6	1·36
Northern	6/6	99·8	7·2	1·46
Southern	4/5	95·9	2·9	0·17
Western	12/16	94·2	15·6	5·33
Asia	31/46	93·7	10·4	37·87
Eastern	2/4	94·4	3·4	3·73
South Central	12/14	99·2	15·4	27·27
South-East	5/10	84·0	10·4	5·75
Western	12/18	70·7	5·1	1·12
Latin America and Caribbean	21/31	97·2	2·9	1·59
Caribbean	4/13	64·8	n.a.	n.a.
Central America	7/8	99·8	4·9	0·79
South America	10/12	99·6	1·8	0·64
Oceania	n.a.	n.a.	n.a.	n.a.
Developing countries	99/147	94·1	9·4	50·59

Adapted from *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Source: WHO (1999).
[a] Number of countries that have national surveys out of the total number of countries for each subregion. n.a., not available due to insufficient data.

disposition to infection can inhibit child growth via several postulated mechanisms. These include reduced food intake and decreased absorption and utilization of ingested nutrients, and reduction in the length of the long bones because of systemic and local disturbances of normal growth (Sherry, 1994). Further, children who show no clinical illness but live in poor conditions are constantly challenged by infectious pathogens which likely activate immunological responses that divert specific nutrients from normal growth and thus restrict length gain (UNICEF, 1997).

The link between stunting and poor intellectual development is receiving increasing attention now because of the importance of alert, intelligent child populations to ensure generally healthy futures of nations (Box 1) and because of the results of new studies strengthening this link. Where the prevalence of stunting is high, one can assume that most short children are stunted because of inadequate food, health and/or care often related to poverty and inequity, and that the majority of children (and not only those below the traditional cut-off point defining stunting) are not reaching their growth potential (ACC/SCN, 1997). The specific causes of stunting vary in different settings, but protein, energy, iron and zinc have been particularly implicated, as have prolonged infections (including parasitic infections [Allen, 1994; also Stephenson *et al.* this volume]), and inadequate care.

Iron-deficiency and anaemias

Iron-deficiency anaemia is the most prevalent nutritional deficiency worldwide, and over 90% of affected individuals live in developing countries (Table 1). Adverse consequences are most common and severe in women of reproductive age and young children. In pregnant women, IDA contributes to maternal morbidity and mortality, and increases the risk of foetal morbidity, mortality, and low birth weight (Viteri, 1997).

Worldwide, over half of anaemia is due to nutritional deficiencies of iron, and sub-clinical iron deficiency is as widespread as IDA. Indeed, just as PEM is the 'tip of the iceberg' regarding suboptimal growth, in areas with high prevalences of anaemia ($> 50\%$), one can assume that almost all of the population is iron deficient to some degree (ACC/SCN, 1997; de Benoist, 1999). In non-industrialised countries, the prevalence of anaemia is three to four times that in industrialised countries (ACC/SCN, 2000). The prevalence and causes of anaemia vary greatly by area and age and gender group; in non-industrialised countries, 53% of children 5–14 years, 56% of pregnant women, 43% of all women, and 34% of all men are anaemic (Tables 5, 6, Figs 1, 2).

The South East Asia region of WHO, which includes South Asia, contains the greatest number of anaemic persons – an estimated 184·8 millions

Table 4. *Estimated incidence of low birth weight (LBW) and intrauterine growth retardation-low birth weight (IUGR-LBW) and expected number of affected newborns in year 2000*

United Nations regions and sub-regions	LBW		IUGR-LBW	
	Incidence % (< 2500 g)[a]	Total No. (thousands)[b]	Incidence % (< 2500 g; $\geqslant 37$ weeks)[a]	Total No. (thousands)[b]
Africa	–	–	–	–
Eastern	–	–	–	–
Middle	21·3	853	14·9	597
Northern	–	–	–	–
Southern	–	–	–	–
Western	17·2	1451	11·4	962
Asia[c]	18·0	13774	12·3	9344
Eastern[c]	5·8	1250	1·9	409
South Central	28·3	10917	20·9	8062
South-East	10·3	1190	5·6	647
Western	8·3	417	4·5	226
Latin America and Caribbean	11·5	1329	6·5	755
Caribbean	11·7	91	6·7	52
Central America	12·3	422	7·2	247
South America	11·1	816	6·2	456
Oceania[d]	15·0	29·2	9·8	19
Melanesia	15·4	29	9·9	19
Micronesia	–	–	–	–
Polynesia	4·0	0·2	0·2	0·03
All developing countries[e]	16·4	17436	11·0	11677

[a] Sources: WHO, 1996*a*; de Onis *et al*. 1998. [b] Total live births for 2000 are based on the UN World Population Prospects (United Nations 1998). [c] Excludes Japan. [d] Excludes Australia and New Zealand; –, not applicable because coverage of live births < 80 %. [e] Weighted average of incidences in each country.

(Table 6). Over 70 % of pregnant women are anaemic in this region (ACC/SCN, 1997; de Benoist, 1999), as are over 60 % of children, both those under 5 years and those 5–14 years of age (de Benoist, 1999) (Figs 1, 2). The major causes of anaemia in likely order of priority for all age groups in sub-Saharan Africa have been presented in detail by the Micronutrient Initiative (Table 7; Gillespie & Johnston, 1998). They include diet, malaria (Weatherall, 1988), helminth infections (hookworm and schistosomiasis are acknowledged, but *Trichuris trichiura* and *Ascaris lumbricoides* should be added [Stephenson & Holland, 1987; Stephenson *et al*. 1993; Hadju *et al*. 1996]), genetic (congenital) factors, other infections, low birth weight and maternal nutrition; other micronutrient deficiencies (e.g. Vitamin A [see below], folic acid, and vitamin B_{12}) may also contribute. In sub-Saharan Africa, bioavailability of dietary iron was considered the most important determinant of anaemia in every age group except pregnant women. In pregnant women, malaria is a more important determinant of anaemia in primigravidae, but for multigravidae iron deficiency appears to be more important (Table 7, Gillespie & Johnston, 1998).

The reported effects of iron deficiency on immune function are listed in Table 8. Mechanisms clearly identified are impaired phagocytic killing power, diminished response to lymphocyte stimulation, decreased numbers of natural killer cells, reduced interferon production and depressed delayed cutaneous hypersensitivity. Apparently B cell and antibody formation are less, or not, affected (Scrimshaw & SanGiovanni, 1997). As the most widespread nutrient deficiency in the world today, iron deficiency is consistently associated with increased morbidity from infectious disease (Scrimshaw & SanGiovanni, 1997).

Iron-deficiency anaemia, and anaemias in general, have profound physiological and practical significance for the developing world: the productivity losses attributed to iron deficiency in South Asia alone are estimated to be close to \$5 billion annually (Ross & Horton, 1998); and for all countries, the dominant effect of the deficiency is thought to be the intellectual toll associated with cognitive deficits in children. The weakness and fatigue in anaemic adults that reduce physical work capacity and productivity have received more attention in the past, perhaps due to their more easily appreciated direct translation into economic losses, but severe anaemia is considered a contributory factor in as

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Box 1. Stunting and Mental Development

Stunting in poor populations is usually associated with poor mental development. However, the many socio-cultural and economic disadvantages that coexist with stunting (Martorell *et al*. 1988) may also detrimentally affect mental development. This makes it difficult to determine whether the poor development of stunted children is due to nutritional deficiency or whether stunting is just an indicator of poverty. Thus it is important to control for social background as much as possible in study design and statistical analysis.

Most cross-sectional studies have found significant associations between height-for-age and children's cognitive development in preschool and school-age children. Even after controlling for socio-economic conditions, investigators have found significant associations between height-for-age and IQ, cognitive function and school achievement levels in school-age children in many countries. Significant associations have also been found between stunting and poor psychomotor development, fine motor skills and neuro-sensory integration. In populations with high levels of stunting, height in early childhood also predicts IQ at school age. Stunted children's cognitive function is more likely to be detrimentally affected by short-term hunger than non-stunted children (Simeon & Grantham-McGregor, 1989).

The only supplementation study aimed specifically at stunted children was conducted with stunted and non-stunted Jamaican children aged nine to 24 months (Grantham-McGregor *et al*. 1991). The stunted children received nutritional supplementation for two years with or without psychosocial stimulation. Supplementation and stimulation produced independent benefits to the children's mental and motor development. The benefits from a combination of supplementation and stimulation were additive, and only the children receiving both treatments caught up to the non-stunted control group in development levels. The implications of these findings are that at least part of the deficit in the development of stunted children is due to poor nutrition. However, both stimulation and supplementation are necessary to improve the development of stunted children to culturally appropriate levels.

The precise mechanism linking stunting to poor mental development is unknown. It is possible that the mechanism varies according to which nutrients are deficient, or that several mechanisms could act together. One possibility is that undernutrition causes poor motor development and apathy which in turn reduce a child's ability for environmental exploration and skill acquisition (Levitsky, 1979). Reduced activity has been described in iron, zinc and energy deficiencies. Another possible mechanism is that the children's small size could lead adults to treat them like younger children and not provide age-appropriate stimulation. Undernutrition could have a direct effect on children's central nervous system. Stunted children have smaller heads than non-stunted children, and in one study, head size in early childhood was a stronger predictor of IQ at 7 years of age than other previous or current anthropometric measures (Grantham-McGregor *et al*. 1997). A more speculative explanation is that raised anxiety levels, as evidenced by heightened cortisol, could contribute to poor cognition and behavior.

Adapted from: *Third Report on World Nutrition Situation*, ACC/SCN, 1997; Source: short paper prepared by SM Grantham-McGregor and LC Fernald for ACC/SCN's Commission on Nutrition Challenges of the 21st Century. December 1997).

Table 5. Cut-off points for blood haemoglobin concentration to define anaemia in various age groups

Age group	Cut-off points g/l
6–59 months	110
5–11 years	115
12–14 years	120
Non-pregnant women	120
Pregnant women	110
Adult male	130

Adapted from *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Source: Gillespie & Johnston (1998).

many as 50 % of maternal deaths, and is the main cause of up to 20 % of maternal deaths in developing countries (ACC/SCN, 1991).

Vitamin A deficiency

Vitamin A deficiency is of major concern both because it is the single most important cause of blindness in children in developing countries and, even more importantly, because vitamin A supplementation can lower a deficient child's risk of dying of infectious disease by an estimated 23 % (Fig. 3, Table 9, Fig. 4). Severe vitamin A deficiency (causing blindness) is declining but subclinical VAD still affects as many as 250 million preschool children

Table 6. Prevalence of anaemia among different populations, based on national data

Regions[1]	Children				Women (15–59 years)				Men (15–59 years)	
	0–4 years		5–14 years		All		Pregnant			
	%	Pop (millions)	%	Pop (millions)	%	Pop (millions)	%	Pop (millions)	%	Pop (millions)
Africa Non-industrialized	33·1	35·5	52·0	85·2	37·9	57·6	46·9	9·6	28·0	41·9
Americas	22·9	13·0	36·9	39·5	31·0	44·9	39·0	3·8	11·0	15·8
South East Asia	52·7	93·8	63·9	207·8	60·0	218·6	79·6	22·2	42·4	184·8
Eastern Mediterranean Non-Industrialized	38·3	28·1	30·8	37·9	51·1	60·6	63·9	8·8	32·7	41·5
West Pacific	14·7	19·7	56·9	156	33·8	152·9	38·5	9·4	36	172·5
Total	34	190	53	526	43	535	56	54	34	456·5

[1] WHO regions as defined in WHO's World Health Report, 1997 (Note: South Asian countries are included in the South East Asia Region). From *Third Report on the World Nutrition Situation*, ACC/SCN, 1997; Source: WHO (unpublished).
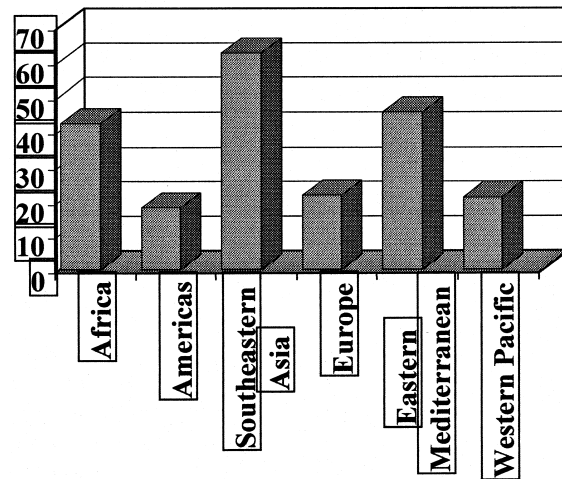

Fig. 1. Prevalence (%) of anaemia in children 0–5 years by WHO region. Adapted from: *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Source: WHO Global Database on Anaemia and Iron Deficiency (1998).
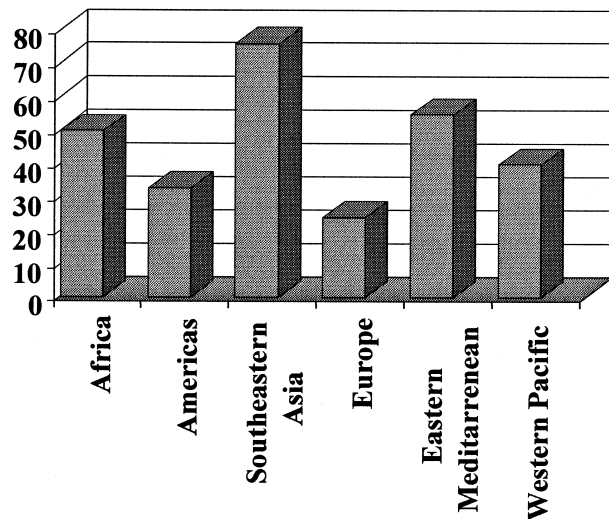

Fig. 2. Prevalence (%) of anaemia in pregnant women by WHO region. From *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Source: WHO Global Database on Anaemia and Iron Deficiency (1998).

(Table 1; WHO/UNICEF, 1995; ACC/SCN, 2000). Many more school-aged children, pregnant women and others are also affected, and sub-clinical deficiency contributes significantly to raised morbidity and mortality in at-risk populations (Table 8; ACC/SCN, 2000).

Vitamin A deficient children experience infections that are both more frequent and of greater severity than vitamin A sufficient children. Indeed, three separate trials of children hospitalized with measles have shown that case fatality rates were significantly lower for children given high-dose vitamin A supplements than for unsupplemented children: improving vitamin A status appears rapidly to alter some aspects of cellular responsiveness and re-

Table 7. Causes of anaemia and their relative importance at different stages of life in sub-Saharan Africa*

Determinants	Infant (0–1 years)	Preschool (1–5 years)	School-age (5–15 years)	Adolescent (12–19 years)	Reproductive-age women (15–45 years)	Pregnant Women	Adult men (20 years+)
Diet	Iron content of complementary foods Composition/ bioavailability of dietary iron Lack of exclusive breastfeeding (1 or 2)	Iron content and bioavailability of complementary foods Continuity of breastfeeding within 2nd year Content and bioavailability of family diet Vitamin A? (1)	Bioavailability of dietary iron (1)	Bioavailability of dietary iron High iron requirements Iron density of diet Seasonality (1)	Bioavailability of dietary iron (1) Increased iron demand Folate deficiency (3) Lactation may increase iron absorption?	Primigravidae (2) Low iron stores High demand Folate deficiency Multigravidae (1) Inadequate intake and bioavailability of dietary iron (need for supplements)	N/A
Malaria	Biggest cause of anaemia (1 or 2)	Diminishing with age as immunity acquired Dependent on local transmission (2, but main cause of life-threatening anaemia)	(4)	(4)	(5)	Primigravidae (1) Multigravidae (2) Cause of low birth weight and low iron stores in newborns Seasonality	Some resistance
Helminths		Increasing problem, unknown scale in Africa (3)	Hookworm (2) Schistosomiasis increasing (3)	Helminths and schistosomiasis (2) but little data on schistosomiasis related to anaemia	Hookworm (3) local transmission variable	Hookworm (4) regional differences	High risk occupations, especially farmers, miners (1)
Genetic	Sickle cell disease (4) (1–2% newborns)	Surviving sickle cell disease (4)	Sickle cell disease diminishing (5)			Sickle cell disease (5)	
Other infections	Poor appetite, catabolic losses, raised requirements, AIDS	Poor appetite, catabolic losses, raised requirements		AIDS, TB (3) especially girls	AIDS, TB and related infections (2) HIV and malaria interaction	AIDS (3)	AIDS, TB, trauma, chronic infections (2)
Other factors	Low birth weight Maternal nutrition			Excess blood loss			

* The numbers within parentheses represent the priority attached to the determinant at each life cycle stage, with 1 being the most important. Adapted from *Third Report on the World Nutrition Situation*, ACC/SCN (1997); Source: Gillespie & Johnston (1998).

Table 8. *Decreases in immune function caused by deficiencies of iron, zinc, vitamin C or vitamin E**

Function	Iron	Zinc	Vitamin C	Vitamin E
Thymic structure or function	R3	M11, R3, P2, C3, H4		
Cell-mediated immunity functions		M3, H1		
T lymphocyte response	M1, H8	M11, H4	G1, H1	M1, R1, P1, S1 D1, H3
Delayed cutaneous hypersensitivity	H3	M5, H4	G2, H3	H3
Cytokine or lymphokine function or production	R1	M3, H1		R1, H2
Humoral response, B cell function	R2, H3	R2		M4, R1
Immunoglobulins	R1	M5, H1		M1
T cell-dependent antigens (SRBC)	–	M11		
T cell-line-dependent antigens (dextran)	–	M4		
Hemagglutination titers				M2
Phagocytic function	R1	M6, H1	G5	M1, R3, P1, H3
Killing power	R1, H1	M3	G2	
Complement formation or function	–		G2, H1	

* Species in which defect was demonstrated: R, rats; M, mice; H, humans; P, pigs; C, cattle; G, guinea pigs; S, sheep; D, dogs. Number following the letter indicates the number of published reports describing this effect. Compiled from Tables 3–6 of Scrimshaw & SanGiovanni (1997); see those tables for citations to studies tallied here and similar lists for studies on copper and magnesium in experimental animals. Immune decreases in Vitamin E deficiency apply to severe deficiency, premature infants, or the elderly.

Body status of vitamin A

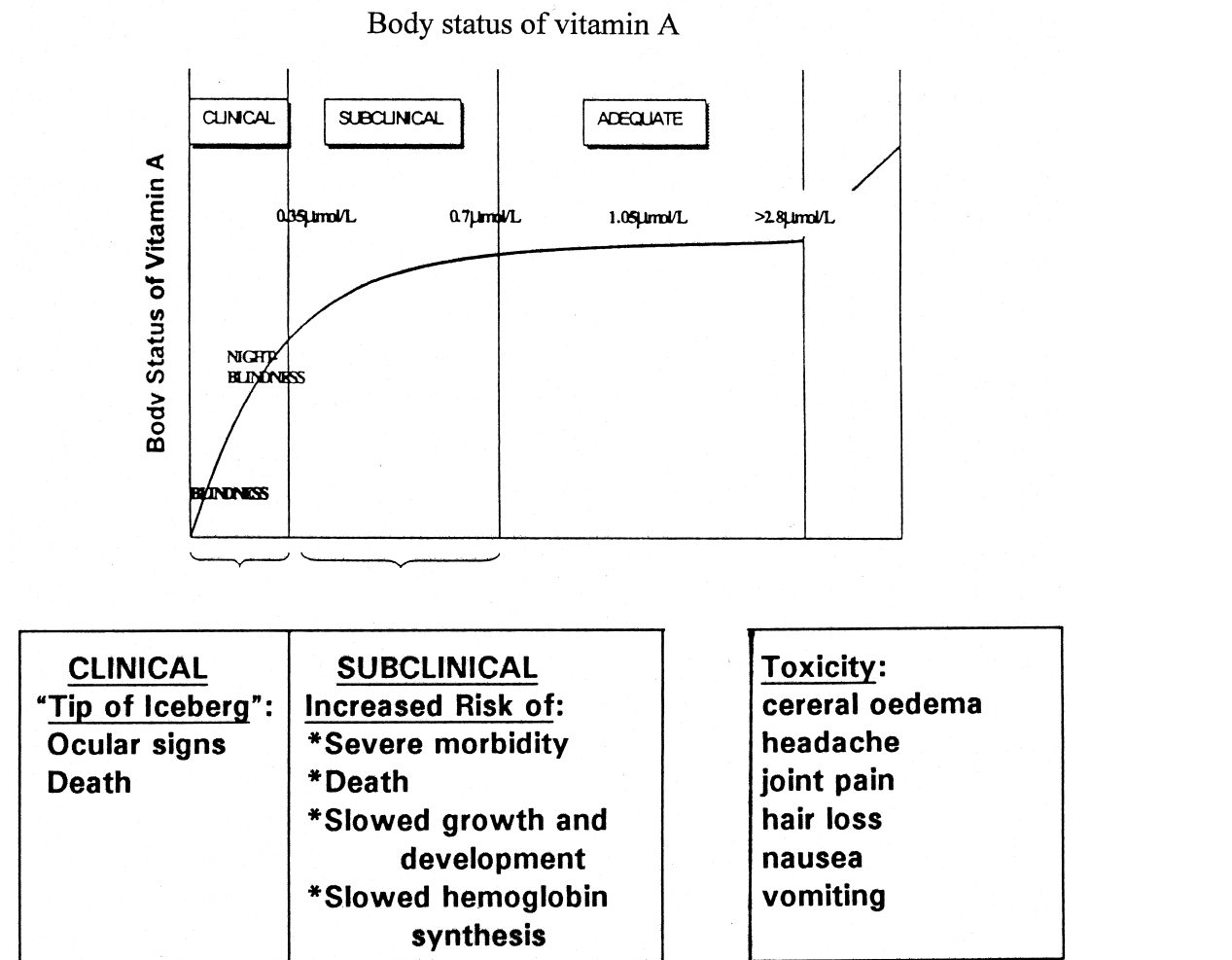| CLINICAL "Tip of Iceberg": Ocular signs Death	SUBCLINICAL Increased Risk of: *Severe morbidity *Death *Slowed growth and development *Slowed hemoglobin synthesis	Toxicity: cereral oedema headache joint pain hair loss nausea vomiting

Fig 3. Sequelae of levels of vitamin A status, showing that subclinical deficiency slows growth, development and haemoglobin synthesis. Adapted from ACC/SCN (1997).

Table 9. *Public health implications of Vitamin A deficiency by risk group*

	Infants 6–12 months	Preschool Children	School Children	Adoles- cents	Pregnant Women	Lactating Women
Mortality	+	+	+	?	+	+
Morbidity	−	+	?	?	+	+
Mild Anemia	+ / −	+	+	+	+	+
Growth	?	+ / −	?	?	?	−

Adapted from UNICEF Regional Office for South Asia, 11/97.
+ = well-documented outcome in areas where VAD is common; + / − = found in some studies/areas/children but not in others; ? = insufficiently studied.
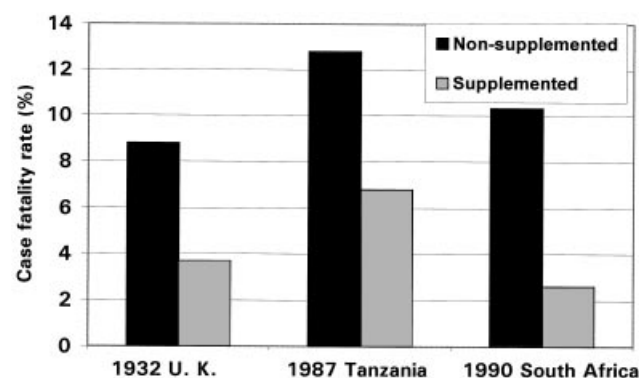
Fig. 4. Measles deaths and vitamin A supplementation. In 3 separate trials of children hospitalized with measles (the first in 1932) deaths among children given high-dose vitamin A supplements were significantly lower than among children not supplemented. Adapted from UNICEF (1997), data from Sommer & West (1996).

sistance to infection and thus decrease mortality (Fig. 4).

Subclinical vitamin A deficiency increases risk of severe morbidity and death, and it also slows growth, development and haemoglobin synthesis (ACC/SCN, 1997); interestingly, too, the ability of infections to decrease vitamin A status and the capacity of infections to precipitate xerophthalmia and keratomalacia in those already marginally deficient is well established. The effect is particularly severe with measles and chickenpox, but a significant drop in serum vitamin A concentrations has even been observed in children with acute respiratory infections and gastroenteritis with concentrations returning to normal after recovery. Vitamin A blood concentrations also have been reported to be reduced in pneumonia, rheumatoid arthritis, acute tonsilitis and infectious hepatitis.

Importantly for this volume, lower serum carotene and vitamin A concentrations also have been found with hookworm disease (Scrimshaw & SanGiovanni, 1997; Crompton, this volume); hence the importance of vitamin A nutriture in worm-infested children. Indeed, the possibilities for synergism between nutritional deficiency and parasitic disease that can be reversed through interventions are particularly relevant in assessing benefits from

controlling intestinal nematode infections. The relationships between VAD and *Ascaris lumbricoides* infection in children have been the most extensively studied (see O'Lorcain & Holland, this volume). Many developing countries have recently conducted nationally representative surveys on the extent of VAD that include population-based data on serum retinol levels (Fig. 5). A prevalence of low serum retinol levels ($< 0·7 \mu$mol/l) that is greater than 10 % defines VAD as a public health problem in an area or country.

Iodine deficiency diseases

Iodine deficiency leads to goitre, and during pregnancy can result in cretinism or mental retardation in the child. The progress made in control of iodine deficiency diseases (IDD) in the past 10 years is spectacular and especially notable because IDD includes not only goitre (some 834 000 000 persons; Table 1) but also endemic cretinism (16 500 000 cases who are mentally retarded), cretinoids (49 600 000 people with some mental impairment), and others with spastic diplegia or dwarfism. Iodine deficiency is the single most important cause of preventable brain damage and mental retardation, most of the damage occurring before birth (UNICEF, 1997). Data published jointly by WHO, UNICEF and ICCIDD in 1999 show that at least 130 countries are affected by IDD, including almost every country in Africa (Table 10). The scale of the global problem is enormous; globally about 740 million people are affected by goitre, and over two billions (38 % of the global population living in 130 countries) are estimated to be at risk of IDD; many countries, including India and China, have concluded that their entire population is at risk of IDD (Table 11; ACC/SCN, 2000). The role of intestinal *Ascaris* infection in the absorption of iodine from the gut has been studied in children in Malawi; see O'Lorcain & Holland (this volume).

Zinc deficiency

The fact that zinc deficiency can limit child growth in malnourished populations is increasingly appreci-
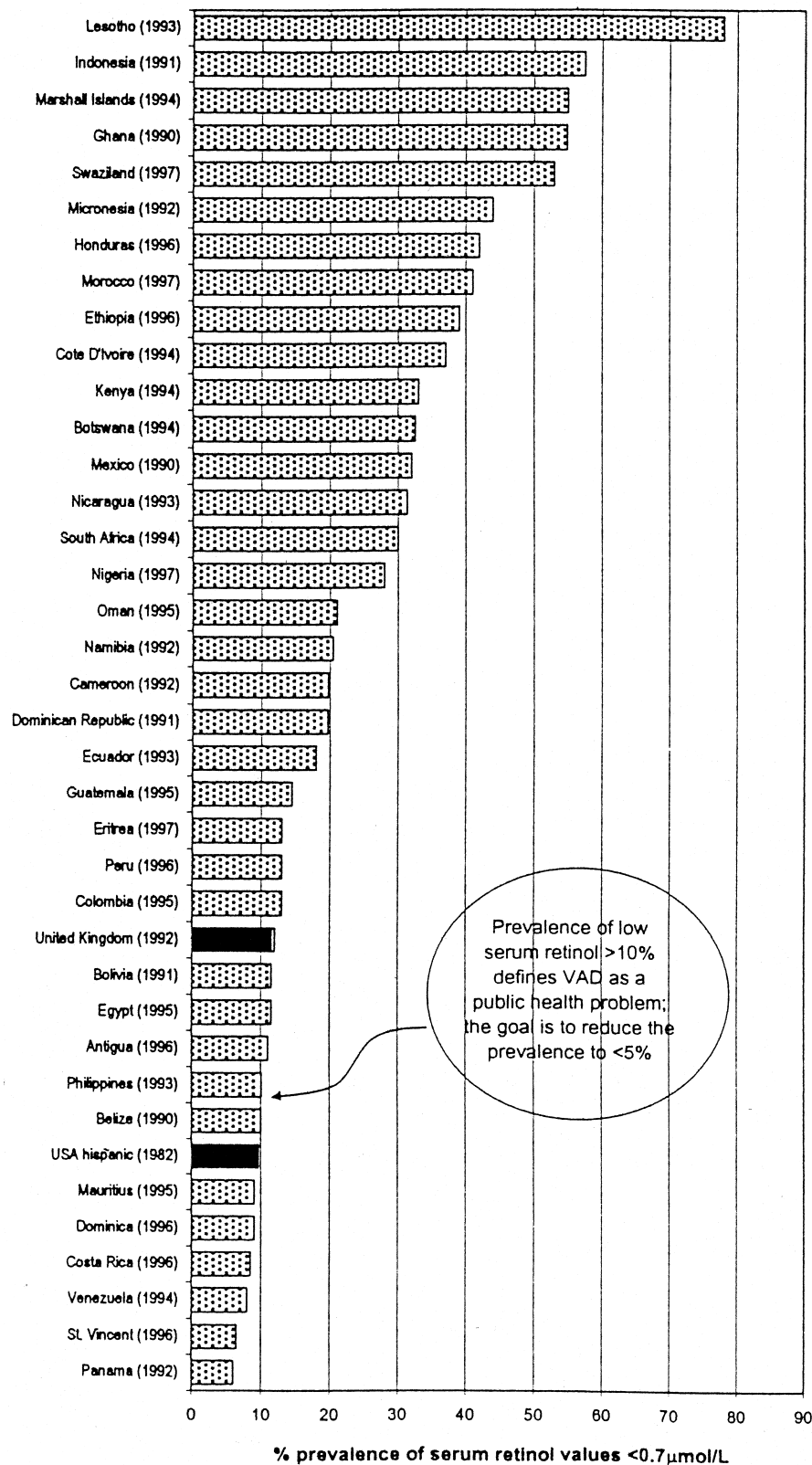
Fig 5. Prevalence of low serum retinol levels in countries in which nationally representative surveys have been undertaken since 1990. Adapted from ACC/SCN (1997) data from UNICEF, Tulane University and the Micronutrient Initiative (1997*b*).

ated, after a decade of understandable skepticism because there still is no easy reliable method to determine zinc nutritional status at the population level. A 15 month follow-up of zinc supplemented Ecuadorian preschoolers with previous low zinc intakes, as compared with paired unsupplemented children, showed clearly a slow, steady gain in height in those receiving zinc (Fig. 6). As do deficiencies of

Table 10. *Number of countries affected by Iodine Deficiency Disorders (IDD)*

Region	Total number of countries in region	Number of countries IDD a public health problem	IDD eliminated[a] or no IDD	Insufficient data[b]
Africa	46	44	1	1
Americas	35	19	3	13
South East Asia (includes India)	10	9	0	1
Eastern Mediterranean	22	17	1	4
Europe	51	32	13	6
Western Pacific (includes China)	27	9	2	16
Total	191	130	20	41

From: *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000); Source of data: WHO/UNICEF/ICCIDD (1999).
[a] IDD elimination is defined as a total goitre rate (TGR) of $< 5\%$ in school-age children. [b] Data are insufficient to categorize countries.

Table 11. *Current magnitude of Iodine Deficiency Disorders (IDD)*

Region	Population[a] (millions)	Population affected by goitre (millions)	% of the region	At risk population (millions)	% of the region
Africa	612	124	20%	295	48%
Americas	788	39	5%	196	25%
South-East Asia	1477	172	12%	599	41%
Eastern Mediterranean	473	152	32%	348	74%
Europe	869	130	15%	275	32%
Western Pacific	1639	124	8%	513	31%
Total	5857	740	13%	2225	38%

[a] Based on UN Population Division 1997 estimates.
Adapted from *Fourth Report on the World Nutrition Situation*, ACC/SCN (2000);
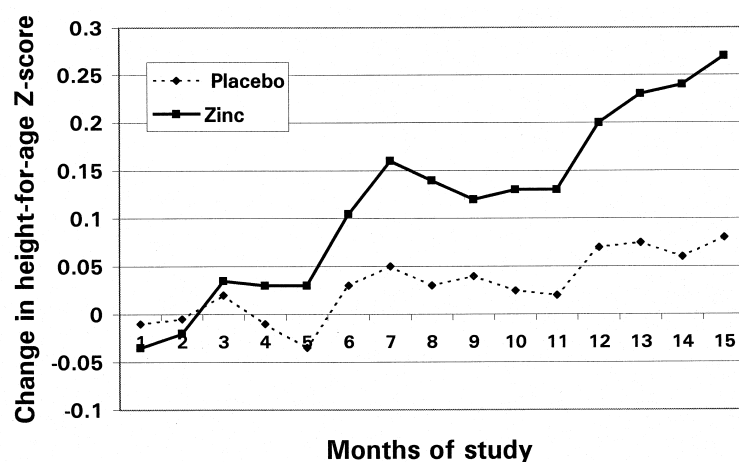Source: WHO/UNICEF/ICCIDD (1999).

Fig. 6. Zinc supplementation and child growth (Ecuador, 1986). Children were paired for gender, age, and height; height-for-age Z-scores refer to number of standard deviations below or above the median height for healthy children in the same age group. Adapted from UNICEF (1997); data from Dirren *et al.* (1994).

iron and vitamin A, zinc deficiency contributes to growth failure, susceptibility to infections, and complications of childbirth. The impact of these deficiencies on growth may, in part, derive from their influence on appetite.

In the case of zinc, it is quite likely that growth improves with zinc supplementation via improved appetite because diarrhoea and pneumonia decrease; food energy intakes have been shown to decrease by 630–735 kJ per day of illness in undernourished

Guatemalan and Kenyan preschool children with diarrhoea, respiratory infections or fever (Martorell *et al.* 1980; Neumann *et al.* 1988). The reported effects of zinc deficiency on immune function are listed in Table 8.

MALNUTRITION: DIMINISHED HOST RESISTANCE AND ITS RELATION TO INFECTIONS

Host resistance mechanisms can be divided into 2 primary tiers: those that are nonspecific and those that are antigen-specific. The nonspecific defenses include the skin and mucous membranes, phagocytic cells, mucus, cilia, complement, lysozyme, interferon, and other humoral factors. These are innate 'effectors', not necessarily influenced by prior contact with an infectious agent. Though they may also act in response to memory-dependent immune processes, they are usually the first line of protection, and retard the establishment of patent infection.

The antigen-specific mechanisms include the B cell system of antibody production and the T cell system of cell-mediated immunity. These two systems are adaptive in that they initiate and effect specific reactions in relation to repeated exposure to a microorganism or its antigenic determinants. Their effectiveness may be through checking the spread of infection, through destroying the invading organism, or through protective immune responses that form the basis of prophylactic immunisation against common communicable diseases. In the host, these nonspecific and specific defense systems act in concert (Chandra, 1997).

The thesis of the influential publication 'Interactions of Malnutrition and Infection' (Scrimshaw, Taylor & Gordon, 1968) postulated "that each worsened the other and that the biological effects of malnutrition and infection combined were greater than the sum of the two for this reason" (Scrimshaw & SanGiovanni, 1997). Since then, the understanding of malnutrition and its interactions with infection has expanded enormously, particularly during the past decade, with respect to types of nutrients and immune responses involved, types of morbidity and disease consequences and the nature of the specific interactions among these components.

Indeed, nutrition is now recognized as a critical determinant of immune responses, with malnutrition being the most common cause of immuno-deficiency worldwide (Chandra, 1997). Protein-energy malnutrition is associated with significant impairment of cell-mediated immunity, phagocyte function, complement function, secretory immunoglobulin A antibody concentrations, and cytokine production. Deficiency of single nutrients also results in diverse types of changes in immune function, as shown in Table 8 for deficiencies of iron, zinc, vitamin C and vitamin E (Scrimshaw & SanGiovanni, 1997). Other

micronutrients (selenium, copper, vitamins A, B_6, and folic acid) can also have important influences on immune responses. Indeed, both epidemiological and clinical studies suggest that nutritional deficiencies alter immunocompetence and increase the risk of infection. Concomitant poor sanitation and personal hygiene, overcrowding, contaminated food and water, and insufficient nutrition knowledge all compound the effects of poor nutrition on susceptibility to infection and public health (Chandra, 1997).

QUANTITATION OF MALNUTRITION AND ITS CONSEQUENCES

Quantifying the relationship between degrees of protein-energy malnutrition (assessed by underweight) and increased child mortality rates (Pelletier *et al.* 1993, 1995; Pelletier, 1994; Csete, 1995; Murray & Lopez, 1996) has been an extremely important recent achievement with enormous public health implications.

One of the most important conclusions from such research is that the contribution of malnutrition, especially mild and moderate malnutrition, to child mortality is much greater than previously thought. Indeed, Pelletier *et al.* (1993) developed a mathematical model to represent the synergy of malnutrition and infection, based on eight prospective studies of malnutrition and disease in developing countries. This model includes two equations that can be used to estimate the contribution of malnutrition to mortality in any country that has reliable information on weight-for-age of young children. The first equation estimates the overall contribution of malnutrition to mortality, while the second estimates the contribution of only mild and moderate malnutrition (MMM). When they applied the model to nationally representative anthropometric data from 53 developing countries, their most important conclusions were the following: (1) The average percentage of child deaths caused by the potentiating effect of malnutrition on illness was 56 % (weighted for country size), and ranged from 13 % in Paraguay to 67 % in India (Table 12). (2) Of this 56 % of child deaths due to the potentiating effect of malnutrition, the average percentage of deaths attributable to the potentiating effect of mild and moderate malnutrition alone is 83 % (weighted average). Even in countries with high prevalences of severe malnutrition, at least 3/4 of all the malnutrition-related mortality was due to mild and moderate malnutrition.

This finding of the predominant importance of moderate and mild malnutrition to mortality is extremely important for public health policy, especially because it is opposite to the conclusions from an early and influential study of preschoolers in Bangladesh by Chen, Chowdhury & Huffman (1980)

Table 12. *Percentage of child deaths attributable to the potentiating effects of malnutrition (total PAR) and the proportion of this that is related to mild-to-moderate malnutrition (MMM) in 53 countries or areas. Adapted from: Pelletier et al. 1995*

Country or area	Total PAR (%)	Related to MMM (%)	Country or area	Total PAR (%)	Related to MMM (%)
Paraguay	13	100	Senegal	39	89
Dominica	14	100	Uganda	39	91
Seychelles	15	100	Thailand	40	94
Barbados	15	100	Zambia	40	91
Jordan	17	100	Togo	41	88
Trinidad & Tobago	17	100	Sierra Leone	42	83
Jamaica	18	100	Ghana	42	90
Uruguay	19	100	Djibouti	43	80
Nicaragua	23	100	Namibia	44	90
Dominican Republic	23	100	Rwanda	44	96
Tunisia	23	100	Philippines	46	93
Peru	23	100	Madagascar	48	85
Zimbabwe	24	100	Mali	48	82
Colombia	25	100	Guatemala	48	83
Antigua	25	92	Myanmar	49	83
Iraq	25	100	Sri Lanka	50	86
Côte d'Ivoire	26	100	Burundi	52	83
N. E. Brazil	26	99	Nigeria	52	80
Egypt	27	100	Haiti	53	79
Bolivia	27	100	Tanzania	53	93
Lesotho	29	100	Indonesia	54	92
Morocco	31	95	Pakistan	55	79
Ecuador	32	94	Viet Nam	56	78
China	35	98	Nepal	65	80
Honduras	36	94	Bangladesh	66	73
Guyana	37	94	India	67	74
Cape Verde	38	85			
			Weighted Average	56	83

reporting that only severe malnutrition in preschoolers was associated with increased mortality rates. Those earlier findings guided policy for years and led incorrectly to the assumptions that: (1) infectious disease control was much more important in lowering child death rates than was improving nutritional status of young children, except in cases of severe malnutrition; and (2) a concentrated effort should be made to control severe PEM, rather than mild or moderate malnutrition.

Fortunately, the studies and analyses of the past decade have led to the appropriate changes in this earlier approach to the problems of malnutrition and infection control. Micronutrient status was not explicitly considered in this work even though micronutrient deficiencies themselves may contribute importantly to mortality, especially Vitamin A (see below), iron and some other micronutrients.

REVERSAL OF MALNUTRITION THROUGH SPECIFIC NUTRIENT REPLACEMENT

Iron supplementation and the reversal of disease

Prevention and control of IDA are more complex, both technically and operationally, and are usually more expensive than for vitamin A deficiency or iodine deficiency disorders (IDD) because frequent (at least weekly) supplementation is usually necessary in groups at high risk. By contrast, vitamin A supplements can be given 2 or 3 times per year, and IDD have decreased markedly because of mandatory salt iodisation. While many foods in industrialised countries are enriched or fortified with iron, and some studies in developing countries have proved this to be feasible and effective, neither the type of iron salt to be used nor the vehicle for such fortification has been agreed. As a result, iron fortification is still not in use nationally in non-industrialised countries. In most developing countries the primary and usually the only main effort to control anaemia is provision of daily or weekly medicinal supplementation.

One of the most interesting and very recent developments that might greatly speed up control of IDA in developing countries is the use of iron cooking pots, which has been shown in a small study of Ethiopian children to improve iron status and to enable small but important improvements in length and weight gain in this malnourished population (Adish *et al.* 1999). Iron availability from foods cooked in iron pots was especially high for meat and

Table 13. *Mortality decrease found in young children in eight vitamin A intervention trials**

Site	Reference	Effect (%)
Aceh, Indonesia	Sommer *et al.* (1986)	−27
Sudan	Herrera *et al.* (1992)	4
Hyderabad, India	Vijayaraghavan *et al.* (1990, 1992, 1993)	−6
Jumla, Nepal	West *et al.* (1991)	−26
Sarlahi, Nepal	West *et al.* (1991)	−29
Ghana (VAST Study)	Ghana VAST Study Team (1993)	−20
Bogor, Indonesia	Muhilal *et al.* (1988)	−30
Tamil Nadu, India	Rahmathullah *et al.* (1990)	−50

* Mean relative risk: 0·77; 95 % CI: 0·68, 0·84. From Beaton *et al.* (1993).
Adapted from Scrimshaw & Sangiovanni (1997).

green vegetables. The authors rightly point out that it may take more studies and many years before general guidelines suggesting distribution or even use of iron pots to prevent IDA emerge, but there appears to be no harm in disseminating this knowledge and hoping that it is used soon where feasible in areas where IDA is a public health problem. Other measures which could play some role in reducing anaemia include control (and early treatment) of malaria, family planning, and nutrition education.

If there is a single, classic parasite-malnutrition interaction of major public health importance that is widely known and well-proven, surely it is that of blood loss caused by hookworm precipitating iron deficiency and anaemia (Roche & Layrisse, 1966). Hookworm infection and its important relation to IDA and its control and prevention are discussed by Crompton elsewhere in this volume. Other infections such as schistosomiasis which cause blood loss (in the urine with *S. haematobium* and in the stool in *S. mansoni* and *S. japonicum* infections) will also result in iron loss and contribute to iron deficiency anaemia.

Iron supplementation of iron-deficient populations clearly results in decreased frequency of infectious episodes (Scrimshaw & SanGiovanni, 1997). Moreover, Chandra *et al.* (1977) demonstrated in Indian children that as iron status (transferrin saturation) improved, so did the capacity of their lymphocytes to respond to antigenic stimulation.

Vitamin A supplementation

Effective, low-cost approaches to control of vitamin A deficiency are available and are being applied in many countries (ACC/SCN, 2000); three main approaches in use are to improve dietary diversity (for example, with horticulture), to fortify foods with vitamin A (for example sugar or MSG), and to administer medicinal high-dose supplements every 4 or 6 months.

Decreased mortality in childhood and in pregnancy following vitamin A supplementation

The results of eight studies conducted in 5 countries to assess the effects on child mortality of vitamin A administration to preschool-age children are shown in Table 13. In 6 of the 8 studies, large decreases in mortality ranging from 20 % to 50 % were seen; two studies showed no effect, possibly because other deficiencies were limiting. Most communities studied had high rates of PEM, poor health services, and low levels of immunisation. Surprisingly, despite their impressive decreases in mortality, these and certain other studies failed to show a reduction in morbidity caused by gastrointestinal or respiratory infections, the most common causes of death in young children. Thus, the childhood disease most clearly proven to be markedly alleviated by vitamin A supplementation still remains as measles (Fig. 4).

Recently, a study in Nepal on the efficacy of weekly, low-dose supplementation of vitamin A or β-carotene on pregnancy-related mortality has reported that women of childbearing age, given 7000 μg retinol equivalents of vitamin A weekly, showed a reduction of 40 % in mortality related to pregnancy; and weekly dosing with 42 mg β-carotene (approximately equal to the vitamin A supplement) yielded a 50 % lower mortality rate related to pregnancy (West *et al.* 1999). The results are especially important because only half the women who became pregnant during the trial took 80 % or more of their supplements, an observation suggesting that maternal mortality risks in vitamin A-deficient pregnant women could be significantly decreased even with modest increases in intake of vitamin A or β-carotene. The study needs to be repeated elsewhere to confirm these important findings.

Such decreases in mortality, achieved with so little intervention, show why vitamin A supplementation programmes are being undertaken so widely and

enthusiastically in needy populations. However, there still is no understanding of exactly how vitamin A deficiency exerts its effect on human resistance to infection (Gershwin, Beach & Hurley, 1985). Vitamin A is essential for maintaining epidermal and mucosal integrity, but these barriers do not appear to be compromised in the populations studied (Scrimshaw & SanGiovanni, 1997). In experimental animals, vitamin A deficiency leads to decreased thymus and spleen sizes, reduced natural-killer cell activity, decreased interferon production, impaired delayed cutaneous hypersensitivity, less effective fixed fat macrophage activity, and a lower lymphocyte response to stimulation by mitogens (Gross & Newberne, 1980); phagocytic activity may also be affected (Scrimshaw & SanGiovanni, 1997). However, most clinical studies report no effects on T cell function (Tomkins & Hussey, 1989), but dietary vitamin A in patients with pulmonary disease has been found to increase T cell mitogenesis in lung patients and to reverse postoperative immunosuppression (Gross & Newberne, 1980).

Decreased morbidity from childhood malaria following vitamin A supplementation

Though earlier intervention studies failed to show that vitamin A supplementation reduced morbidity from respiratory infections or diarrhoea in young children (see above), a major new study of vitamin A supplementation to undernourished children under 5 years has also reported a large decrease in morbidity from falciparum malaria in children 6–60 months old given high-dose vitamin A (100 000 or 200 000 IU) every 3 months for 13 months (Shankar *et al*. 1999). The study, which was placebo-controlled, demonstrated 30 % fewer falciparum malaria episodes in the supplemented group, with children in the 12–36 months age category benefiting most. The public health importance of these findings, provided they are confirmed elsewhere, is clear when one considers that malaria is estimated to cause the deaths of over 1 million children annually in subSaharan Africa. In other areas it is also one of the 5–10 most common infectious and immediate causes of death in young children.

Reversal of iron deficiency anaemia following vitamin A supplementation

That vitamin A deficiency can cause anaemia in adult humans maintained on iron sufficient diets has been known for 2 decades (Hodges *et al*. 1978). Studies in animals have confirmed that vitamin A plays a role in haemopoesis (Mejía, Hodges & Mohanran 1976 *a*, *b*; Roodenburg *et al*. 1996). This fact can be important for the study and control of anaemia related to intestinal helminths, particularly hookworm, which, when common, is the most likely of the intestinal nematodes to cause iron-deficiency anaemia, especially in areas where vitamin A deficiency is a public health problem.

The International Vitamin A Consultative Group [IVACG] in 1998 issued a powerful statement on vitamin A and iron interactions that is important for those concerned about nutritional anaemias and parasitism, summarised as follows. Vitamin A deficiency can modify iron status and lead to anaemia, but the mechanisms are poorly understood. Haemoglobin synthesis is reduced and, based on studies in animals, mobilisation of iron stores is thought to be impaired in VAD. The magnitude of improvement in anaemia when vitamin A and iron are given compared to iron alone can be substantial. In pregnant Indonesian women, combined supplements eliminated anaemia in 97 % of women, compared with only 68 % when given iron supplements alone (Panth *et al*. 1990; Suharno & Muhilal, 1996). Indonesian adolescent girls also exhibited higher rises in haemoglobin levels with a combined supplement as compared with iron alone (Angeles, Schultink & Sastroamidjojo, 1996). However, the combination is not always effective. In Nepalese women with a high prevalence of hookworm infection, vitamin A supplements had little impact on haemoglobin levels (Stoltzfus, 1998). It is important to remember, though, that the primary cause of the anaemia is iron deficiency, and that vitamin A supplements cannot overcome severe iron deficiency. The IVACG states that the interventions most likely to reduce anaemia are improvements in iron intake and bioavailability and a reduction in common infections, especially hookworm and malaria where they are endemic.

Iodine supplementation and the reversal of disease

Implementation of universal salt iodisation has been so successful in some regions that in just 3 years, between 1994 and 1997, the proportion of the global population at risk of IDD decreased by half, from 28·9 % to 13·7 %. Globally 68 % of households in countries with IDD now consume iodised salt; there is 63 % usage for African countries as a whole. Countries in which spectacular progress towards elimination of IDD has been made include: China, DR Congo, Cameroon, Nigeria, Tanzania, Zimbabwe, and Kenya (ACC/SCN, 2000).

Until 1990, 40 million infants or one third of all babies born each year, were at some risk of mental impairment due to too little iodine in their mothers' diets. But because of the increased use worldwide of iodised salt, 12 million babies (and their families and health systems) were expected to be spared that risk; the number of babies born as cretins was expected to have dropped by over half, from approximately 120 000 worldwide in 1990 to < 55 000 (UNICEF, 1997). In areas where for some reason iodised salt is

not available, it is possible to prevent IDD using medicinal iodine preparations, either very small doses weekly or larger doses orally each year or by injection every 2–4 years.

Zinc supplementation

A pooled analysis of 10 randomised controlled zinc supplementation trials in children aged 6–60 months in Asia and Latin America has shown an overall reduction of 18 % in diarrhoea incidence (number of new episodes per total days of observation) and 25 % in diarrhoea prevalence (number of days with diarrhoea per total days observation) (Bhutta *et al.* 1999). In addition the incidence of pneumonia was reduced by 41 % in children receiving zinc supplements vs. unsupplemented children. Since diarrhoeal disease and acute respiratory infections are the major infectious killers of children under 5 years, those who work with malnourished tropical populations especially must now consider zinc supplementation as a potential tool for decreasing morbidity and mortality. Addition of zinc supplements to ongoing vitamin A and iron supplementation programmes must be considered. The role of zinc in psychomotor development is also essential to define more precisely.

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