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LETTERS TO THE EDITOR

RE: "ARSENIC INGESTION AND INTERNAL CANCERS: A REVIEW"

In their review of the cancer risk associated with exposure to inorganic arsenic, Bates et al. (1) noted interesting discrepancies in the occurrence of bladder and kidney cancer in different exposed populations. Residents of the blackfoot disease endemic area of Taiwan who were exposed to high levels of arsenic through artesian well water showed steep dose-response relations for the two cancers in both sexes (2). Blackfoot disease, a severe occlusive peripheral arterial disease, is associated with arsenic ingestion (3), and persons with blackfoot disease are at higher risk of cancer death than other residents of the same area (4). In contrast, a low occurrence of bladder cancer was observed in an autopsy study of Moselle, Germany, vintners who had also ingested high levels of arsenic (5).

Suspecting the importance of dietary factors in the etiology of blackfoot disease, Yang and Blackwell (6) discussed the "miserable nature" of the diet consumed in the blackfoot disease endemic area. Based on the food consumption patterns of members of 30 families with and 11 families without blackfoot disease patients, they reported that methionine (involved in arsenic methylation and detoxification (7)) may have been low, with a ratio of actual to recommended intake of 0.7. However, Bates et al. (1) pointed out that by today's standards (10), methionine was adequate, although they noted that low intakes of micronutrients may have led to a greater susceptibility to carcinogenesis. We have extended this analysis by examining the full range of nutrients in the diet of the Taiwanese living in the blackfoot disease area in the late 1950s. We calculated the subjects' nutrient intake on the basis of the aggregated food consumption data presented by Yang and Blackwell (6) and an international food composition table (International minilist) (8).

Our table 1 shows daily nutrient intakes in the blackfoot disease area and recommended daily intakes (9, 10). Intakes of protein and essential amino acids were adequate, and fat intake accounted for only 5.3 percent of the energy intake. Vitamin intakes (except for intake of B_{12}) were probably overestimated, because the subjects consumed mainly dried sweet potatoes, while our estimates were based on fresh sweet potatoes. Our results indicate an inadequate zinc intake at 58 percent of the recommended daily allowance (10), which is based on the maintenance of existing zinc status in healthy young adults on a mixed US diet. Actual zinc intake depends on the accuracy of the data and on a variety of fac-

TABLE 1. Estimated nutrient intakes in a blackfoot disease endemic area* compared with recommended dietary intakes†

Nutrient	Intake/day (male equivalent)	
	Blackfoot area	Recommended
Macronutrients		
Energy (kcal)	2,738	2,700‡
Protein (g)	60	43§
Carbohydrates (g)	585	NA‖
Fat (g)	16	NA
Minerals (mg)¶		
Iron	10	10
Zinc	9	15
Copper	3 2	1 5–3 0
Calcium	508	800
Phosphorus	1,271	800
Vitamins¶		
Vitamin A (μg RE‖)	826	1,000
Vitamin E (mg α-TE‖)	27	10
Vitamin C (mg)	242	60
Thiamin (mg)	1 2	1.5
Riboflavin (mg)	1 9	1 7
Niacin (mg NE‖)	15	19
Vitamin B_6 (mg)	3 9	2.0
Folate (μg)	466	200
Vitamin B_{12} (μg)	1.1	2.0
Essential amino acids (mg/g protein)#		
Histidine	23	16
Isoleucine	48	13
Leucine	78	19
Lysine	52	16
Methionine + cystine	37	17
Phenylalanine + tyrosine	89	19
Threonine	42	9
Tryptophan	12	5
Valine	60	13

* Data from tables 6 and 7 of Yang and Blackwell (6)
† From published reports (9, 10)
‡ Energy intake adequate to support agricultural physical activity for a 55-kg male aged 18–30 years (9)
§ Protein intake was calculated for a 55-kg male on the basis of 0 75 g/kg/day and was adjusted upward by 1.05 to account for the difference in digestibility compared with the reference protein (9)
‖ NA, not applicable, RE, retinol equivalent; TE, tocopherol equivalent, NE, niacin equivalent.
¶ Recommended dietary allowances for 25- to 50-year-old males (10)
# FAO/WHO/UNU, Food and Agricultural Organization/ World Health Organization/United Nations University (9)

tors unknown to us, such as the amount of zinc in the soil and the amount of phytate in the diet (11). The observations of growth retardation, a known effect of zinc deficiency (11), among rats fed on the typical diet of the blackfoot disease area (12) support the possibility of a zinc-deficient diet, although a zinc deficiency may not fully account for the observed weight loss.

While nutritional deficiencies may act in concert, we would like to focus on zinc. The relevance of a zinc deficiency in blackfoot disease is supported by the observation of low zinc levels in whole blood, plasma, and urine in blackfoot disease patients (13). A role for zinc deficiency in human carcinogenesis is supported by an association of low zinc intake with esophageal cancer rates (14). Furthermore, zinc is involved in gene expression, DNA synthesis, free radical reactions, and membrane integrity (11, 15). Zinc also induces the synthesis of metallothionein, a protein which may provide protection against the cytotoxic effects of metals (16) and affect cellular repair, growth, and differentiation (17).

Unfortunately, no data on the food consumption of the Moselle vintners are available, but zinc status may have been low too (Engel et al., unpublished manuscript). Nevertheless, zinc deficiency may behave synergistically with arsenic in carcinogenesis and atherosclerosis. If this is so, it may also help to answer questions concerning the mechanism of carcinogenesis for the nonmutagen arsenic and the lack of a convincing animal model for carcinogenicity (1).

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Editor's note: In accordance with Journal *policy, Dr. Bates and his coauthors were asked if they wished to respond to Engel and Receveur's letter but chose not to do so.*