

mechanisms and therefore should have been analyzed separately. In addition, the authors should have indicated the number of preexisting stones per patient in each group, since the rate of subsequent enlargement obviously depends on this value. Finally, the authors did not indicate the mean duration of follow-up and the date of the evaluation of treatment efficacy in both groups. The conclusion that allopurinol can provide clinically important protection therefore remains questionable.

ANDRÉ ULMANN, M.D., PH.D.
Centre Medico Chirurgical
de la Porte de Choisy

F 75013 Paris, France

The above letter was referred to Dr. Ettinger, who offers the following reply:

To the Editor: Our paper compares pretreatment and treated calculous events for the purpose of emphasizing the serious methodologic problems that could easily invalidate such comparisons. Trials relying on "before" and "after" calculous events are strongly biased toward a beneficial outcome. The proper test of the efficacy of allopurinol is our prospective, randomized, placebo-controlled, double-blind trial, which yielded a significantly higher rate of remission of calculi in subjects treated with the active drug.

In all but the five subjects specified, the duration of follow-up was 36 months unless a calculous event was observed. The numbers of preexisting calculi seen on radiographs are shown in Table 1 of our report; the allopurinol and placebo groups are similar. Furthermore, after including preexisting calculi as a variable in our proportional-hazards model, we were still able to demonstrate a significant contribution of treatment.

Our published data allow calculation of the prevalence of treatment failure evidenced by the development of new calculi; with use of this restricted criterion, failures were observed in 35.5 percent of the placebo group and in 17.2 percent of the allopurinol group. This ratio is similar to that observed for failure due only to growth of preexisting calculi (22.6 percent of the placebo group vs. 13.8 percent of the allopurinol group).

BRUCE ETTINGER, M.D.
San Francisco, CA 94115 Kaiser Permanente Medical Center

MICRONUTRIENTS AND THE RISK OF LUNG CANCER

To the Editor: The observation by Menkes et al. (Nov. 13 issue)¹ that serum beta-carotene and vitamin E were inversely associated with the risk of lung cancer, and that retinol and selenium showed no relation, prompted us to investigate this question in an ongoing follow-up study of 10,532 subjects in the Netherlands.²

At the base-line examination of this cohort in 1975, risk factors for chronic diseases were measured and blood was collected and stored. In the subsequent nine years, 114 subjects died of cancer. Deaths in the first year of follow-up were excluded, as were eligible cases for which base-line data were incomplete or serum samples unavailable, leaving 69 cases (18 cases of lung cancer) for statistical analysis. Base-line serum micronutrient levels in these subjects were compared with levels in 138 controls who were matched for sex, age (five-year interval), and smoking status (current smokers — yes or no; and number of cigarettes smoked daily — 5 or less, 6 to 14, or 15 or more).

Our results concerning retinol and selenium do support those of Menkes et al., whereas for vitamin E the differences in mean levels between our cases and controls reached statistical significance only when all cancers were considered (Table 1). Risk analyses according to quintile showed a strong negative trend for vitamin E (chi-square = 7.31, with 1 degree of freedom; $P < 0.01$), suggesting an increased risk of all cancer associated with lower serum levels of vitamin E. The relative risk in the lowest quintile for serum vitamin E was 4.4 (95 percent confidence interval, 1.1 to 18.3) when the highest quintile was used as the reference category. Adjustments in a logistic regression model for the matching variables and other

Table 1. Serum Levels of Nutrients in Subjects with Cancer and Controls.

NUTRIENT	CASES*	CONTROLS	PERCENTAGE DIFFERENCE†	
			means ±SD	
Retinol (μg/dl)	Lung cancer	56.4±17.4	58.1±21.8	-2.9
	All cancers	60.2±19.8	59.8±18.1	+0.7
Vitamin E (mg/liter)	Lung cancer	7.7±2.2	8.5±3.8	-9.4
	All cancers	7.2±2.0	8.5±3.0	-15.3‡
Selenium (μg/dl)	Lung cancer	12.1±2.5	12.6±2.5	-4.0
	All cancers	12.3±2.9	12.8±2.8	-3.9
Cholesterol (mg/dl)	Lung cancer	244.1±35.3	243.2±34.7	+0.4
	All cancers	236.7±42.9	238.8±41.8	-0.9

*There were 69 cases of cancer and 18 cases of lung cancer.

†The significance of the difference in means was assessed by a t-test that accounted for the matched design and that was based on log_e-transformed values.

‡ $P < 0.005$ by two-tailed t-test.

potentially confounding factors (i.e., serum cholesterol, retinol, selenium, week of blood collection, and years of education) resulted in only a minor change in this effect. No evidence for an effect on lung cancer was observed for vitamin E.

The lack of association between serum levels of retinol and selenium and the risk of lung cancer is in agreement with the Menkes findings. A protective effect of vitamin E against lung cancer was demonstrated by Menkes and her colleagues. However, no relation between vitamin E and lung cancer (17 cases) as well as all cancer (111 cases) was observed in the Hypertension Detection and Follow-up Program study.³ Our data suggest that a low serum level of vitamin E may be a risk factor for cancer. The number of patients with lung cancer was probably too small to make the 9 percent difference in mean serum levels of vitamin E between cases and controls statistically significant.

FRANS J. KOK, PH.D., COCK M. VAN DUIJN, M.Sc.,
ALBERT HOFMAN, M.D., PH.D., RENE VERMEEREN, B.Sc.,
ANTHONY M. DE BRUIJN, M.Sc.,
AND HANS A. VALKENBURG, M.D., PH.D.

3000 DR Rotterdam,
The Netherlands

Erasmus University

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2. Kok FJ, de Bruijn AM, Hofman A, et al. Is serum selenium a risk factor for cancer in men only? *Am J Epidemiol* (in press).
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RESTRICTIONS ON IMPORTATION OF TOBACCO BY JAPAN, TAIWAN, AND SOUTH KOREA

To the Editor: Under Section 301 of the 1974 Trade Act, the government of the United States has recently charged Japan, Taiwan, and South Korea with unfairly restricting importation of U.S. cigarettes and has threatened retaliatory trade sanctions if the restrictions are not removed.¹ If these efforts are successful, smoking and smoking-related deaths and disabilities will increase. The three countries have, or recently had, state-owned tobacco monopolies protected from foreign imports by tariffs and, in the case of South Korea,² by a law prohibiting possession of foreign cigarettes. In the absence of competition, the state companies generally produce a less "flavorful" cigarette than American brands, and cigarette advertising is more limited.³⁻⁴ Annual per capita cigarette consumption is 1600 in Taiwan, 1800 in South Korea, and 2600 in Japan.⁵

The Office of the U.S. Trade Representative is responsible for the