Letters

Vitamin A and Cancer

Gina Kolata's article "Does vitamin A prevent cancer?" (Research News, 16 Mar., p. 1161) emphasizes certain aspects of the evidence in its presentation of the facts. The logic for pursuing further investigations of retinoids as anticancer agents is compelling. At the cellular level, they promote differentiation (*1*), a process that is aberrant in most cancer cells. In animals, the retinoids have been repeatedly shown to reduce the incidence of experimentally induced tumors (*2*). The epidemiological data, contrary to statements in Kolata's article, provide evidence of a negative relation between human cancer and various indices of vitamin A consumption.

In more than a dozen large, controlled epidemiological studies, such a relation has been found. In several of these (*3–5*), the index reflected total vitamin A from both preformed retinol and its provitamins. In one study (*3*), when the relation was analyzed by cell type, the protective effect was found to be strongest for squamous carcinomas of the lung. This is consistent with laboratory evidence of an effect of vitamin A on epithelial differentiation. Another epidemiological study has shown a protective effect from dietary carotene, but not from dietary retinol (*6*). Finally, in a few studies no apparent relation was found between certain cancers (notably gastrointestinal and esophageal) and the derived indices of retinol or carotenes, but in some of these an apparently protective effect of the consumption of fruits and vegetables known to be rich in the vitamin A precursor beta-carotene was observed (*7*).

Kolata states that these results are "not terribly impressive—the relative risks tend to be less than 2." But relative risks in this range can have great public health importance. For example, the relative risk of dying prematurely from coronary heart disease for smokers is only around 2, but smoking contributes to 170,000 deaths in the United States each year. A true relative risk of 2 or less may be tremendously important, but requires the more sensitive clinical trial (rather than observational epidemiological studies) for confirmation.

The mixed evidence from studies of serum vitamin A is not surprising, since homeostatic control maintains serum retinol within a narrow range and may not reflect what is in the tissues (*8*). Concentration differences at the target tissues may be far more relevant, and these have not been examined.

The National Cancer Institute (NCI) believes that clinical (human) cancer prevention trials are needed to test the hypotheses of protective effects of the retinoids in a definitive way. There are many high-risk groups to study; currently no more than two of the 23 NCI-sponsored trials use any single agent and focus on the same type of population. While these early trials tend to use naturally occurring agents, synthetic agents need to be developed and tested in the laboratory as a step toward future clinical trials. Studies of cross-species comparisons, safety, and dose response must be carried out before these agents can be considered for human intervention.

Present data are sufficient to hypothesize a protective effect of one of these agents or their analogs or metabolites. While animal and epidemiological investigations continue, controlled trials in humans will be needed to provide convincing evidence of a useful protective effect. Even a modest effect, if borne out for the common cancer sites, could potentially prevent thousands of cancers per year.

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8. W. C. Willett *et al.*, *Am. J. Clin. Nutr.* **38**, 559 (1983).

Kolata states: "Researchers who looked, including Walter Willett and Charles Hennekins of Harvard Medical School, saw no difference in the carotene levels in the blood of persons who subsequently got cancer and those who did not. Unlike vitamin A levels, the levels of carotene in the blood vary with diet." The article also states: "Hennekins, whose study of nearly 22,000 U.S. physicians is the largest, describes the carotene hypothesis as 'soft.' "

Both these statements are incorrect. With respect to the former, I was not a collaborator in the study. As regards the latter, I did not make the statement.

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I was misquoted in Kolata's Research News article of 16 March.

There are now few data from epidemiological studies to suggest that increased intake of *preformed* vitamin A protects against human cancer. Thus, taking vitamin A supplements to prevent cancer cannot be justified scientifically. However, I certainly did not say that "There is no basis now for proposing that vitamin A protects against human cancer," which implies that this general hypothesis should not be actively pursued.

On the contrary, the field of carotene, retinoids, and cancer is promising (*1*) and appropriately the subject of considerable research activity.

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1. W. C. Willett and B. MacMahon, *N. Engl. J. Med.* **310**, 633 (1984).

As the NIH group and Underwood point out, the epidemiological data on vitamin A and cancer are not at all clear-cut. The studies indicating that vegetable consumption might protect against cancer do not show that it is the *carotenes* in the vegetables that are protective. And there is almost no evidence that carotenes protect laboratory animals against cancer.

The authors compare the relative risks in the most promising of the cancer stud-

ies to the relative risk that smokers have of dying from heart disease. But the diet-cancer risks are inconsistent—some studies show them and others do not. The smoking–heart disease relation is far better established. Of course, if there were good evidence of a relative risk of 2 in the cancer studies, it would be of great importance.

Hennekens says he did not describe the carotene hypothesis as "soft." He did, however, call it "immature."

Although Willett may well believe the vitamin A hypothesis should be actively pursued, he was not misquoted. The quote comes from our lunchtime conversation, not from his remarks at the meeting.—GINA KOLATA

Contamination of Arizona Corn

In his article of 5 August 1983 (News and Comment, p. 526), Eliot Marshall discusses the assertions of Chester Mirocha regarding the effect of corn contaminated with *Fusarium moniliforme* that was used as feed for chickens in Arizona. This moldy corn caused the death of many chickens, which led to serious financial losses for chicken farmers and feed suppliers.

Mirocha is quoted as affirming that *F. moniliforme* does not produce trichothecenes and that corn samples from Arizona contaminated by this fungus did not contain trichothecenes. These affirmations have been challenged by a number of scientists.

There are many published reports (*1*) that *F. moniliforme* produces some trichothecenes, mainly vomitoxin and diacetoxyscirpenol, in addition to zearalenone, moniliformin, and some other compounds (antibiotics, gibberellin, complex hormone substances from *Gibberella fujikuroi*—the perfect stage of *F. moniliforme*; and other related gibberellin fractions, including gibberellic acid). *Fusarium moniliforme* is a field fungus common in soil and many crops, including maize, oats, millet, sorghum, barley, and wheat.

Mirocha is quoted as saying that there is "no significance" in the fact that Arizona corn feed contained extremely high counts of *F. moniliforme* spores. He also is quoted as saying that "Nobody has demonstrated a correlation between spore counts and toxicity of cereal grains."

During my investigative work on alimentary toxic aleukia, I have consistently found a correlation between spore counts and toxicity of cereal grains. Cultures of *F. poae, F. sporotrichioides*, and other fungi have been shown to be most toxic during the period of abundant sporulation (*2*).

Toxic strains of *F. moniliforme* and their varieties, isolated from various substrates in Israel, have been characterized morphologically by abundant production of spores, and those strains that did not produce abundant spores have not been toxic. It is logical to propose that high spore counts of *F. moniliforme* in Arizona are also correlated with an increase in toxicity of corn and thus are a significant factor that should be taken into account.

Fusarium moniliforme is common in Israel and has been found in light, medium, and heavy soils and loess. It has been isolated in Israel from the following agricultural plants: maize, sorghum, onion, cucumber, pepper, cotton, groundnuts, and various fruits, such as bananas, grapefruits, Valencia oranges, avocados, and mangoes (*3*). In all, 133 isolates of *F. moniliforme* from Israel, in addition to 13 isolates from other countries, have been examined for phytotoxic and other toxic properties (*4*). In Israel, *F. moniliforme* is the most prevalent fungus. It has been found mainly on maize kernels, and our evidence indicates that toxic metabolites produced by this fungus are a major cause of disease. Crude extracts from *F. moniliforme* have caused moderate to strong inflammatory reactions, edema, and necrosis when applied to rabbit skin.

The role that *F. moniliforme* plays in the potential mycotoxicoses of farm animals consuming agricultural commodities that have been produced in semitropical and tropical countries has not been determined. However, it is suspected that mycotoxicoses do occur in these regions. Most research on fusariotoxin outbreaks have centered on crops produced in the temperate zone. Considerably less is known about mycotoxins other than aflatoxin in semitropical and tropical climates.

A comprehensive survey of *F. moniliforme* and its varieties, which belong to the Liseola section, would provide valuable information about their role in mycotoxicoses.

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Gene Therapy Researchers

I would like to correct two statements made in the article "Gene therapy method shows promise" by Gina Kolata (Research News, 30 Mar., p. 1376).

Our laboratory did not develop the β-thalassemic mouse. This mutant was developed by Susan Lewis, Chemistry and Life Sciences Group, Research Triangle Institute, Research Triangle Park, North Carolina, under contract with the National Institute of Environmental Health Sciences (NIEHS) as part of the National Toxicology Program. The development was part of a long-term program to obtain medically and biologically significant mouse mutants. Our laboratory joined with Lewis as well as with Loren Skow and Frank Johnson at NIEHS and Ray Popp at the Oak Ridge National Laboratory to study the molecular defect in the β-thalassemic mouse. These mice are available from Lewis.

Eli Gilboa is at Princeton rather than Yale.

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Erratum. In the article "NSF plans help with big computer problems" (News and Comment, 24 Feb., p. 797) by John Walsh, a reference to Kenneth G. Wilson's work was incorrectly printed. The third sentence in the second full paragraph of the third column should have begun, "Kenneth G. Wilson of Cornell, who won the 1982 Nobel Prize for his theoretical work on phase transitions. . . ."

Erratum. On page 1426 of the report "Association of parvoviruses with rheumatoid arthritis of humans" by R. W. Simpson *et al.* (30 Mar., p. 1425), a portion of the text beginning on line 18 of the first full paragraph in column 3 was incorrectly printed. It should have read, "We were unable to detect 24-nm particles in brains of normal mice from our colony or mice intracerebrally inoculated with extracts of synovial cells from patients with noninflammatory degenerative joint disease (DJD). More conclusive evidence for the identity of RA-1 as a parvovirus comes from our recent success in demonstrating that CsCl gradient fractions containing the infectious 24-nm particles can be extracted for a single-stranded DNA which is approximately 4.5 kilobases in size."