compared with girls, but this difference did not approach statistical significance. No consistent differential effect of exposure attributable to sex was found for the other outcome measures.

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To the Editor: Coggins raises several points that could have been resolved by a more careful reading of my editorial. He also rails against the EPA's recent report and the performance of the meta-analysis contained therein.[1] Those interested should read the original report.

It appears that my editorial has been the subject of detailed dissection, and Coggins has responded with the tobacco industry's objections, which are mainly irrelevant to the points I raised. For example, I stated, "Research on the hazards of smoking has turned recently to the association between exposure to environmental tobacco smoke . . . and brain tumors in children"; this statement does not imply any positive association. However, the most interesting feature of Coggins's response is its implicit acceptance of many of the points concerning tobacco-related cancer that I refer to in my editorial: the strong link between tobacco smoking and cancer; the devastating effects of tobacco smoking on cancer-related mortality and premature mortality currently being seen in Eastern Europe and building up in China; and the increasing rates of death from smoking-related lung cancer among women throughout the world. Such an implicit acceptance of the hazards of smoking by tobacco manufacturers introduces a new element into the continuing debate on many issues, including what labeling information should be included on cigarette packages; whether cigarette advertising should be banned, smoking should be restricted in public places, or cigarettes should be promoted in developing countries; and how to foot the bill for the medical costs incurred by smokers.

Coggins, who is from the R.J. Reynolds Tobacco Company (motto: "We work for smokers"), provides no facts, only bluster, to challenge my conclusion, "There is, however, no need for new evidence to justify strict measures to curb the use of this deadly substance [tobacco], which claims more lives around the world each year than war." As the tobacco epidemic continues, governments are increasingly turning to legislation as part of their campaign to reduce the morbidity and mortality from tobacco-related diseases. The most recent survey[2] indicates that over 90 countries and territories have some type of legislation to control tobacco use, and many of the recently enacted statutes are stronger and more effective than earlier laws. It is obvious that there is an ever-increasing need for activities to control the use of tobacco throughout the world and support for these activities from everyone concerned with public health.

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1. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, D.C.: Environmental Protection Agency, 1992.
2. Roemer R. Legislative action to combat the world tobacco epidemic. 2nd ed. Geneva: World Health Organization, 1993.

MORE ON THE NICOTINE CONTENT OF VEGETABLES

To the Editor: Domino et al. (Aug. 5 issue)[1] suggest that nicotine obtained from the consumption of vegetables could complicate the interpretation of studies of exposure to environmental tobacco smoke based on the detection of nicotine or its metabolite cotinine. The crux of their argument was that typical levels of vegetable consumption could result in an exposure to nicotine equivalent to that from inhalation of air with "a low concentration of nicotine from tobacco smoke." In fact, exposure to the 1 μg of nicotine that Domino et al. predicted could be absorbed from such tobacco smoke is so low that it would not produce systemic levels of nicotine or cotinine detectable by any of the techniques currently used to assess such exposure. The main problem with the inferences in these authors' letter is a 500-fold error in the calculations used to determine the vegetable equivalent of toxicologically meaningful exposure to tobacco smoke.

Previous studies indicate that approximately 500 μg of injected or inhaled nicotine is needed to produce the plasma cotinine level of 5 ng per milliliter typically observed in persons exposed to moderate levels of environmental tobacco smoke.[2,3] One microgram of nicotine might produce a few picograms of cotinine per milliliter of plasma, which would not be detected by the assays commonly used to assess exposure to environmental tobacco smoke,[3] or by the assay used by Domino et al.[4]

Determining the amount of vegetable consumption suggestive of exposure to cigarette smoke is also more complicated and physiologically difficult than implied by Domino et al. First, it would take an approximately 500-fold increase in the amount of vegetables estimated by Domino et al. to produce exposure equivalent to half a cigarette a day — e.g., more than 100 kg of tomatoes would have to be consumed in one day. Second, as acknowledged by Domino et al., nicotine exposure would be greatly reduced if vegetable skins, which contain most of the nicotine, were not eaten or if they were cooked in water, thereby extracting the nicotine. Third, ingesting nicotine is not equivalent to inhaling it, since absorption from the stomach is poor and 70 percent of the nicotine entering the circulation is metabolized during its first pass through the liver. Finally, it has been well confirmed that the exposure to tobacco smoke indicated by a plasma concentration of 5 to 10 ng of cotinine per milliliter is of clear toxicologic importance,[3] whereas there is no evidence that daily exposure to the equivalent of 1 percent of the smoke from one puff of a cigarette would be of toxicologic importance or could possibly confound assessment of environmental exposure.

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1. Domino EF, Hornbach E, Demana T. The nicotine content of common vegetables. N Engl J Med 1993;329:437.
2. Jarvis MJ. Application of biochemical intake markers to passive smoking measurement and risk estimation. Mutat Res 1989;222:101-10.
3. The health consequences of involuntary smoking: a report of the Surgeon General. Rockville, Md.: Department of Health and Human Services, 1986.
4. Domino EF, Hariharan M, VanNoord T, Demana T. Current experience with HPLC and GC-MS analyses of nicotine and cotinine. Med Sci Res 1992;20:859-60.

Dr. Domino replies:

To the Editor: Eating vegetables does not make you an addict to nicotine. Since the publication of our letter, I have

been overwhelmed by dozens of inquiries and commentaries from all over the world, ranging from the appropriate to the curious and bizarre.

The purpose of our letter was to point out that small amounts of nicotine in some vegetables may be one possible explanation for the presence of nicotine and its metabolite cotinine in the body fluids, especially urine, of nonsmokers. The amount of nicotine in certain vegetables is obviously too small to produce any pharmacologic or toxicologic effects. The difference between the small amount of nicotine in certain vegetables and the large amount in one average tobacco cigarette offers a marvelous lesson, both pharmacologic and toxicologic, on the importance of dose–effect relations. We never intended to suggest that vegetarians could become nicotine addicts, or that children who hate vegetables have a legitimate reason for refusing to eat them.

Dr. Henningfield apparently agrees with us that nicotine can be found in certain vegetables. Certainly, 1 μg of nicotine inhaled from tobacco smoke or eaten in certain vegetables will not cause any detectable physiologic changes, and its level in blood cannot be measured with most chemical assays, including ours. Urinary cotinine levels are a far better measure of nicotine exposure than plasma levels. The statement that it takes 500 μg of injected or inhaled nicotine to produce a cotinine level of 5 ng per milliliter refers to plasma, not urine. Urinary cotinine levels would surely be measurable in persons eating less than 100 kg of tomatoes a day.

I agree that determining the amount of vegetable consumption that would be comparable to a reasonable level of passive exposure to cigarette smoke is very difficult. Someone should conduct the crucial experiment of recruiting nonsmoking volunteers to eat reasonable amounts of vegetables containing nicotine and measuring their plasma and urinary levels of nicotine and cotinine. Only then will we know the contribution of eating such vegetables to the presence of cotinine, especially in the urine of nonsmokers not exposed to tobacco smoke. I stand behind our letter and say loud and clear — let us do more research.

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CUTANEOUS DISEASE AND DRUG REACTIONS IN HIV INFECTION

To the Editor: Coopman et al. (June 10 issue)* found that cutaneous diseases, including drug reactions, are extremely common in patients with human immunodeficiency virus (HIV) infection, and that their incidence increases as immune function deteriorates. They discussed ascertainment bias as a possible contributing factor to these associations, with cutaneous abnormalities possibly precipitating the discovery of HIV infection in some people. They did not mention the possibility of ascertainment bias in the reverse direction — i.e., the presence of HIV infection may have increased the likelihood that cutaneous disorders would come to medical attention. People with HIV infection see physicians more frequently as their disease progresses. This increased contact would predictably lead to more medical-record entries related to skin problems per patient per unit of time among HIV-infected patients than among patients without HIV infection, even in the absence of true differences between these groups in the prevalence of skin disorders. Furthermore, the greater importance attached to skin disorders by patients and physicians alike in the context of HIV infection would be likely to bring to medical attention skin conditions that might otherwise be disregarded or that might be addressed without producing a medical-record entry. Thus, differences in the frequency and intensity of patient evaluation, related to HIV status, rather than (or in addition to) true biologic differences between groups of patients could have produced the associations noted.

*Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med 1993;328:1670-4.

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To the Editor: Coopman et al. do not mention cutaneous pigmentary changes that accompany clofazimine therapy. This phenazine dye has been used in the treatment of leprosy, discoid lupus erythematosus, and pyoderma gangrenosum and in combination with other agents, such as clarithromycin, in the treatment of patients with AIDS who are infected with *Mycobacterium avium* complex.[1]

Clofazimine reportedly produces pink-to-brownish-black discoloration in up to 75 to 100 percent of patients receiving it,[2] and it has been associated with ocular disorders, including keratopathy and retinal degeneration.[3] We have noted intense, mahogany-brown darkening of the skin in relation to clofazimine therapy in patients with AIDS who were being treated for *M. avium* complex infection. The changes become obvious after a six-month course of therapy with the usual dose (100 mg daily). There is no association with exposure to light, cortisol deficiency, or hyperbilirubinemia. Light-microscopical and electron-microscopical studies of the skin in one of these patients did not demonstrate specific histologic abnormalities like those described in two patients with leprosy.[4]

Since clofazimine is likely to be used more frequently as adjunctive therapy when drug-resistant strains of *M. avium* complex are encountered, clinicians should be aware of this dramatic side effect.

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1. Holdiness MR. Clinical pharmacokinetics of clofazimine: a review. Clin Pharmacokinet 1989;16:74-85.
2. Clofazimine. In: McEvoy GK, ed. AHFS drug information 93. Bethesda, Md.: American Society of Hospital Pharmacists, 1993:493-7.
3. Font RL, Sobol W, Matoba A. Polychromatic corneal and conjunctival crystals secondary to clofazimine therapy in a leper. Ophthalmology 1989;96:311-5.
4. Job CK, Yoder L, Jacobson RR, Hastings RC. Skin pigmentation from clofazimine therapy in leprosy patients: a reappraisal. J Am Acad Dermatol 1990;23:236-41.

The authors reply:

To the Editor: We shared Dr. Johnson's concern that the high frequency of dermatologic diagnoses that we observed in our cohort with HIV infection and the increases in these rates as HIV infection progressed might in part reflect the biases that he suggests. Our data, partly presented in Table 3 of our article, suggest that these biases did not substantially affect our results. To evaluate the extent to which members of our cohort were more likely to have skin diagnoses recorded independently of an increase in their rate of occurrence, we examined the frequency of common disorders, including epidermal cysts, acne, and nevi, whose occurrence and diagnosis are unlikely to be related to either HIV infec-