Correspondence

Comments on “Trouble in Paradise”

There are statements I wish to protest in the Focus article “Trouble in Paradise” by John F. Lauerman published in Environmental Health Perspectives [105:914–917 (1997)]. These statements appear to have been attributed to me, but I can assure you I would never have made them.

First, there is the suggestion that I included atrazine among a list of agricultural chemicals used in pineapple cultivation. To my knowledge, atrazine was never used on pineapple fields. It does appear in Hawaiian groundwater, however, as a result of widespread use on sugar cane fields.

Second, I would never say that “none of these chemicals have been conclusively linked to adverse health effects,” as the article appears to paraphrase me having said. I believe that scientific studies conclusively link all these chemicals, and still more, with harmful health effects in exposed populations. What I recall having said to Lauerman is that it is almost impossible to link, with any confidence, the cancer or other health problem of a given individual with exposure to pesticides. Thus, although a population may experience an increase in cancers or other health problems in the aggregate, the likelihood of a person with a cancer being able to prove to the satisfaction of a court of law that his or her disease was the result of exposure to a chemical is vanishingly small.

The state of Hawaii has very serious contamination problems as a result of the application of agricultural chemicals and other pesticide products. I do not wish to have my statements be interpreted in any way as minimizing this problem or my own concern for the health risks that these poses.

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Note: Atrazine was mistakenly included in the list of agricultural chemicals used in pineapple cultivation. EHP regrets the error.

The α2u-Globulin Discussion

One of the most valuable things to emerge from the recent series of letters published in EHP in connection with the proposed α2u-globulin mechanism of male rat renal carcinogenesis was the title of the final letter in the series by Melnick et al. (1)—“Weight of Evidence Versus Weight of Speculation to Evaluate the Hypothesis.” This arresting title made me realize, for the first time, that evidence and speculation are usually irretrievably confused in the Discussion section of most papers, certainly in most of mine. It would be useful if all papers had a formal discussion of the data presented, followed by a separate section titled “Speculative Significance of the Data.” When an issue assumes an importance in its own right, as with the α2u-globulin controversy, the way forward should be to list the evidence for and against the hypothesis, leading, in turn, to an estimate of its likely validity. Weak points in the hypothesis would thereby be revealed, and these could become the focus of further experiments; alternatively, the hypothesis could be abandoned. This path was not taken in the recent debate and, as a consequence, we are left with opposing speculations and no resolution.

I took part in the EPA review of the α2u-globulin mechanism referred to by several of the discussants in this debate, and most of the data recently discussed were reviewed at that time. However, the trend in that meeting was to hear the opposing arguments and to then draw a conclusion—in fact, speculations were weighed, and the balance happened to come out in favor of the probable validity of the hypothesis. What was missing from that exercise was a dissection of each of the component data sets, leading to a decision as to their individual validity. That process was started during the course of the EHP debate.

The α2u-globulin mechanism of renal carcinogenesis is among the richest in data and speculation of all proposed nongenotoxic mechanisms of rodent carcinogenesis. It is therefore critical that advantage is taken of the impetus provided by the recent debate and that this hypothesis is reevaluated according to rigorous scientific criteria. Apart from the obvious need to advance our understanding of the potential carcinogenic hazard implicit in this mechanism, there is the subsidiary question of whether an agent such as limonene is formally required to be active in the TgAC and the p53 mouse abbreviated carcinogenicity bioassays. As things stand at the moment (2), a positive result in both of these assays would define limonene as a genotoxic carcinogen, whereas a positive result in only the TgAC skin painting assay would define it as a nongenotoxic carcinogen. A negative result in both assays would probably be rationalized along the lines that limonene represents the type of nongenotoxic carcinogen that modern methods should not be required to detect, i.e., that it should be classified as “generally regarded as safe” (2). In fact, the suggested need for such abbreviated carcinogenicity bioassays of limonene would probably flow from a full analysis of the α2u-globulin hypothesis, but that, in turn, would imply that these two assays are already confirmed as giving mechanistically diagnostic data, which they are not. Thus, the importance of resolving the α2u-globulin debate.

Science proceeds by way of informed speculation. However, such speculations should not become personal property to defend at all costs. Rather, they should be vigorously challenged with the aim of either refuting them or transforming them into generally accepted facts. The sooner that happens with the speculations surrounding the α2u-globulin hypothesis, the better.

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Re: “A Pilot Study of Urinary Estrogen Metabolites (16α-OHE1, and 2-OHE1) in Postmenopausal Women with and without Breast Cancer”

Unsin et al. (1) report data on the absence of a difference in the 2-hydroxyestrone/16α-hydroxyestrone (2-OHE1/16α-OHE1) ratio between breast cancer cases and controls. These findings contrast with pilot data recently reported by Kabat et al. (2), indicating a strong and statistically significant inverse association of the ratio with postmenopausal breast cancer, as well as in other recently reported studies (3). There are a number of methodological aspects of the study by Unsin et al. (1) that require comment.

First, although it is not explicitly stated, the authors recontacted women who participated in an earlier case–control study of breast cancer (4) to obtain urine samples from those qualified survivors who agreed to participate. The cases had been diagnosed between March 1987 and December 1989 and were recontacted approximately 7 years later. In the original population-based study, 1,510 matched case–control pairs were interviewed. Only stage I and II cases were included in that study. For the urinary estrogen study, the authors estimated that 55–60% of the original participants were excluded because they were receiving chemotherapy or other medication or weighed more than 200 pounds, which might affect estrogen metabolism.

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Volume 106, Number 3, March 1998 • Environmental Health Perspectives
Second, the authors excluded patients with advanced breast cancer because of the significant mortality in this group.

Third, the authors argued that exclusion of women with specific exposures is unlikely to have introduced bias. However, we are not told how many of the original study group were successfully contacted, what proportion had died, and what proportion of those contacted, and eligible, agreed to participate in the second study. Did these proportions differ between cases and controls?

Fourth, in addition to the possibility of selection bias due to differential recruitment in the second study, the lack of a significant difference between cases and controls may be due to the restriction of the study to early stage cancer. In the study by Kabat et al. (2), among postmenopausal women the ratio of 2-OHE1/16α-OHE1 was strongly and inversely associated with breast cancer. However, this association was driven primarily by a strong association with later stage cancer (stages III and IV).

Finally, in the small sample for which the results were reported, adjustment for breast cancer risk factors (including age at menarche, age at first pregnancy, parity, family history of breast cancer, and ethnicity) was apparently not carried out. This is critical because the matched-pair design of the original study was not maintained in the current study.

We look forward to the full report, which will hopefully provide more detailed information on these questions. It should be clearly understood that these results, as they now stand, are in no way inconsistent with our hypothesis that the metabolite ratio is a valid biochemical marker for breast cancer.

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Response

Our pilot study (1) did not confirm Bradlow et al.’s hypothesis of an inverse association between the urinary ratio 2-OHE1/16α-OHE1 and breast cancer risk. Kabat and Bradlow raise a number of issues that they believe might pose problems in our study. We examine them in the order in which they were raised.

Bradlow and Kabat note that we excluded approximately 55–60% of participants in the original study. As we explicitly state in our description of our pilot study (1), we contacted women who had participated in a previous case-control study at our institution. For the current study, we only contacted women with early stage (< stage II) cancers. This was out of concern that the levels of the urinary metabolites might be altered by the disease in later stage patients and that any association would be the result of the disease rather than the cause of it. We also had a number of exclusion criteria that applied both to cases and to controls. We excluded cases and controls who were current smokers, who were obese, or who had recently used chemotherapy, had anesthesia, or had used other medications that could interfere with estrogen metabolism. We agree that this might limit the generalizability of the findings, but it should not result in selection bias because the criteria were applied equally to both cases and controls. These restrictions were essential because of concern that these factors could influence urinary metabolite levels and thus produce a noncausal association between the ratio of 2-OHE1 to 16α-OHE1, and disease.

In our pilot study publication, we provided the data for the first 25 cases and 23 controls we studied. We did not provide the participation rates/exclusion rates in each group at that time since the data collection was ongoing, so the sample in our pilot study should be regarded as a convenience sample. Further information will be provided in the full study, which will be completed shortly.

Kabat et al. (2) provided no information on choice of cases and controls. In their study, cases were 4 times as likely as controls to currently use alcohol and 3.8 times as likely to have a chronic condition (such as hypertension, arthritis, diabetes, asthma, glaucoma, heart disease, and allergies); these large differences suggest that their control group may not have been an appropriate comparison group.

Bradlow and Kabat are concerned that lack of adjustment for various breast cancer risk factors would have biased our results toward the null. Although this is possible, their interpretation of their own results makes it appear unlikely. They reported that the 2-OHE1/16α-OHE1 ratio "did not show any consistent associations with age, race/ethnicity, age at first birth, parity, body mass index, family history of breast cancer, smoking or alcohol intake" (2). Bradlow and Kabat give no discussion of why the confounding would be negative. Indeed, positive confounding would appear to be equally, and possibly more, likely. In reality, it should be remembered that most of the breast cancer risk factors are relatively weak and their association with urinary metabolites would need to be rather strong to influence the associations substantively. We will evaluate all these factors as potential confounders in our full study.

Our results are, in fact, in agreement with those reported by Kabat et al. (2), who also found no association between the ratio of urinary 2-OHE1 to 16α-OHE1 and early stage breast cancer. As they indicate in their letter, the association they found overall was driven primarily by strong associations with later stage cancer in postmenopausal women (the same association was not found for premenopausal women). The strong association Kabat et al. (2) report in postmenopausal women with advanced disease may simply be an artifact of subgroup analysis, a result of the disease process itself, or the treatment their cases obtained. While it would be useful if they attempted to evaluate whether treatment or some other confounder might explain their result, in reality, it is difficult to be certain that it did not. For this reason, we excluded women with advanced disease from our study.

The 2-OHE1 and 16α-OHE1 assays reported in our study were conducted in the laboratory of Bradlow and colleagues at the Strang Cornell Research Laboratory, and we are indebted to him for this and for other help he gave in the execution of the study.

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