CORRESPONDENCE

Radiation-Induced Sarcoma–50 Years Later

In his editorial on radiation-induced sarcoma, Cahan[1] concludes that "it currently is unthinkable to irradiate patients with benign bone and joint conditions." This relatively far-reaching conclusion is drawn on the basis of various case reports. It is mentioned that between 1966 and 1996 there were 185 references describing radiation-induced sarcoma in $>$ 350 patients, corresponding to an average of 2 cases per publication. It appears necessary to evaluate the data of these references in quantitative terms to obtain the probability of cancer induction in relation to the radiation dose applied. In particular, it must be differentiated which portion of the secondary tumors observed is due to the action of radiation and which portion might result from the benign conditions that were treated originally. The mere consideration that there is a risk is not sufficient to draw clear-cut conclusions. The risk must be quantified. A valid assessment of any therapeutic intervention requires the consideration of both risk and benefit. Only in this way may any advantage to palliate or cure a benign disease be related to the relatively low risk of developing a sarcoma after an average latency period of 40 years.

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Author Reply

In taking issue with my editorial, the writers object to my closing phrase "it currently is unthinkable to irradiate patients with benign bone and joint conditions" believing it is a "far-reaching conclusion [drawn] on the basis of various case reports." These reports, they state, were derived from relatively few examples of radiation-induced sarcoma (185 references from 1966–1996) that described this condition in $>$ 350 patients or, as they state, "two cases per publication." (This is not an inconsiderable number that, it must be assumed, is swelled by large numbers of unreported cases). They also suggest that the tumor dosage of these and future cases be examined as to whether radiation could be incriminated as the sole cause of the sarcomas without specific knowledge 1) of the dosages and 2) whether the underlying pathology of the bone lesion could have become sarcomatous spontaneously.

In our original article[1] great pains were taken to estimate the

tumor dose to bone and, although preradiation therapy diagnoses were based largely on X-ray images, these had the classic appearance of benign tumors. In one patient, joined by several others in later reports, a sarcoma developed in a rib in a field of radiation therapy for breast cancer.

The writers also propose that the dosage of the 350 cases (as well as future ones) be quantified so that if a safe ratio of risk to dosage is determined, it could be used to "palliate or cure a benign disease." Beneficial as such a suggestion may appear to be, there always is the possibility that so-called "harmless" or "low risk" amounts of radiation underestimate its potential to cause malignant changes. However, more to the point, nonradiation techniques, medicines, and materials currently used to treat bone and joint pathology are not only more effective than radiation therapy but do not have a malignant potential.

In short, although radiation therapy is a valuable modality for treating certain cancers, it should not be used for benign conditions whether these are in bone, skin, or soft tissue.

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Resection of Hepatic and Pulmonary Metastases in Patients with Colorectal Carcinoma

We read with interest the article by Ambiru et al.[1] concerning the resection of colorectal hepatic and pulmonary metastases. In a population of 156 patients with resected hepatic metastases from colorectal carcinoma, they identified 6 in whom pulmonary metastasectomy was performed. They concluded that hepatic and pulmonary metastasectomy can result in long term survival for selected patients.

Recently, we analyzed data on 239 patients who underwent colorectal pulmonary metastasectomy at the thoracic surgery departments of two French institutions during the period 1970–1995. Among these patients, 43 (18%) underwent hepatic resection for metastasis from colorectal carcinoma before lung metastasectomy.[2]

At the time the study was completed, 21 patients were still alive, 14 free of disease. The median survival after lung metastasectomy was 19 months, and the 5-year probability of survival, considering the date of the first pulmonary resection as the starting date, was 11% (95% confidence interval, 2–39%). A univariate analysis by the log rank test revealed two prognostic factors, namely, the blood carcinoembryonic antigen (CEA) levels before pulmonary metastasectomy and the number of pulmonary resections (i.e., repeats of lung surgery). A borderline significant prognostic factor was the interval time (>36 months) between hepatic and pulmonary resection.

Taking into account the new system of prognostic grouping proposed by the International Registry of Lung Metastases (IRLM),[3] our series reviewed the classification of patients into different groups according to the presence of risk factors. There were 2 patients in Group 1 (resectable, solitary metastasis and disease free interval [DFI] >36 months; no risk factor), 16 patients in Group 2 (resectable, multiple metastases or DFI <36 months; 1 risk factor), and 25 patients in Group 3 (resectable, multiple metastases and DFI <36 months; 2 risk factors). No statistically significant differences were observed between Groups 2 and 3.

Our data suggest that survival depends on the biologic characteristics of the colorectal metastases (CEA, DFI, and repeat surgery) rather than the diffusion of the metastatic disease per se.

The prognostic role of CEA level before lung metastasectomy has recently been reported in several series.[4,5] The confirmation of its prognostic value even in patients with combined hepatic and pulmonary metastases strongly identify this marker as one of the main prognostic factors in metastatic colorectal disease.

We fully agree with the authors that, at present, surgery remains the only potentially curative treatment for metastases from colorectal carcinoma, but only highly selected patients with combined hepatic and pulmonary metastases can benefit from surgical resection. Resection could improve survival, but its role in the cure of the disease localized to the liver and lung is yet to be proven; in fact, in our series, the mortality after pulmonary metastasectomy was due mainly to both liver and lung recurrences.

Finally, the indications for the resection of lung metastases after liver metastasectomy for colorectal metastatic disease should be more selective; considering the poor outcome of our series (5-year survival, 11%), the indication for lung resection should be, at present, restricted to patients in Group 1 (according to

the IRLM classification) with normal prethoracotomy CEA levels until more reliable data becomes available.

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Author Reply

We are pleased to respond to the comments of Spaggiari et al. in regard to our article,[1] which discussed whether aggressive surgery of both hepatic and pulmonary metastases from colorectal carcinoma is of value.

We make a point of performing surgical resection on patients with hepatic and pulmonary recurrences whenever they are consistent with our criteria for resection, as described previously.[1] However, only 6 of 156 patients at our institution who underwent hepatic metastasectomy underwent resection of both hepatic and pulmonary metastases from colorectal carcinoma. Surgical resection of isolated hepatic or isolated pulmonary metastases from colorectal carcinoma has been widely accepted as the appropriate therapy.[2–4] Thus, although only the surgical approach to treating patients with hepatic and pulmonary recurrences can improve outcome, there are few long term survivors. Therefore, in order to examine surgical indication, limits of surgery, and adequate adjuvant chemotherapy, significant numbers of these patients must be analyzed.

The data cited in the comments by Spaggiari et al., which are based on an analysis of 43 patients who underwent both hepatic and pulmonary metastasectomy, revealed that survival depended on the biologic characteristics of the colorectal metastases (serum carcinoembryonic antigen [CEA], disease free interval [DFI], and repeat surgery). In fact, in our series, 1 patient with a normal CEA level, a long DFI (61 months), and a solitary pulmonary nodule was alive 64 months after pulmonary metastasectomy. We are in agreement with the belief expressed by Spaggiari et al. that good candidates for resection are patients with solitary metastasis, DFI $>$36 months, and a normal CEA level before surgery.

Concerning a preoperative CEA level as a prognostic factor, numerous studies have reported that the CEA level was correlated with outcome after resection of primary and metastatic disease.[3–5] On the other hand, contrary to these studies, a few studies have supported the notion that the value of a preoperative CEA level is limited.[6,7] In our series, two patients had a normal CEA level before pulmonary resection. One patient died of recurrent disease 32 months after pulmonary resection, and 1 was still free of disease 64 months after surgery. We also agree that it is likely that CEA plays some role as a facilitator or catalyst in the development of carcinoma metastases.

Although the common sites for recurrence after resection are the liver and lung, we think that surgical resection should be considered, because in our series 1 patient with an elevated preoperative CEA level was still free of disease 38 months after surgery and patients with unresectable pulmonary metastases had very poor outcomes.

Prognostic factors that can be used to select patients who will benefit from surgical resection are of value, and these reliable factors may lead to the identification of patients who are in need of perioperative adjuvant chemotherapy.

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Undifferentiated Carcinoma with Osteoclast-Like Giant Cells of the Pancreas and Periampullary Region

We read with interest the article by Molberg et al.[1] on undifferentiated carcinoma with osteoclast-like giant cells of the pancreas. We have recently studied a similar group of cases, and our results agree with theirs in many respects.[2] In 6 of 9 of their cases, the mononuclear cells stained with epithelial markers, which was also true for 7 of our 11 cases. Like them, we found that in some cases the nuclear pleomorphism of these cells approached that of undifferentiated carcinoma of the pancreas. The most striking difference concerned staining with mesenchymal markers. We found that not only the osteoclast-like cells but also the mononuclear cells in virtually all our cases stained for CD68, LCA, and A_1ACT, and often for HMA as well. Molberg et al. found these cells to be uniformly negative for CD68 as well as their other mononuclear marker, lysozyme. We have reviewed their illustration of CD68 staining (Fig. 7b)[1] and believe that a small proportion of the mononuclear cells are in fact positive. It is possible that differences in technique are responsible for the differences in our findings, although it appears that we used the same antibody (supplied by DAKO, Carpinteria, CA). On the basis of our results with mesenchymal markers, we concluded that these tumors have both epithelial and mesenchymal characteristics and may arise from an undifferentiated pancreatic stem cell.

Two of our patients were long term survivors. Their tumors were negative for p53 staining and had few or no pleomorphic cells. One of the patients in the series of Molberg et al. also had prolonged survival. We would be very interested in the p53 staining of this case, as well as whether this tumor had significant numbers of pleomorphic cells.

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We appreciate the interest and the response to our recent publication on undifferentiated carcinoma of the pancreas with osteoclast-like giant cells.[1] In contrast to our study, Deckard-Janatpour et al. found that the mononuclear cells in their series of undifferentiated carcinomas stained with mesenchymal markers in virtually all their cases and with epithelial markers in 7 of 11 of their cases.[2] In reviewing our Figure 7b, which is a photomicrograph of an undifferentiated carcinoma stained with CD68, they claim that "a small proportion of the mononuclear cells are in fact positive." We believe these cells are tangentially cut osteoclast-like giant cells, not mononuclear cells.

Deckard-Janatpour et al. have concluded that

their results support a dual epithelial-mesenchymal origin for undifferentiated carcinomas with osteoclast-like giant cells of the pancreas, perhaps from an "undifferentiated pancreatic stem cell." On the other hand, our results support an epithelial derivation for these unusual tumors and suggest that the osteoclast-like giant cells are a reactive and nonneoplastic component of the tumor. It is now believed that the multinucleated cells result from fusion of bone marrow–derived monocytes recruited into the tumor by chemotactic factors elaborated by the neoplastic mononuclear cells.[3] Moreover, mutations at codon 12 of the K-*ras* oncogene found in over 80% of ductal pancreatic adenocarcinomas have consistently been detected in the mononuclear cells of undifferentiated carcinoma with osteoclast-like giant cells, supporting the epithelial derivation of the mononuclear cells.[4] Furthermore, the existence of an undifferentiated pancreatic stem cell with an ability to give rise to tumors of both epithelial and mesenchymal origin is not consistent with the developmental anatomy of the pancreas. The epithelial components of the pancreas are derived from endoderm, whereas the connective tissue components are derived from splanchnic mesenchyme.[5] However, we do believe that a primitive pancreatic epithelial cell can give rise to a tumor that has both carcinomatous and sarcomatous differentiation (i.e., carcinosarcoma).

Finally, a review of our data revealed that our single long term survivor's tumor was negative for p53 and did not contain a significant population of pleomorphic cells.

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Expression of Cytokeratin 20 in Urinary Cytology of Patients with Bladder Carcinoma

We have grave concerns regarding the recent article by Klein et al.,[1] which described the use of a reverse transcriptase–polymerase chain reaction (RT-PCR) technique for the detection of cytokeratin 20 (CK20) expression in exfoliated cells of the urine as a noninvasive diagnostic test for transitional cell carcinomas (TCCs) and premalignant urothelial lesions.

Unfortunately, the work and its interpretation is based on the misconception that normal urothelium does not express CK20. In fact, the differentiation-associated expression of CK20 in normal urothelium has been well documented, both by the original group who described CK20[2–3] and by us.[4–6] Klein et al. quote just one of these articles,[4] and do so erroneously. In this article, we clearly describe the pattern of CK20 expression in normal urothelium in situ but report that normal urothelial cells grown in vitro fail to achieve terminal cytodifferentiation and do not express CK20.[4]

Of relevance to their study, but not referred to by Klein et al., are several reports of CK20 expression in TCCs.[3,5] Some noninvasive tumors retain a normal superficial cell localization pattern, which is associated with nonrecurrence in our experience.[5] However, in the majority of TCCs, expression is dysregulated and extended to all cell layers.[3,5] We have also reported observing this phenomenon in premalignant urothelial lesions, in which CK20 immunolabelling may be used to confirm an equivocal morphologic diagnosis.[6] The larger number of cells expressing CK20 in premalignant lesions and TCCs may account for an increase in voided CK20 positive cells to a level above the threshold of detection by RT-PCR.[1] This could occur in inflammatory or irritative states in which

increased numbers of normal CK20 positive superficial cells may be shed.

We feel that it is important that the results of Klein et al. are interpreted correctly, within the context of the available literature. We also feel strongly that the citing of our article to support an incorrect statement should be withdrawn.

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Author Reply

We took great interest in the comments provided by Southgate et al. regarding our article.[1] In our study, we used reverse transcriptase–polymerase chain reaction (RT-PCR) methods to determine the expression of CK20 in cells separated from the urine of 87 participants. Fourteen of the participants were healthy volunteers, and 73 had hematuria suspected for transitional cell carcinoma (TCC) of the bladder. No CK20 positive results were detected in the healthy volunteers group, whereas 55 of 73 were positive in the hematuria group (sensitivity, 91%; specificity, 67%).

Although Southgate et al. expressed concern regarding our article, we think that their comments, on one hand, and the data described in our article, on the other, contribute mutually to the understanding of the role CK20 is playing in normal and malignant urothelium.

In interpreting our article, one should take into consideration that the conditions were absolutely different from those described by other investigators, including Moll et al.[2] and the authors of the current correspondence.[3] Our work, as far as we know, was the first attempt to measure CK20 expression in shed urothelium cells extracted from voided urine, whereas the other aforementioned studies were performed with tissues. It is absolutely possible for normal shedding cells not to express CK20, whereas shed tumor cells continuously express it. This notion with respect to normal cells is supported to a certain extent by Southgate et al. themselves,[4] who demonstrated that the growing of urothelium cells in vitro resulted in the cessation of CK20 gene expression.

Measurement of mRNA presence by RT-PCR is the best available approach to detecting gene expression—much better than the immunohistochemistry method used by Southgate et al. and Harnden et al.

Southgate et al. and Harnden et al. suggest that a larger number of cells in the voided urine of TCC patients was the cause of CK20 positivity in these patients. With regard to this, we would like to stress that CK19, which was run in parallel, was positive in all nonmalignant patients, showing that the number of urothelium cells of these patients exceeded the threshold of detection by RT-PCR.

Regarding the comment that an inflammatory state may be used as a possible control for the effect of cell number on the threshold of detection, our results demonstrated that, of six patients with bladder inflammation, only one was CK20 positive.

As to the articles by the authors of this correspondence,[3–5] they were published after our project came to an end. However, if we had started the project with the information in these articles known to us, we would perhaps have missed the point and would not have discovered the potential of CK20 as a biomarker for malignant cells in voided urine.

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Hand–Foot Syndrome following Prolonged Infusion of High Doses of Vinorelbine

Four patients with chemotherapy-induced desquamative acral erythema or palmar-plantar erythrodysesthesia are described by Hoff et al. as having the hand–foot syndrome.[1] The latter term has been used for decades by hematologists to describe a painful swelling of the hands and feet in very young patients (age $<$ 18 months) with sickle cell disease.[2] This vasoocclusive manifestation involves the metacarpals, metatarsals, or phalanges and is presumed to result from avascular necrosis.[3] The term hand–foot syndrome should be reserved for this condition in sickle cell disease patients. Acral erythema or palmar–plantar erythrodysesthesia should be the preferred term for the chemotherapy-related side effect described by Hoff et al.[1]

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We appreciate the attention of Dr. Rosner to our article.[1] It is true that the term "hand–foot syndrome" has been used by hematologists for many years to describe dactylitis,[2,3] a painful swelling of the hands and feet in young patients with sickle cell disease. This process clearly is different in pathogenesis and clinical presentation to the one occurring after prolonged administration of chemotherapy agents. We agree that the term "palmar–plantar erythrodysesthesia" is more specific to the latter condition and should be preferred. However, it is important to note that the term "hand–foot syndrome" also is well established and has gained wide acceptance in the oncology community, being used extensively in recent literature.[4–6] Finally, even though the use of a very specific name for any pathology always is preferred, the scenarios in which these two pathologies arise are so different that we doubt there will be any confusion due to the use of the same name for these syndromes.

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Cancer among Spouses

Review of 195 Couples

The method used by Walach et al.[1] to assess spousal aggregation of cancer occurrence is biased toward exaggerating spousal concordance. They asked patients with cancer, seen in the Assaf Harofe Medical Center in Israel, whether their spouses had also had cancer. Apparently such spouses could be drawn from source populations outside of the population that visited the Assaf Harofe Medical Center. By this method, the only persons with cancer who could be identified from outside sources were those married to cancer patients. There were most certainly cancer patients in these outside sources whose spouses had not had cancer, but these nonconcordant spouse pairs were not identified. Had they been identified and included in the study, the observed proportion of concordant pairs would have been lower, i.e., closer (or perhaps equal) to the proportion that could be expected by chance.

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Unfortunately, Drs. Friedman and Quesenberry did not realize that we used a "proportional rates" approach[1] and that our sample consisted only of concordant-spouse couples. Assuming independence of cancer sites in spouses, the expected sampling distribution of cancer sites in husbands (or wives) should be equal to the one calculated from the background population. This was the hypothesis tested in our study. The well-known limitations of the proportional rates were also briefly discussed in our article.

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Intensified Therapy for Infants with Acute Lymphoblastic Leukemia

Results from the Dana–Farber Cancer Institute Consortium

We read with great interest the report by Silverman et al.[1] summarizing treatment outcome in 23 infants treated with Dana–Farber Cancer Institute Consortium protocols. Intensified multidrug therapy resulted in significantly improved long term, event free survival in 54% ± 11% of infants. This included at least three patients with *MLL* gene rearrangements, which are known to be associated with multidrug-resistant disease.

The authors describe two infants in whom the blasts at the time of recurrence differed phenotypically from those at diagnosis. They considered the possibility of secondary leukemia, but also speculated about recurrence of the leukemia with a phenotypic shift. In our opinion, the latter explanation appears most probable. In acute lymphoblastic leukemia (ALL) occurring in infants, particularly in cases with *MLL* gene rearrangements, leukemogenesis affects early progenitor cells. In such patients cross-lineage expression of myeloid antigens such as CD13, CD15, CD33, and CD65 frequently is observed,[2] in a minority of cases even biphenotypic acute leukemia has been diagnosed based on simultaneous expression of lineage specific antigens.[3] Using clone specific markers such as clonal immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangements, it is possible to distinguish between recurrence and secondary, therapy-related leukemia. We previously described a pre-B-ALL patient who developed acute myeloid leukemia 17 months after diagnosis, suggesting the development of secondary leukemia. However, the Ig and TCR gene rearrangement pattern was identical between diagnosis and recurrence, implying cytomorphologic and immunophenotypic evolution of the same clone.[4]

In contrast to previous reports,[3] Silverman et al.[1] clearly showed that infant ALL in principle can be cured. However, 50% of patients still recur. This implies that analysis of specimens at diagnosis is not sufficient for predicting treatment response and that more insight is needed into *in vivo* effectiveness of treatment during the follow-up. This is possible with the currently available standardized techniques for the detection of minimal residual disease (MRD).[5] To exemplify this strategy we show the monitoring of MRD in a 10-month-old infant with common ALL using a patient specific oligonucleotide probe to the junctional region of an IGK gene rearrangement (Fig. 1).[6] Despite cytomorphologic remission at the end of induction therapy, we still could detect low levels of malignant cells. The recurrence 14 months after diagnosis was predicted 3 months earlier with molecular MRD analysis. We believe that such prospective MRD monitoring can be used for the assessment of treatment response and can be applied toward individualization of therapy to improve the outcome of infant leukemia further.

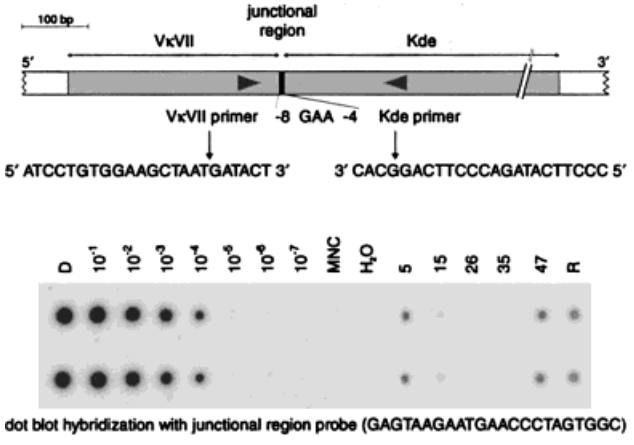

FIGURE 1. VκVII and Kde primers were used for polymerase chain reaction (PCR) amplification of bone marrow DNA samples at diagnosis (D) as well as during follow-up. The PCR products were spotted onto a nylon membrane, which was hybridized with the ^{32}P-labeled junctional region probe. Tenfold dilution series of diagnosis DNA revealed a sensitivity of 10^{-4} (one acute lymphoblastic leukemia cell between 10^4 normal cells). During follow-up the bone marrow became negative after Week 15, but at Week 47 PCR positivity was found again (i.e., 3 months before clinical recurrence [R]). bp: base pairs; MNC: DNA from normal mononuclear cells.

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Report of a Panel on the Relationship between Public Exposure to Pesticides and Cancer

The report of the National Cancer Institute of Canada (NCIC) on cancer risks from exposures to pesticides[1] poses a narrow question, applies an insensitive analytic tool to a very limited data base to try to answer that question, and then draws sweeping conclusions that go far beyond the data examined.

To assess whether pesticides in the diet pose a risk of cancer to the Canadian public, the NCIC Panel conducted a review of the epidemiologic literature on occupational exposure to pesticides. They did not examine the extensive literature on pesticide exposure and cancer risk in the general population,[2,3] nor did they review the relevant toxicologic literature. They did not undertake any independent analyses modeling pesticide exposure patterns or risks.

The most fundamental weakness in the Panel's approach lies in the extreme paucity of the epidemiologic data base that they considered. Of some 400 synthetic chemical pesticides registered for use on food crops in North America in 1997, the NCIC Panel was able to identify adequate epidemiologic data to permit assessment of human carcinogenicity for only 21, and they restricted their analysis to three compounds and classes: 2,4-dichlorophenoxyacetic acid (2,4-D); triazine herbicides; and certain chlorine-containing compounds, such as DDT. It is perilous, if not impossible, to draw wide-ranging conclusions in these circumstances.

A second weakness is that, even for those pesticides that have been examined, epidemiology is a relatively insensitive instrument for assessing carcinogenicity. The root cause of this insensitivity is inadequate assessment of exposure. Typically, exposure assessment in epidemiologic studies has been forced to rely on imperfect retrospective indices, such as "average number of days per year spent applying chemicals." Thus, for a study population such as farmers, who are exposed to multiple pesticides of inadequately characterized toxicity over many years in ever-changing formulas and combinations, it is little wonder that data on dose-response are few and that the ability of epidemiologists to identify causal associations has been limited. Without adequate assessment of exposure, statistical power tends to be low, and the results are almost always biased toward the null. Inevitably, therefore, a purely epidemiologic analysis that fails to consider toxicologic data will tend to underestimate the full extent of the problem of pesticide carcinogenicity.

Those shortcomings in the data are compounded by the NCIC Panel's unwillingness to consider relevant to the general population even those pesticide exposures that have credibly been found to cause cancer in occupationally exposed groups, such as farmers. The Panel opines, for example, that even if the herbicide 2,4-D were ever proven conclusively to be capable of causing non-Hodgkin's lymphoma in farmers, it would be unlikely to produce any cancer in the general population. That conclusion totally ignores the extensive recent literature on the broad range of exposures to pesticides that occur in the general population. Children, for example, consume considerably more pesticides on a per-kilogram basis than adults, and some children consume much more.[2] Moreover, children are often more vulnerable than adults to the pesticides that they ingest. In ignoring those variations in exposure and susceptibility, the NCIC Panel appears stuck in two outmoded notions: 1) that a single-point estimate of exposure can be used to judge risk for the entire population, and 2) that exposure so estimated will not overlap or even approach that of occupationally exposed groups. Neither of those assumptions is correct.

One must ask, Why are pesticides not considered as great a public health problem as tobacco? After all, analyses undertaken by the U.S. Environmental Protection Agency have established that 5 of the 400 food-use pesticides that have been systematically studied are proven human carcinogens, that 71 are probable human carcinogens (Groups B1 or B2), and that 101 are possible human carcinogens (Group C).

The answer to this question would appear to lie

in government's intelligent responses to the abundant toxicologic data on the carcinogenicity of pesticides. In contrast to the situation with tobacco, where government took no meaningful regulatory action until hundreds of thousands of North Americans had already been heavily exposed for decades, government has long taken vigorous action to limit exposures to pesticides. More than 9000 standards ("tolerances") for pesticides used on food crops have been established in the United States under federal law.[2] The Food and Drug Administration regularly inspects fruits and vegetables and seizes those that contain excessive levels of pesticides. The U.S. National Research Council estimates that, between 1954 and the 1980s, as a result of those regulatory actions, the carcinogenic potency of pesticides residues in food declined 100-fold for the average U.S. consumer.[4] All of this has contributed to the high quality of the food supply in North America.

We support the NCIC Panel's call for continuing regulatory scrutiny of pesticides on a regular basis, particularly scrutiny of older chemicals that were registered prior to the introduction of contemporary testing requirements. Such scrutiny will continue the trend toward ever-safer food. We support the Panel's call for continuing research into the preventable causes of cancer; apart from smoking-related cancers and certain cancers of occupational origin, we really know very little about the environmental causes of cancer. The often-cited estimate of Doll and Peto that less than 5% of all cancer is due to environment[5] reflects more a lack of knowledge than a calculation based on data. We enthusiastically join the Panel's conclusion that standards for food-use pesticides should be set at levels that protect children.

The threats of synthetic chemical pesticides to human health cannot be wished away. Chemical pesticides are inherently toxic chemicals. Their use must be controlled meticulously and eliminated wherever possible. Risk communication is an important, but not a sufficient, strategy for reducing the risks of carcinogenic pesticides in the diet. The great danger of the NCIC report and of the editorial that accompanies it is that these overly reassuring commentaries will lead readers to trivialize the threats to human health of pesticides in the diet.[6]

A balanced diet rich in fruits and vegetables is important for the prevention of cancer, but so is a diet low in residues from carcinogenic pesticides. The North American diet is one of the healthiest and most varied in the world. It is healthy because regulators have worked vigilantly to make it so. It is necessary to maintain our vigilance.

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In their correspondence, Drs. Landrigan and Goldman draw some rather critical and sweeping conclusions regarding the quality and validity of the work of the National Cancer Institute of Canada Panel on the Relationship between Public Exposure to Pesticides and Cancer.[1] We noticed that Drs. Landrigan and Goldman cite Dr. Landrigan's own work as Chairman of the Committee on Pesticides in the Diets of Infants and Children[2] in support of their criticism. The authors offer a number of criticisms related to the paucity of data utilized by the NCIC Panel in reaching its conclusions. It is evident that they have not entirely understood the mandate of the NCIC Panel, and hence the basis for its conclusions.

The Panel did not attempt to carry out an exhaustive review of the carcinogenicity of pesticides *per se*. Rather, in accordance with its mandate (which is described in the report), the Panel specifically sought to examine the evidence that exposure of the general public to pesticides was a significant

risk factor for cancer, in order to be able to advise the Canadian Cancer Society as to the appropriateness of shifting cancer control priorities away from tobacco in favor of greater control of public exposure to pesticides.

To address this issue, the Panel reviewed relevant laboratory and epidemiologic evidence related to the carcinogenicity of pesticides, but focused its attention on the exposure of the general population to dietary pesticide residues, the primary source of exposure for the general population. The Panel was certainly aware of the very limited experimental and epidemiologic data available to carry out a comprehensive review, specifically noting this limitation in its conclusions. Notwithstanding, the Panel also noted that approximately 75% of all man-made pesticides used in Canada are herbicides and that more than 90% of herbicide use occurs in the agricultural sector. Because of this large-scale use of herbicides, many long term health effects studies in humans have been directed at this class of pesticides. The Panel did not deliberately choose to focus on studies related to herbicides, triazines, and chlorine-containing pesticides, but rather made a genuine effort to examine the epidemiologic and laboratory data that were actually available. Like Drs. Landrigan and Goldman, the Panel also noted in its conclusions that pesticide exposure is indeed complex and that the Doll and Peto estimate rests on an incomplete understanding of potentially complex exposures and biologic mechanisms. Notwithstanding, the Panel noted that the Doll and Peto conclusions are similar to those of other authors.[4–5] Contrary to the assertion by Drs. Landrigan and Goldman, the Panel did not hold the view that even if the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) were ever conclusively proven to to cause cancer, it would be unlikely to produce cancer in the general population. The Panel noted reports suggesting a link between occupational exposure of pesticide applicators and farmers to certain agricultural chemicals, and specifically phenoxy herbicides, and an increased risk of non-Hodgkin's lymphoma in farmers. The point is not whether 2,4-D has been or could be conclusively proven to cause cancer in humans. Rather, it was the view of the Panel, as stated in its report, that studies of occupational groups who are exposed to high levels of pesticides for extended periods and over the course of many years may not be useful for estimating risks related to the infrequent and extremely low levels of exposure more typical for the general population. To fail to recognize the importance of this difference in exposure when estimating risks is to ignore the most fundamental and important toxicologic principle of dose-response.

More to the point, the Panel felt that, regardless of the strengths or weaknesses in the experimental data base, the real issue relates to the magnitude of the risk likely to be experienced by the general population as a result of their potential exposure to pesticide residues in fruits and vegetables (potentially significant sources of pesticide residues) as well as any increased risk associated with repeated advice to the public to increase their intake of these food groups. The Panel recognized that, in accordance with widely accepted principles of risk assessment, the important modifier in the assessment of risk for the general population would relate to the exposure component, not the toxicologic properties of the pesticide. To estimate exposure, the Panel examined food monitoring data from Canada, the U.S. nationally, and the state of California. The Panel found that results from the 1994 Agriculture Canada monitoring program revealed that, of the 303,038 samples analyzed, fully 85% of domestic foods and almost 75% of imported foods contained no detectable residues whatsoever. These observations have been confirmed in a more recent Agriculture Canada monitoring program[3] in which almost 90% of domestic and 83% of imported samples contained no detectable residues. The Panel quite properly concluded that the absence of any detectable residues in the large majority of samples certainly supported the view that the general population is most unlikely to be at any meaningful or measurable increased cancer risk as a result of exposure to dietary pesticide residues. More to the point, and in accordance with the views expressed by Drs. Landrigan and Goldman, the Panel recognized and stated the importance of a diet rich in fruits and vegetables as an important cancer reduction strategy and could find no evidence to suggest that increased intake of such a diet would significantly increase exposure to dietary pesticide residues (and hence increase the risk of cancer). The Panel noted that the U.S. National Research Council[4] had previously concluded that there is no evidence that pesticide residues in food contribute significantly to cancer risk in the U.S. More recently, the American Institute for Cancer Research[5] has also concluded that there is no evidence that chemical contamination of food and drink, resulting from the properly regulated use of these chemicals, significantly affects cancer risk. The Panel certainly recognized that children represent a special subset of the population that demand special attention, but noted that no violative residues had been detected in programs that monitored

baby foods.[6] The Panel certainly agrees with Drs. Landrigan and Goldman that continuing research to reduce cancer risks is important. Equally, as noted in its conclusions, the Panel agreed with Drs. Landrigan and Goldman on the importance of a strong regulatory framework in assuring the availability of a safe food supply and the importance of a diet rich in fruits and vegetables in our fight against cancer.

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