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Information for Contributors appears on pages 37–39 of the 7 January 1994 issue. Editorial correspondence, including requests for permission to reprint and reprint orders, should be sent to 1333 H Street, NW, Washington, DC 20005.
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LETTERS

Reacting to Gasoline Additives

The short article "Alaskan illnesses remain a mystery" (Random Samples, 14 Jan., p. 177) states that the U.S. Environmental Protection Agency (EPA) has dismissed the gasoline additive methyl tertiary butyl ether (MTBE) as a possible cause of illness in Alaska. However, some health officials have not. In November 1992, after complaints were received from residents in Fairbanks, Alaska, epidemiologic studies were undertaken jointly by the Alaska Division of Public Health and the National Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. These studies found an association between exposure to oxygenated gasoline and the reporting of symptoms such as headaches, dizziness, and nausea. Higher amounts of MTBE were detected in the blood of persons exposed to motor vehicle exhaust or gasoline fumes in Fairbanks during the period of oxygenated fuel use than were detected after its use was suspended (*1*). Evaluation of the data resulted in a decision to not use MTBE in Alaska during 1993 and 1994 pending results of additional research.

MBTE is added to fuels to reduce carbon monoxide and smog. But smog is not a problem in Alaska. Both Anchorage and Fairbanks have implemented comprehensive inspection and maintenance programs and other measures to improve ambient air quality. Carbon monoxide levels have fallen dramatically in the past decade. During the past several years, each city has experienced only a few days in which EPA carbon monoxide standards were exceeded.

More research on MTBE is needed, as more than 100 million Americans are being exposed to MTBE and its combustion products. Unfortunately, federal funding for further study has not been made available to CDC or to the Alaska Division of Public Health, leaving the EPA and state and local communities with scant data about the use of MTBE at arctic temperatures to assist in developing strategies for the upcoming winter season.

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1. R. L. Moolenaar, B. J. Hefflin, D. L. Ashley, J. P. Middaugh, R. A. Etzel, in preparation.

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Is Dioxin a Human Carcinogen? (Continued)

Alex Apostolou (Letters, 7 Jan., p. 14) states that "[d]ioxin's link with human cancer has not been established." His letter was prompted by Ann Gibbon's statement (Research News, 26 Nov., p. 1373) "[i]n human beings, there is evidence that high doses of [dioxin] cause cancer. . . ." Gibbons in turn responds to Apostolou's letter by citing five recent epidemiological studies that "show an increased risk of cancer for humans who have been exposed to high concentrations of dioxin" (Letters, 7 Jan., p. 14). These studies (*1–5*) leave much to be desired in terms of confirming such a risk.

Fingerhut *et al.* (*1*) in the abstract of their paper state, "[e]xcess mortality from all cancers combined, cancers of the respiratory [system], and soft tissue sarcoma may result from exposure to TCDD [dioxin], although we cannot exclude the possible contribution of factors such as smoking and occupational exposure to other chemicals." Further, in an editorial accompanying the paper, J. C. Bailar states (6, p. 260),

> Fingerhut *et al.* . . . present a new study of the matter. Results are again equivocal . . . the differences were for the most part not statistically significant, and the exceptions might be explained by a combination of small, unavoidable biases in the data and the multiple post hoc comparisons. (Examine enough data at the usual 5 percent level of significance, and about 1 time in 20 you will find a statistically significant result where there is no real effect.)

This fallacy I refer to as "Bailar's syndrome."

The Bertazzi study (*2*) of Seveso accident victims in Italy is difficult to summarize with so many different tumors showing an increased, and others a decreased, incidence of different types of cancer. Further, three population zones with different exposure concentrations were analyzed. The zone with the highest concentration had no increased cancer incidence, and this was attributed to a "small population size, youth of the subjects, and short follow-up period"

(2, p. 404). In a lesser exposed group, the "mortality findings were only suggestive of a possible involvement of the hematopoietic system" (2, p. 404). On the other hand, breast cancer was decreased in the two highest zones of concentration, and "endometrial cancer showed a remarkable decrease" (2, p. 404). I am afraid that at most what we have here is a case of Bailar's syndrome.

Kogevinas *et al.* state (3, p. 549) that "[i]n women with probable exposures to TCDD, a statistically significant excess in occurrence of all cancers was observed . . . based on nine cases. . . ." Two of the nine cases had a [l]atency and length of exposure until diagnosis of cancer" of less than 1 year (3, p. 550). Three others had a latency of 1 to 4 years. These are extraordinary short latency periods. Further, three cases were melanomas from New Zealand; Kogevinas *et al.* (3, p. 552) note parenthetically that, for melanomas, "[t]he main identified risk-factor . . . is ultraviolet radiation."

Manz *et al.* (4, p. 963) state that "[t]he increase in cancer risk . . . that we found . . . cannot be explained completely by confounding factors, and our results suggest that this increase is associated with exposure to TCDD." Aha! you say, but Manz *et al.* continue (4, p. 963), "[e]xposure to chemicals other than TCDD also occurred in different areas of the plant, and some of these are known or suspected carcinogens. Benzene was used extensively. . . ."

In the last sentence of their summary Zober *et al.* (5, p. 139) state that "[i]n general, our results do not appear to support a strong association between cancer mortality and TCDD, but they do suggest that some hazard may have been produced."

It is well over 40 years since occupational exposure to dioxin first began for workers, and by now better evidence certainly should have been apparent for a human carcinogenic effect. We shall have to wait, in vain I fear, for the definitive epidemiological study.

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2. P. A. Bertazzi *et al.*, *Epidemiology* **4**, 398 (1993).
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4. A. Manz *et al.*, *Lancet* **338**, 959 (1991).
5. A. Zober *et al.*, *Int. Arch. Occup. Environ. Health* **62**, 139 (1990).
6. J. C. Bailar III, *N. Engl. J. Med.* **324**, 260 (1991).

Cell Transplantation and Research Design

As a neuroscientist studying the plasticity of aging dopamine neurons, I applaud the review committee of the National Institute of Neurological Disorders and Stroke for having the courage to finally fund an adequately controlled study [to be conducted by Curt Freed at the University of Colorado Health Sciences Center and others (*1*)] on the usefulness of fetal brain cell transplants in Parkinson's disease patients, as reported by Jon Cohen ("New fight over fetal tissue grafts," News & Comment, 4 Feb., p. 600). The field of brain cell transplantation, particularly in primate brain, is replete with studies that shed confusion rather than light on underlying mechanisms. Equally lacking is a credible body of data showing that transplants of any kind work in aged as opposed to young brains, even in rodents (*2*)—seemingly a prerequisite for transplantation into aged humans with Parkinson's disease.

The investigators who protest the funding of a single large fetal transplantation study at this time (Letters, 11 Feb., p. 737) appear to be howling mainly with self-interest. The last thing we need is yet more "smaller" studies with multiple approaches, inadequate controls, insufficient sample sizes, and unblinded short-term follow-ups. I wholeheartedly agree with Freed's experimental design, which uses double-blinding (neither the patients nor the investigators will know who is receiving the transplants) and sham operative procedures (a small burr hole will be drilled into patients' skulls, without the subsequent transplantation of cells) in an attempt to eliminate any "placebo effect." Not only is sham surgery (with informed consent) ethical, it is absolutely essential. I would consider it unethical to carry out investigations with invasive procedures whose results would be scientifically uninterpretable.

It is time for surgical procedures to be scrutinized by the same standards to which pharmaceutical agents are held, those of safety and efficacy. Freed may be taking an important first step in the best interest of patients with Parkinson's disease.

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References and Notes

1. The study is being done collaboratively with Stanley Fahn of New York's Columbia-Presbyterian Medical Center and David Eidelberg of Cornell University.
2. I. Date, S. Y. Selten, D. L. Felten, *Exp. Neurol.* **107**, 197 (1990).

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