GILLIS — Edwin J. Gillis, M.D., of Westfield, died on April 18 at the age of 89.

Dr. Gillis received his degree from Tufts College Medical School in 1931. He was a member of the American Medical Association and the Society of Abdominal Surgery. Dr. Gillis was a 50-year member of the Massachusetts Medical Society.

HEERDEGEN — Dorothy K. Heerdegen, M.D., of Jamaica Plain, died on April 8. She was 85.

Dr. Heerdegen graduated from Ohio State University College of Medicine in 1937. She was a member of the American Medical Association and the American Society of Anesthesiologists.

KELLEY — Robert Aloysius Kelley, M.D., of Springfield, died on May 3. He was 75.

Dr. Kelley received his degree from the University of Rochester School of Medicine–Dentistry in 1947. He was a member of the American Medical Association and the American Urological Association. He was also a fellow of the American College of Surgeons.

LIMENTANI — Davide Limentani, M.D., of Waban, died on May 3. He was 76.

Dr. Limentani received his degree from the Facolta di Medicina e Chirurgia dell'Universita di Roma, Italy, in 1939. He was a member of the American Psychiatric Association. Dr. Limentani was a professor at Tufts University School of Medicine.

O'TOOLE — Francis Austin O'Toole, M.D., of Clinton, died on April 29 at the age of 81.

Dr. O'Toole received his degree from Tufts College Medical School in 1935. He was a member of the American Medical Association, the American Academy of Otolaryngology — Head and Neck Surgery, the American Academy of Facial Plastics and Reconstructive Surgery, the American Academy of Otolaryngic Allergy, the American College of Allergy and Immunology, and the American College of Surgeons. Dr. O'Toole was a 50-year member of the Massachusetts Medical Society.

PAINE — David Paine, M.D., formerly of Belmont, died on April 20 at the age of 86.

Dr. Paine received his degree from Syracuse University College of Medicine in 1931. He was a member of the American Lung Association. Dr. Paine was a 50-year member of the Massachusetts Medical Society.

STRACHAN — Harry L. Strachan, Jr., of Longmeadow, died on April 6. He was 89.

Dr. Strachan received his degree from Harvard Medical School in 1935. He was a member of the American Medical Association and the American Society of Anesthesiologists. He was also a 50-year member of the Massachusetts Medical Society.

TURNER — John William Turner, M.D., of Longmeadow, died on May 4. He was 78.

Dr. Turner received his degree from Baylor College of Medicine in 1934. He was a member of the American Cancer Society, the American College of Nuclear Medicine, the American College of Radiology, the American Roentgen Ray Society, and the Society of Nuclear Medicine. Dr. Turner was a 50-year member of the Massachusetts Medical Society.

CORRESPONDENCE

DIOXIN AND MORTALITY FROM CANCER

To the Editor: The lessons that Dr. Bailar gleaned from the recent dioxin study by Fingerhut et al. of the National Institute of Occupational Safety and Health (Jan. 24 issue)[1] reached far beyond, and at times contradicted, what the authors presented.[2] Moreover, Bailar did not acknowledge the growing body of evidence suggesting that low-level dioxin exposure does not present a risk of cancer in humans.

The study by Fingerhut et al. was designed to test hypotheses regarding dioxin exposure and stomach, liver, and nasal cancers, Hodgkin's disease, and non-Hodgkin's lymphoma. No significant elevations in mortality from these cancers were identified. An apparent excess of soft-tissue sarcoma was an equivocal finding, because pathological examination showed two of the four cases not to be soft-tissue sarcoma. Moreover, the soft-tissue sarcomas in the study were discussed in previous epidemiologic studies; the report by Fingerhut et al. did not provide new or confirming evidence.

The reported excess in mortality from all cancers is a case of combining apples and oranges. Cancers at various sites are different diseases. We know of no instances in which a carcinogenic agent has caused a generalized increase in cancer overall. In fact, in the key animal bioassay by Kociba et al.,[3] which has been used universally to establish carcinogenic potencies for dioxin, an overall deficit of cancer was observed.

The reported excess of respiratory cancer is difficult to link to dioxin because the investigators were unable to control adequately for smoking and for occupational exposure to other substances. On average, members of the high-exposure subcohort were theoretically exposed to dioxin for only 6.8 years but were employed at the plants and therefore subject to other exposures for 19.2 years. Exposure to dioxin was not the predominant type among the cohort.

The study addressed high levels of occupational exposures and found no conclusive evidence of cancer risk even at these levels. This result is very reassuring in regard to exposure to low levels of dioxin and is also consistent with the concept — presented at an international Banbury Center Conference in 1990 — that dioxin

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toxicity is receptor-mediated and therefore has a practical effect threshold.

Dioxin has been well studied and appears not to be as dangerous as once feared. Certainly, there is strong evidence suggesting that exposure to low background levels of dioxin may not be dangerous at all.

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1. Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. N Engl J Med 1991; 324:212-8.
2. Bailar JC III. How dangerous is dioxin? N Engl J Med 1991; 324:260-2.
3. Kociba RJ, Keyes DG, Beyer JE, et al. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol Appl Pharmacol 1978; 46:279-303.

To the Editor: The paper by Fingerhut et al. is not a single study but a meta-analysis of 12 cohorts, each with unique exposures to substances other than dioxin. Like many such cohorts, those studied by Fingerhut et al. had limited exposure data. The levels of dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD) in 253 survivors from 2 plants and the correlation with years of exposure may be valid for survivors in those 2 plants but say nothing of other plants, where exposures probably differed, given the diverse processes in the 12 plants.

For cancers for which the authors had a priori hypotheses, the only significant elevation in the standardized mortality ratio (SMR) — for cancers of connective and soft tissue — was found in a subcohort with only three such deaths. Because of the small numbers, and because half of certified soft-tissue sarcomas failed to pass tissue review, a causal association was not supported. The SMR for lung cancer became nonsignificant when adjusted for smoking. Since one cannot accurately adjust the SMR for 5172 workers at 12 plants on the basis of data on 233 surviving workers at 2 plants, however, no conclusions can be drawn concerning dioxin and lung cancer.

A single plant had significant increases in cancer of all sites. However, meta-analysis of all 12 cohorts changes a series of mostly nonsignificant excesses and deficits into a statistically significant meta-SMR. Interpreting this finding as causal ignores Bradford Hill's criteria of specificity, dose/response, and consistency.*

The authors consider their data consistent with TCDD's being a carcinogen. However, the data are also consistent with exposure of some cohorts to other carcinogens, differences in cigarette smoking, and chance. The study is limited in power by the small size of the cohort; it would have been useful if the authors had provided power calculations for specific sites.

The Bailar editorial also requires comment. It is not apparent that "there is some weakening of the position of those who believe that low levels of exposure to TCDD are entirely safe for humans." First, Fingerhut et al. point out that "the exposure of our cohort was substantially higher than that of most nonoccupational populations." Second, no responsible scientist is ever likely to say that any exposure to anything is "entirely safe." Finally, in explaining his tilt toward a causal relation, Bailar hazards a risk assessment based on three deaths of questionable diagnosis.

The Scottish verdict "not proven" appears to apply best here.

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*Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965; 58:295-300.

To the Editor: The study by Fingerhut et al. seems to corroborate our earlier finding of an association between soft-tissue sarcoma and exposure to dioxins, especially TCDD, or chemicals that may have been contaminated with dioxins.[1-4] The results may also be taken to suggest a general carcinogenic effect of TCDD. Moreover, the risk appears to have increased with exposure time as well as latency period.

Table 1. Mantel–Haenszel Odds Ratios for Soft-Tissue Sarcoma among Persons Exposed to All Dioxins, TCDD, and Dioxins Other than TCDD in Four Case–Control Studies Involving 434 Cases and 948 Controls.*

SUBSTANCE AND VARIABLE	NO EXPOSURE	EXPOSURE <1 YR†		EXPOSURE ≥1 YR	
		LATENCY 5–19 YR	LATENCY ≥20 YR	LATENCY 5–19 YR	LATENCY ≥20 YR
All dioxins					
No. of cases	352	24	34	3	21
No. of controls	865	22	52	0	9
OR	1.0	2.4		6.4	
90% CI	—	1.7–3.4		3.5–12	
TCDD					
No. of cases	352	18	22	1	5
No. of controls	865	14	25	0	2
OR	1.0	3.0		7.2	
90% CI	—	2.0–4.5		2.6–20	
Other dioxins					
No. of cases	352	6	12	2	16
No. of controls	865	8	27	0	7
OR	1.0	1.7		6.2	
90% CI	—	0.98–2.9		2.9–13	

*OR denotes odds ratio, and CI confidence interval.

†All subjects were exposed for at least one day. Data for latency periods were combined to determine the odds ratios.

Our studies have been criticized because we found no apparent dose–response relation. However, such analyses were not feasible because of the small number of exposed persons in each study. We have now aggregated the data from four similarly designed studies and have reanalyzed them using the same criteria for duration of exposure and latency period as Fingerhut et al. (Table 1). When the data were stratified according to study, this analysis showed an effect of duration of exposure (in years) both within the exposed categories and with regard to trend. The result of the Mantel–Haenszel extension test for trend was significant ($P<0.01$) for all strata. As indicated in Table 1, a separate analysis was also performed including data on exposure to dioxins other than TCDD. Similar effects were found, indicating that there is also a need for studies on the carcinogenicity of dioxins other than TCDD in humans. Indeed, hexa-CDD has been shown to be carcinogenic in animals, also inducing soft-tissue sarcoma.[5,6]

It is also of interest that results are on the way from the International Agency for Research on Cancer registry of persons exposed to phenoxy herbicides, chlorophenols, and their contaminating dioxins. The preliminary results[7] again show an increased risk of soft-tissue sarcoma, influenced by latency period; this is certainly an interesting finding in view of the fact that both these cohort studies were undertaken to see whether the findings of the positive case–control studies could be confirmed.

Thus, the results of our case–control studies together with those of the cohort investigations by Fingerhut et al. strongly support the view expressed by Bailar in his editorial that for now TCDD must be regarded as a human carcinogen, at least in regard to soft-tissue sarcoma.

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2. Eriksson M, Hardell L, Berg NO, Moller T, Axelson O. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med 1981; 38:27-33.

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5. National Toxicology Program, Carcinogenesis Testing Program. Bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins for possible carcinogenicity (gavage study). National Cancer Institute carcinogenesis technical report series no. 198. Washington, D.C.: Government Printing Office, 1980. (DHHS publication no. (NIH) 80-1754.)
6. *Idem.* Toxicology and carcinogenesis studies of two pentachlorophenol technical-grade mixtures in B6C3F$_1$ mice. National Cancer Institute carcinogenesis technical report series no. 349. Washington, D.C.: Government Printing Office, 1989. (DHHS publication no. (NIH) 89-2804.)
7. Kogevinas M, Saracci R, Bertazzi PA, et al. The IARC international register of persons exposed to phenoxy herbicides and contaminants. Presented at the 23rd International Congress of Occupational Health, Montreal, Canada, September 27, 1990.

To the Editor: The recent study by Fingerhut et al. looked at cancers in workers exposed to TCDD in the manufacture of trichlorophenol. Neither the previous studies cited nor the study in question actually measured exposure in the occupational cohort under study. Since risk is dose-dependent, the conclusion that the existence of a high relative risk among such workers was not confirmed is not warranted.

It is interesting to compare the cancer rates reported in the Fingerhut study with the rates that would have been predicted by risk-assessment techniques that extrapolate from toxicity testing in animals. We used a pharmacokinetic model to calculate past dosages and constructed three scenarios for workers with at least 1 year of employment in "exposed" areas, assuming that the serum TCDD levels in the 2 plants reported by Fingerhut et al. were representative of those in all 12 plants, using the reported half-life of 7 years for TCDD in human serum[1] and assuming that the workers weighed an average of 70 kg, had a mean of 7 years of employment, and had an estimated median of 21 years since employment.

Scenario 1 (worst case): the worker with the maximal serum TCDD level measured, or approximately 3.4 ng of TCDD per gram of fat.

Scenario 2 (average case): the worker with a serum TCDD level equal to the median TCDD level found in the two plants where measurements were taken (0.25 ng of TCDD per gram of fat).

Scenario 3 (best case): the worker with a serum TCDD level equal to the minimal TCDD found in the two plants where measurements were taken (0.01 ng of TCDD per gram of fat).

The number of excess cancers can be computed from the data presented in the paper. For the group with more than 1 year of exposure and more than 20 years of latency, the excess numbers observed were as follows: all cancers — 36 per 1520 (2.4 per 100); cancers at "other sites" — 9 per 1520 (5.9 per 1000); and soft-tissue sarcoma — 2.7 per 1520 (1.8 per 1000).

The Environmental Protection Agency (EPA) has used a linear multistage model to derive a unit cancer-risk number on the basis of the results of toxicity testing in animals.[2] In the case of TCDD, the EPA used tumors of the lungs, liver, hard palate, and nasal turbinates in female rats. The EPA unit cancer risk for a 70-year lifetime exposure is 1.56×10^5 $(ng/kg \cdot day)^{-1}$. To calculate the predicted rate of excess cancer for a seven-year exposure, we assumed a seven-year exposure (the median).

For the three scenarios it is therefore possible to estimate the daily work-related dose, predict the number of excess cancers over a seven-year period, and compare the predicted number with the number observed in the epidemiologic study, as follows:

Scenario	Dose (ng/kg/day)	Excess Cancers Predicted/ Persons Exposed/7 Yr
1	2.9	4/100
2	0.22	3/1000
3	0.0087	1/10,000

Thus, between 1 per 10,000 and 4 per 100 excess cancers are predicted, with a median estimate of 3 per 1000. This is very close to the observed rate of 2 per 1000 for soft-tissue sarcomas alone.

In conclusion, the data presented by Fingerhut et al. seem to support the current numbers that are used by the EPA to regulate dioxin exposure. They do not support a conclusion that dioxins are less carcinogenic to humans than to animals. Recently, there has been speculation that because dioxins cause cancer by receptor-mediated mechanisms, methods used by regulatory agencies may need to be revised.[3] These data indicate that, at least in this dosage range, the linear multistage model comes close to predicting the number of excess cancers in humans. It would be interesting to see whether these conclusions were borne out by calculations from individual rather than median exposure levels and times.

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1. Poiger H, Schlatter C. Pharmacokinetics of 2,3,7,8 TCDD in man. Chemosphere 1986; 15:1489-94.
2. Environmental Protection Agency. Health assessment documents for polychlorinated dibenzo-p-dioxins. Washington, D.C.: Office of Health and Environmental Assessment, 1985. (EPA/600/8-84/014F.)
3. Roberts L. Dioxin risks revisited. Science 1991; 251:624-6.

The above letters were referred to the authors of the article and editorial in question, who offer the following replies:

To the Editor: Bailar was prescient in predicting that "parties on both sides of the continuing debate . . . will no doubt cite this work in support of their positions." Carlo and Sund, as well as Morgan, suggest that our study does not support a causal association between soft-tissue sarcoma and exposure to TCDD, but Hardell et al. conclude the opposite. Our opinion is that qualifications must be recognized in interpreting our results regarding soft-tissue sarcoma, largely because of the small numbers and the misclassification of deaths on death certificates in both the cohort and the general population. Additional follow-up in future years may provide more information about our finding. Carlo and Sund conclude that "there is strong evidence suggesting that exposure to low background levels of dioxin may not be dangerous at all," but Goldman et al. conclude the opposite, on the basis of their comparison of our study with animal toxicity data. We reiterate that our high-exposure group had a 46 percent excess of all cancers combined, not a meager shift. Because quantitative risk assessments incorporating our data on humans have not yet been completed, we think it is premature to conclude that TCDD is not harmful at low levels of exposure.

Carlo and Sund state that they are unaware of instances in which a carcinogenic agent has caused an increase in total cancer. Although such increases have been found in some cohorts (e.g., those exposed to chloromethyl ethers,[1] asbestos,[2] and uranium[3]), the excess is generally accounted for by the substantial excess of cancer at a single site. We agree that our cohort is unusual in demonstrating an excess in total cancer not attributable to an overshadowing excess of cancer at one site, but we note that TCDD has produced cancers at a number of sites in animal studies.

Morgan suggests that our paper describes a meta-analysis of 12 cohorts rather than a single study. Louis et al.[4] define a meta-analysis as a study "using the results of collections of research papers to answer specific questions, usually in a quantitative manner." Our study was not a meta-analysis. We identified the workers who worked in similar processes at the 12 companies, and we coded and analyzed all data according to a common protocol. Morgan also points out a common limitation of occupational epidemiologic studies: limited information about exposure. We provided more than the usual estimate of exposure because we reviewed the chemical processes used, because substantial information was available in the work-history records, and because the very long half-life of TCDD made it possible to include biologic measurements made long after

the exposure ceased. Epidemiologic studies, although not perfect, provide valuable information with which to make more rational public health decisions.

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4. Louis TA, Fineberg HV, Mosteller F. Findings for public health from meta-analyses. Annu Rev Public Health 1985; 6:1-20.

To the Editor: Carlo and Sund complain that I "reached far beyond, and at times contradicted" the report by Fingerhut et al. The latter authors are perhaps better judges of this matter than Carlo and Sund, and Dr. Fingerhut has assured me that I have neither contradicted their findings nor made unjustified inferences from their data. Nor do I find any growing body of evidence that low-level dioxin exposure is entirely safe. Taken as a whole, the evidence now points rather sharply toward a real risk. The evidence is not conclusive, as I tried to make clear, but Carlo and Sund seem not to understand that the absence of conclusive proof of an effect is a far different thing from conclusive proof of its absence. Nor do they seem to understand that many carcinogenic chemicals have effects on multiple organs (an example close at hand is TRIS in mice), or that an elevation in the overall incidence of cancer in exposed persons logically entails an increase in cancer at one or more specific sites, whether the rates at those sites reach the usual levels of statistical significance or not.

Morgan concludes with the Scottish verdict of "not proven," and I would agree that dioxin has not been "convicted" beyond a reasonable doubt. But we are not discussing personal guilt or innocence in a context of law and justice. Less rigorous standards of proof are therefore appropriate. Is there sufficient evidence to take some action to protect persons from exposure and to attempt to make them whole if they are exposed and later have certain adverse health outcomes? Yes. The range of such outcomes is narrow, but on present evidence an "average" soft-tissue sarcoma in an "average" exposed worker is more likely than not to have been caused by the exposure. The letter from Hardell et al. substantially reinforces this conclusion.

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CARDIAC HYPERTROPHY IN ATHLETES

To the Editor: The echocardiographic study of Italian athletes by Pelliccia et al. (Jan. 31 issue)[1] provides unique and valuable information about the effect of nonpathologic workloads on heart size in humans. Because this type of data is not readily available, I would request that the authors provide three additional pieces of information they may possess. The first is the ratio of wall thickness to ventricular radius (or diameter or "dimension") in the subjects with thickened walls. The second is the resting systolic blood pressure in these subjects. The third is the heart rate and end-diastolic dimension both before and after regression of hypertrophy in the subjects whose heart size diminished when they discontinued training.

Nearly 100 years ago Woods[2] proposed that the Laplace relation would cause ventricular-wall tension to be increased when the radius of curvature increased. He further showed that wall stress (i.e., force divided by cross-sectional area) was held constant if the wall thickness varied in proportion to the radius of curvature. Within a single ventricle, which had a constant pressure throughout, there was a constant thickness:radius ratio. In a review of the literature, I showed that the thickness:radius ratio was directly proportional to systolic pressure over a 2000-fold range of heart size.[3] I found differences in heart size and pressure by selecting studies of different species of animals and studies in which pathologic loads had been placed on the heart. The data on humans were from the study of Grossman et al.[4] Subsequent studies showed that the same relation held when cardiac hypertrophy was reversed by replacing defective heart valves.[5] It would be very informative to know whether these same relations were observed during exercise-induced hypertrophy and its regression.

Paul Dudley White[6] called attention to the inverse relation between athletic conditioning and heart rate in an anecdotal report of his experience with Leslie MacMitchell, once the world record holder for the 1-mile and 2-mile races. MacMitchell's resting pulse rate would range from 37 to 60 per minute as his level of training changed. These kinds of experiences have led to the use of low pulse rates to determine athletic fitness.[7] A possible physiologic explanation for this inverse relation can be found in the earlier work of Clark.[8] In comparing the hearts of a rabbit and a hare, Clark found that the hare, an endurance runner, had a heart that was three times larger than that of a similar-sized rabbit, a short-distance sprinter. The resting heart rate of the hare was one third that of the rabbit, and when the vagus nerves of the two animals were cut, the hare's heart rate increased 4 times, whereas that of the rabbit increased 1.6 times. The explanation of these findings is that endurance athletes grow larger ventricles to provide larger stroke volumes without changing ejection fraction. At rest these larger stroke volumes would cause higher cardiac outputs and therefore higher systolic pressures if the vagal tone were not increased. If the resting cardiac output of the conditioned athlete and the nonconditioned person is the same, the resting heart rate should be proportional to the inverse of stroke volume. If stroke volume is assumed to be proportional to ventricular diameter to the power of 2.5, the heart rate in the deconditioned athletes of Pelliccia et al. should have increased with the inverse of ventricular diameter to the power of 2.5, which in turn should have varied directly with ventricular wall thickness.

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To the Editor: The study of Pelliccia et al. points out the upper limits of physiologic adaptation of left ventricular mass and thickness in highly trained athletes. The authors have assumed that the upper limit of left ventricular mass indexed according to body-