LETTERS TO THE EDITOR

RE: “EPIDEMIOLOGY OF INSULIN-LIKE GROWTH FACTOR-I IN ELDERLY MEN AND WOMEN. THE RANCHO BERNARDO STUDY”

We wish to comment on the article by Goodman-Gruen and Barrett-Connor (1) pertaining to insulin-like growth factor-I (IGF-I) in elderly men and women.

The gain in body fat and loss of lean mass with age and the health effects consequent to these changes in body composition may be related to decreased growth hormone secretion (1-3). However, growth hormone has pulsatile nocturnal secretion, and measurement is difficult in epidemiologic studies. Hence, we have interest in other indicators of growth hormone activity, such as IGF-I, a growth hormone-dependent hepatic protein. Drs. Goodman-Gruen and Barrett-Connor (1) examined the relation of IGF-I to anthropometric measures, body composition, strength measures, and a number of behavioral measures that influence body fat and provided reliability measurements for IGF-I. Their data show that IGF-I levels were lower with age and female sex and higher with greater alcohol use, but their data do not show associations of IGF-I with anthropometry, body composition, or strength as might be expected based on the physiology of growth hormone. They conclude, “...that IGF-I can be used for epidemiologic studies of the role of both IGF-I and growth hormone in morbidity and mortality in the elderly” (1, p. 975). We disagree with this conclusion. The data of Goodman-Gruen and Barrett-Connor and of other studies, including our data from the Framingham Heart Study, suggest that IGF-I is not a valid indicator of growth hormone in old age despite its excellent reliability.

We measured IGF-I as a growth hormone surrogate in the Framingham Heart Study cohort (4) to determine the past health behaviors that contribute to relative preservation of growth hormone secretion in old age. However, we became concerned because several published population studies did not show expected associations of IGF-I with metabolic or behavioral characteristics known to affect growth hormone (5-7). To establish the validity of IGF-I as a growth hormone indicator, we also examined the relation of IGF-I with several of these growth hormone-related characteristics (2) including heavier weight, larger waist circumference, or body fat and lean mass (from dual-energy x-ray absorptiometry). Similar to the data of Goodman-Gruen and Barrett-Connor, none of these measures was associated with IGF-I. Our conclusion was that “caution may be warranted with regard to use of IGF-I as an indicator of growth hormone” (2, p. 133).

Growth hormone and IGF-I may become “uncoupled” with age. In younger people, IGF-I and growth hormone show similar metabolic correlates; in old age, only growth hormone maintains associations similar to those of younger people (8). Furthermore, growth hormone may decline with age, and the IGF-I level may remain constant (9). IGF-I is influenced by factors that affect liver function, including binding proteins (10) and malnutrition (11, 12). In the Framingham data, the strongest associations were among IGF-I, age, and indicators of poor nutritional status.

IGF-I, independent of its relation with growth hormone, may merit study as a biomarker in relation to bone or to other health outcomes (13), but we do not see evidence supporting its use as a growth hormone surrogate in population studies of older persons.

REFERENCES


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Recently, Kogevinas et al. (1) presented an expanded and updated multinational study of 21,863 workers in 36 cohorts exposed to phenoxy herbicides and chlorophenols. Compared with the previous study (2), the updated study added 12 cohorts from the United States and four from Germany and increased (forward and backward) follow-up periods for several of the original cohorts. With these additions, the standardized mortality ratios for all causes and all cancers increased from 0.93 to 0.97 and from 1.02 to 1.06, respectively, for the entire cohort. The investigators also analyzed separately workers exposed to phenoxy herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin or higher chlorinated dioxins and workers with minimal or no exposure to dioxins. For all cancers, a 12 percent excess was noted for workers exposed to dioxins, compared with a 4 percent deficit for those not exposed.

The authors concluded that exposure to dioxins may be associated with a small increase in risk of specific cancers (soft tissue sarcomas and non-Hodgkin’s lymphomas), as well as a small generalized increase in cancer risk. This latter interpretation raises some interesting questions. Apart from the small number of deaths contributing to the excess of soft tissue sarcomas and non-Hodgkin’s lymphomas, the majority of excess cancers appear in smoking-related categories (i.e., cancers of the lung, kidney, bladder, larynx, oral cavity, and other respiratory organs) and not across all specific sites. Curiously, the non-dioxin-exposed group demonstrates deficits for most of these cancers. Were these differences between dioxin exposure groups seen in the original cohorts with increased follow-up, or were they introduced with the addition of the US and German cohorts? Were these exposure groups systematically different other than with respect to exposure, perhaps on age, smoking (despite no observed excess of nonmalignant respiratory diseases), or socioeconomic status?

A sensitivity analysis presented in figure 1 confirms that the addition of the German and US cohorts positively influences the results for all cancers (1). Individuals from these cohorts comprise 35 percent of the total cohort but represent 54 percent of those exposed to dioxins (and only 4 percent of those not exposed). Subsequently, these cohorts contributed a greater percentage of person-years of follow-up, as several were followed from the earliest periods. Any excesses or deficits observed among this group would influence the overall results, and, because of the lack of variability in exposure within cohorts (100 percent of the subjects from the United States were considered "exposed"), exposure effects may not be separable from effects due to other factors. Is a conclusion of “generalized” increased cancer risk justified, when the results may reflect differences (e.g., in exposure and/or lifestyle factors) largely associated with cohorts from one or two countries?

Given the potential weight and importance results of this study are likely to attend (because of the very large overall sample size, the impressive research team, and their prestigious affiliations), it would seem prudent to withhold a conclusion of increased overall cancer risk and to examine more carefully the interesting patterns seen in the results. Not only might this reveal methodological artefacts associated with combining international cohorts, within which there is little or no variability of exposure, but more importantly it might improve our understanding of the carcinogenic actions and risks associated with dioxin exposure. If a generalized increase in all cancers could be convincingly demonstrated, perhaps the role of dioxin as a tumor promoter might be considered. On the other hand, if the risks appear to be small and/or inconsistent or a result of methodological problems, such findings should substantially challenge the popular belief that dioxin is a potent human carcinogen. Without more detailed examination, the study currently raises more questions and doubts than it addresses.

REFERENCES

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THE AUTHORS REPLY
We thank Drs. Mundt and Dell for their interest (1) in our paper on cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins (2). In their letter, Drs. Mundt and Dell question whether the increase in cancer mortality associated with dioxin exposure was due mainly to the inclusion of cohorts from Germany and the United States. There was, indeed, an increased risk of cancer in the
four German and 12 US cohorts, and it is also true that some of these cohorts included highly exposed workers. However, both exposure (see table 2 of our paper) and risk were not homogenous within these cohorts. Six of these 16 cohorts had standardized mortality ratios for cancer below one and, within each individual cohort, there was a variation in risk depending on exposure-related variables such as latency. Because of their large sample size, the 16 cohorts from Germany and the United States weight more heavily than the cohorts from other countries in the overall standardized mortality ratio of 1.12. Taking out the German and US cohorts from the international database results in a slightly lower risk for the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-exposed group, but the standardized mortality ratio for the remaining 11 TCDD-exposed cohorts is still elevated (standardized mortality ratio (SMR) = 1.09, 316 deaths).

Drs. Mundt and Dell also point out that the elevation of cancer mortality associated with dioxin was attributable mainly to smoking-related cancers, and they suggest that smoking may be one reason for the excess risk of the TCDD-exposed group. When evaluating low risks such as that observed it is, indeed, difficult to exclude a potential confounding effect of smoking. As can be calculated, however, from the data presented in table 4 of our paper, the standardized mortality ratio for the smoking-related cancers in the non-TCDD-exposed group was 0.95, which is similar to that for all cancers in this group (SMR = 0.96); the non-TCDD-exposed group had lower standardized mortality ratios for both smoking-related cancers (as defined by Mundt and Dell) and other cancers. The higher standardized mortality ratio for cancer in the TCDD-exposed group (SMR = 1.12) was, in part, due to the higher mortality from smoking-related cancers (SMR = 1.23). However, even for non-smoking-related cancers, mortality in the TCDD-exposed group (SMR = 1.05) was higher than that in the non-TCDD-exposed group. Furthermore, at 20 or more years since first exposure to TCDD, mortality increased for both the smoking-related cancers (SMR = 1.27) and for the non-smoking-related cancers (SMR = 1.14). The difference in cancer risk between the TCDD- and the non-TCDD-exposed groups could be attributed to smoking only if there were marked differences in the prevalence of smoking between the groups, which is unlikely. Furthermore, as indicated in our paper, other indirect evidence suggests that smoking is not a major factor in explaining the increased cancer risk. For example, the standardized mortality ratio for nonmalignant respiratory diseases was below unity in both the TCDD-exposed and the non-TCDD-exposed workers.

Because of uncertainties regarding possible nonoccupational confounders, we did not claim that our results provided conclusive evidence that dioxins are multisite carcinogens, and we were careful to frame the conclusions of our paper in a way that reflected this uncertainty. We also took care to point out that the exposures to TCDD experienced by our cohort were much higher than those that normally occur in the general population. As stated recently by the International Agency for Research on Cancer, "There are few examples of agents which cause an increase in cancers at many sites. This lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution; on the other hand, the lack of a precedent cannot preclude the possibility that in fact 2,3,7,8-TCDD, at high doses, does act as a multi-site carcinogen" (3, p. 337). In support of this possibility, there is clear evidence that TCDD is a multisite carcinogen in animals, that it acts through a mechanism involving the Ah receptor, and that the Ah receptor functions the same way in both humans and experimental animals.

**REFERENCES**

