terms "suitable" and "proximity" would be done with the help of the couple involved.

To get enough job openings into such a system (or to interconnect the existing systems) is likely to be a substantial effort, but the expense conceivably could be borne by affirmative action programs in public and private institutions.

This kind of help for couples in academia could be extended to other kinds of two-career households. One could simply list the locations of the jobs not by institution and institutional proximity but by zip code.

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Nuclear Accident

Peter A. Morris (Letters, 13 July, p. 148) discusses the "eminently safe nuclear operations in the United States" accomplished during the development and application of high-powered nuclear reactors. No mention is made of the SL-1 accident which occurred at the National Reactor Test Station in Idaho on 3 January 1961 (*1*). At the time, the reactor in question was managed by Combustion Engineering, Inc. This accident is notable in that the entire crew of three persons who were on duty died within hours of the event as a result of their injuries. It is important to note that the development of high-powered reactors in this country was not totally free of safety errors, as Morris' letter might suggest.

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Phenacetin Studies

Macklin *et al.* (Letters, 13 July, p. 144) write that phenacetin is not as harmful as the many reports concerning its carcinogenicity would indicate. We are concerned that their letter and the previous one by Cuatrecasas (5 Jan., p. 6) may introduce a number of misconceptions into the literature if left unanswered.

The case reports concerning the carcinogenicity of analgesics containing phenacetin cannot be considered insignificant. Attention was drawn to the carcinogenic properties of phenacetin by the association of the abuse of this drug with the development of a relatively uncommon type of tumor, that of the renal pelvis. More than 140 cases of kidney and bladder tumors have now been reported in the literature (*1*) among abusers of phenacetin-containing analgesics, that is, those taking more than 1 gram per day—the maximum recommended dose of some products that are currently available in this country without a prescription. Phenacetin-containing analgesics are usually of two types: those containing antipyrine (phenazone), phenacetin, and caffeine and those containing aspirin, phenacetin, and caffeine. The mutagenicity of *amino*pyrine is irrelevant, since the patients in the Swedish studies were known to have taken primarily antipyrine-containing analgesics. Phenacetin and caffeine are the ingredients common to all the analgesic mixtures implicated in the above reports of tumor induction in Sweden, Australia, and the United States. There is no reason to believe caffeine is the causative agent.

In studies (*2*) that show evidence of phenacetin carcinogenicity, doses of 500 milligrams per kilogram or higher were administered. Human abusers of the analgesic mixtures often take 20 milligrams per kilogram per day for 20 years or more before kidney failure or tumor formation occurs. Given the fiscal and statistical limitations of experimental carcinogenesis studies, it appears reasonable to administer 500 milligrams per kilogram per day for 2 years to the relatively small numbers of animals usually employed in such tests.

Unlike the studies cited above, the Burroughs Wellcome study of phenacetin effects on C57BL/6 mice has not been published or made available to the scientific community. A single negative experiment with one inbred strain is not definitive, since the animals may have a genetically restricted capacity to carry out the metabolic events crucial to the carcinogenic process. The metabolic events responsible for the carcinogenic activity of a compound are not necessarily those that contribute to its acute toxicity.

The Data Evaluation/Risk Assessment Subgroup of the National Cancer Institute's (NCI's) Clearinghouse on Environmental Carcinogens considered the NCI bioassay (*3*) of an aspirin, phenacetin, and caffeine (APC) mixture to be inconclusive rather than negative. It was unanimously recommended by this committee that APC be considered for retesting in the bioassay program. Urinary tract and endocrine tumors were found that were considered important, al-

though their incidence was statistically insignificant. The use of Fischer rats in these studies may have resulted in an underestimate of the carcinogenic effects of phenacetin, since Fischer rats are known to be relatively resistant to the induction of extrahepatic tumors by aromatic amines (*4*). In contrast, aromatic amines may induce high incidences of mammary and ear duct tumors in Sprague-Dawley rats (*5*). Such tumors were found by Johansson and Angervall in their 1976 phenacetin study (*2*).

The claims made by Macklin *et al.* concerning the use of pelleted diets are speculative. Much of their argument is based on the premise that the melting point of phenacetin is exceeded in the pelleting process. The melting point (mp) of phenacetin given in their letter is incorrect; phenacetin melts at 134° to 135°C (*6*) (273° to 275°F), not at 134° to 135°F. Even if the melting point were reached, they present no evidence that significant degradation would occur or that *N*-oxidation would occur spontaneously.

The argument that the Charles River Formula diet used by Isaka *et al.* (*2*) contains *N*-nitroso derivatives which might be responsible for tumorigenicity overlooks the fact that control animals fed the same formula developed only a small number of tumors. Whether there may be synergistic effects between nitrosamines in commercial feed and test compounds is a matter of some concern (News and Comment, 13 Oct. 1978, p. 192; Letters, 8 Dec. 1978, p. 1034; Letters, 5 Jan., p. 7) that has not been resolved. While there is no evidence that this phenomenon occurred in this instance, phenacetin can act synergistically with at least one carcinogenic nitrosamine in the induction of urinary bladder tumors (*7*). To minimize this carcinogenic effect of phenacetin would ignore the cumulative effects of the exposure of humans to a multiplicity of carcinogens over their lifetime.

Although the structure of phenacetin allows for a number of metabolic reactions that are not possible with 2-acetylaminofluorene, *N*-hydroxylation of phenacetin does occur, and there is reason to believe that this is a vitally important step in the metabolic activation of phenacetin, as it is for 2-acetylaminofluorene (*8*). *N*-Hydroxyphenacetin is both a carcinogen (*9*) and, when enzymatically activated, a mutagen (*10*). The possibility that phenacetin may be nitrosated has received little attention (*11*).

In contrast to the claim by Macklin *et al.*, both phenacetin and *N*-hydroxyphenacetin *have* been demonstrated to be mutagenic to *Salmonella typhimurium* TA 100, with the supernatant (9000*g*) from hamster liver homogenate as the activating system (*12*).

Although phenacetin is not as potent a carcinogen as some others to which we are exposed daily, we believe that its use in nonprescription analgesics should be banned. The ever-increasing body of data from animal and human studies concerning the metabolism, mutagenicity, and carcinogenicity of phenacetin, is impossible to ignore. Swedish and Australian authorities have long since taken action to minimize exposure to phenacetin. The documented cumulative effects of carcinogens argues strongly for the reduction of exposure to phenacetin. Alternative analgesics are available.

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Erratum: In the report by M. E. Trulson and B. L. Jacobs, "Long-term amphetamine treatment decreases brain serotonin metabolism: Implications for theories of schizophrenia" (21 Sept., p. 1295), the column headings "Norepinephrine" and "Tryptophan" in Table 1 (p. 1296) are transposed. The data under "Norepinephrine" should have been listed under "Tryptophan," and vice versa.

Erratum. A News and Comment briefing, "Carcinogens in Scotch" (24 Aug., p. 769), incorrectly reported that carrot and beet juice contain relatively high levels of nitrosamines. So far as is known, they do not. They do contain nitrates and nitrites, the precursors of nitrosamines.