Letters

Wistar Journals

We at the Wistar Institute are extremely appreciative of the generous remarks included in the letter printed in the 14 December issue of *Science* (p. 1256) by the managing editors of the eight scientific journals published by the Wistar Press. These journals, several of which have been published by Wistar since the beginning of this century, are what they are because of the dedication of the editors of the journals. The priorities of the Wistar Institute are such that the subsidies, both direct and indirect, which the Institute has devoted to publishing the journals over many decades can no longer be justified. Subscribers to the journals and the scientific community at large should know that Wistar will continue to ensure that the quality of these journals is maintained while the institution divests itself of the primary responsibility for their publication. Wistar salutes the many editors, past and present, who have made these journals preeminent in their respective fields and assures them and the readers of the journals of Wistar's continuing interest in and support of their efforts. Further, authors and readers of these journals should know that the Wistar Institute has made arrangements to ensure the continued publication of the journals and provision of services to the editorial offices of the Wistar journals.

WARREN B. CHESTON

Wistar Institute,
36th Street at Spruce,
Philadelphia, Pennsylvania 19104

Phenacetin Safety

Vaught and King (Letters, 9 Nov. 1979, p. 637) write that previous letters from our laboratories (5 Jan. 1979, p. 6; 13 July 1979, p. 144) may introduce a number of misconceptions into the literature if left unanswered. After reviewing these letters, we can only conclude that the misconceptions Vaught and King refer to are possibly related to misinterpretation on their part, a lack of clarity on our part, or both.

The mutagenicity of the pyrazolone analgesic aminopyrine (AM) (*1*) is only irrelevant if examined out of context. It is true that, in the majority of reported cases of urinary tract tumors presumably associated with analgesic abuse, which have originated from Sweden, the most frequently identified formulations have contained the pyrazolone analgesic antipyrine (AT), phenacetin (P), and caffeine (C). However, the availability of AM has been widespread throughout Europe (*1*, *2*) and was a component of at least some of the formulations identified in case reports of neoplasia attributed to P in presumed situations of analgesic abuse.

Aminopyrine, AT, or other related pyrazolone analgesics are very frequent components of analgesic formulations containing P (*3*). According to our review, in only 27 of 146 reported cases of renal pelvic carcinoma attributed to analgesic abuse of P can pyrazolone analgesics be excluded. The pyrazolone analgesics have not been adequately tested for carcinogenicity, even though nitroso compounds of both AM and AT, which are easily produced under physiological conditions, are mutagenic (*4*), and coadministration of AM and nitrite in very low concentrations is a potent carcinogenic regimen (*2*). We are unaware of similar studies with AT, but the mutagenicity results suggest a need for such testing. This is reinforced by the report of renal pelvic papillomas in patients who had abused AT alone (*5*). It is incorrect to imply that either AM or AT can be excluded from suspicion on the basis of current knowledge.

Vaught and King are also incorrect when they state that, in studies showing evidence of P carcinogenicity (*6–8*), doses of 500 milligrams or higher per kilogram were administered. This is correct for only one of the three studies (*6*). When one uses the data provided in these reports (*6–8*), an average daily dose of 755 to 1000 milligrams per kilogram and 1160 to 1550 milligrams per kilogram for the groups of animals receiving low and high doses, respectively, can be calculated assuming a body weight range of 300 to 400 grams for (*6*). An average daily dose approximating 200 to 250 milligrams per kilogram can be computed for (*7*) and (*8*). A study in which more than twice the numbers of *both sexes* of the same strain of rat were used [as opposed to females only in (*7*) and males only in (*8*)] and daily doses of 23, 60, and 200 milligrams per kilogram were administered revealed no evidence of carcinogenicity (*9*). In this study 70 males and 70 females were given doses of 200 milligrams per kilogram per day. One would anticipate that if P were carcinogenic, some evidence of this should have been manifest in (*9*).

The criticism of our study as a single, negative experiment with one inbred strain is inappropriate. We provided an average daily dose of 754 milligrams per kilogram of P, using a strain of mouse selected on the basis of P metabolism similar to that of humans. We did not suggest, as implied by Vaught and King, that metabolic events responsible for the carcinogenic activity of a compound are those that contribute to its acute toxicity. The reference to acute toxicity (*10*) was made to demonstrate that nephrotoxicity had been attributed to the P metabolite mentioned. The results of our study will be published in detail in the near future. An extensive manuscript covering both experimental and epidemiological data is also in preparation.

Vaught and King's comments regarding the National Cancer Institute (NCI) bioassay of APC in Fischer rats and B6C3F1 mice may be inappropriate. The summary states that "evidence was not sufficient for the carcinogenicity of APC in Fischer 344 rats and B6C3F1 mice" (*11*). We have calculated average daily doses of a mixture of aspirin, P, and C (APC) administered in these studies as 350 to 450 and 700 to 900 milligrams per kilograms for those rats receiving low and high doses, respectively, and approximately 700 and 1400 milligrams per kilogram for mice receiving low and high doses, respectively. Phenacetin constituted 50 percent of the APC administered.

The papers cited (*12*) by Vaught and King to discredit the susceptibility of the Fischer rat to extrahepatic carcinogenesis by aromatic amines are of interest. First, only females were used to study carcinogens, which included *N*-2-fluorenylacetamide (2-FAA) and its *N*-hydroxy metabolite (*N*-OH-2-FAA). Second, the carcinogens were given intra-