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.

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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-

peritoneally three times a week for 4 weeks or applied topically once to the mammary gland. Third, animals were killed after 12 months. These papers suggest that Fischer rats are inefficient *N*-hydroxylators, that aromatic amine–induced mammary neoplasia does not require the second activation step (sulfonation), and that earlier positive studies in which the doses were given orally to female Fischer rats (*13*) cannot be confirmed. Several points are relevant. The positive study (*13*) with 2-FAA involved dietary administration (as in the NCI study of APC) for 12 months with continued observations until death. Eight of ten female Fischer rats developed hepatic neoplasms (eight of nine survived beyond 178 days), and two of ten developed malignant mammary tumors. Thus, the female Fischer rat can apparently adequately *N*-hydroxylate aromatic amines. Additionally, the female Fischer rat demonstrates adequate hepatic arylsulfotransferase activity to effect the second metabolic step required for hepatocarcinogenesis by 2-FAA and, by analogy, other aromatic amines (*12*). The NCI bioassay thus provided a treatment period adequate to induce hepatic and extrahepatic tumors in female Fischer rats and also used male Fischer rats. Male Fischer rats are used for studying acetaminophen-induced nephrotoxicity, which requires *N*-hydroxylation mediated by cytochrome P-450 (*14*). It has also been reported that daily dietary administration of 2-FAA increases the urinary excretion of *N*-OH-2-FAA ninefold by 18 weeks (*15*). Also, with a given carcinogen, target tissues may differ among species (*16*). Thus, the Fischer rat is obviously an appropriate strain for investigating the carcinogenic potential of aromatic amines, including P.

We obviously agree that aromatic amines may induce mammary and ear duct tumors in Sprague-Dawley rats. However, we did point out that the type of tumors reported in the studies we question have been induced in rodents treated with *N*-nitroso compounds (*17*). The nasal cavities are particularly susceptible to these carcinogens (*17*). It is of interest that, in the Isaka study (*6*), 22 animals given the lowest dose (P = 1.25 percent of diet) developed tumors of the nasal cavities, while only one male developed a urinary tract tumor (a transitional cell carcinoma of the bladder). Nineteen of 20 urinary tract tumors occurred in the group of animals (13 males and 6 females) that received the high dose (P = 2.5 percent of diet). Seventeen of the 18 malignant urinary tract tumors occurred in the group of animals (13 males and 4 females) that received the high dose. A male preponderance of urinary tract tumors has been observed in animals that were given two carcinogenic *N*-nitroso compounds (*18*).

Although our arguments concerning the use of pelleted medicated diets may be speculative, it remains true that only studies employing P-containing diets that had been pelleted demonstrated a potential carcinogenic effect (*6–8*). All other studies, including one (*9*) in which the same strain of rat used in the positive studies was used [with adequate numbers of *both sexes* and doses comparable to those in two of the three positive studies (*7, 8*)] were negative. The melting point of P was listed as a reference point only. Although we stand corrected as to the melting point of P, the pelleting process still generates temperatures that equal or exceed the melting point (*19*). The high temperatures achieved greatly exceed any that would be encountered in the production of analgesic formulations containing P. Such high temperatures also increase the likelihood of reactive *N*-oxidation. Furthermore, according to our review, approximately 97 percent of the cases of urinary tract neoplasia reported to be associated with analgesic abuse and attributed to P were likely to have been associated with abuse of powder (as opposed to tablet) formulations. Tablet formulations are not manufactured under conditions even remotely simulating the pelleting process used to produce the medicated diets containing P for the "positive" animal studies. Thus the positive animal studies do not simulate clinical reality. Those questioning the negative bioassays should demonstrate that the few positive results were not related to the artifactual study conditions.

Vaught and King appear to have missed the point regarding potential *N*-nitroso derivatives in the diet used in the Isaka study (*6*). The obvious points of concern are the combination of nitrites (either added or endogenously produced) in the fish meal component of the diet, the presence of an amine, P, and the pelleting conditions. The combination of these factors provides optimal conditions for nitrosation of an amine to occur. In the Isaka study, P was mixed with the powdered diet, and then water was added (20 percent) before pelleting; the pellets were dried for 2 to 3 hours at 80°C after pelleting (*20*). As a potentially nitrosatable amine was not added to the diet of the control group, we would certainly not anticipate a comparable tumor incidence in the control animals.

The medicated diet (containing 2.5 percent P) used in the Nakanishi study (*21*), cited by Vaught and King as demonstrating that P can act synergistically with nitrosamines in the induction of urinary bladder tumors, was supplied by the same group supplying the diet for the Isaka study (*6*). The likelihood, therefore, is that a pelleted diet prepared in the same manner was also used in this study.

There are many reasons for questioning the validity of the study (*22*) in which *N*-hydroxyphenacetin (*N*-OHP) was identified as a carcinogen. A more appropriate way to investigate the potential carcinogenicity of the presumed P metabolite (*N*-OHP), as it may relate to the carcinogenicity of P in humans, is not to administer the metabolite orally. Rather, the parent drug (P) should be given orally, with metabolite (*N*-OHP) formation occurring after absorption of P. This would duplicate the way humans may be exposed to *N*-OHP. To ascribe any relevance to the potential carcinogenicity of P based on oral administration of *N*-OHP, it would be mandatory to at least demonstrate oral absorption of *N*-OHP. The above "carcinogenicity" study (*22*) did not demonstrate either absorption or elimination of *N*-OHP. In addition, the urinary levels of presumed *N*-OHP metabolites reported were in no way an accurate reflection of the dose of *N*-OHP administered. There is only one report of the formation of *N*-OHP in a human after oral administration of P, and the method used for detection of *N*-OHP was not considered entirely satisfactory because of background interference (*23*). *N*-OHP was not identified in one of the two subjects given P, and only trace urinary amounts of *N*-OHP were identified in the other subject (*23*). *N*-OHP may at some point be definitively identified as a metabolite of P, other than by analogy with other aromatic amines. At that time it would be logical to suggest that the P bioassays have also been *N*-OHP bioassays. In any event it would be reasonable to suggest that P bioassays are appropriate for assessing the potential carcinogenicity of P and its metabolites as it may relate to clinical reality.

The value of mutagenesis testing rests in the identification of potential carcinogens. Confirmation of potential carcinogenicity still depends on the results of appropriate bioassays. All P bioassays, conducted under nonartificial conditions, have been negative. We are indebted to Vaught and King for identifying the first report, however, demonstrating P to be mutagenic (*23*) after metabolic activation. Again, however,

the results of appropriate bioassays are the relevant consideration.

Vaught and King state that the potential nitrosation P has received little attention (*25*). In fact, nitrosation of P was achieved under nonphysiological conditions, whereas under conditions more nearly physiological, nitrosation was quite inefficient (*25*). Perhaps bioassays of nitrosation products of P have already been conducted (*6–8*), as these studies employed extreme and artifactual conditions. We obviously feel that this is a likely possibility. Therefore, the negative bioassays of P and APC, which were conducted under conditions more closely duplicating the manufacturing practices employed in pharmaceutical production and clinical reality, argue strongly against the carcinogenicity of P. We emphasize that AM and nitrosation products of AM and AT, which can be produced under physiological conditions, are mutagenic. We are not aware that bioassays of AM and AT alone or of nitrosation products of AT have ever been conducted. As ingredients in analgesic formulations that may or may not also contain P, neither compound can be removed from suspicion in cases of urinary tract neoplasia presumably resulting from chronic abuse of compound analgesic formulations.

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A Scientist's Tithe?

Edward Wenk's editorial (16 Nov., p. 771) on the responsibility of scientists to devote part of their intellectual energies to informing their fellow citizens about their own fields and advances therein is long overdue. The lesson of Harrisburg is clear. The basic perceptions of the American public have been shaped by the failures of communities—that of the scientists first and of the press second. One needs no further proof of the latter than to examine the very different treatment of the incident in, say, the United States on the one hand (with a free but antinuclear leaning press) and, say, India (with a free but pronuclear leaning press) with Britain in the middle. The "3P" risk equation holds. Perception = Probability × Propaganda. The brokering of science information to and by unaided journalists is surely one of our culture's grossest failures: we have created a nation of tourists in their native technological land.

But what of the scientist's responsibility? Whose fault is it that we have a scientifically illiterate populace? Mainly our own. Our reductionist-specialization model has led us to encourage increasingly narrow training. Our imperial instincts suggested that what we should be concerned with in high schools was making superb curricula so that young scientist-geniuses might bud even earlier. Each professional society recited its Latin masses within its own set, closed not only to laymen, but more and more to other scientists and engineers.

Who was supposed to interpret all this to our colleagues in a university, to our families, to our representatives in government? Not me. I had to write that proposal, give that paper in London, tinker with the new equipment until 3 a.m., seek the recognition of my peers. The Wenk editorial points especially to the responsibility of the professional societies, or every *group* of scientists. And it is indeed astonishing that, even today, the National Academy of Engineering (and the National Academy of Sciences) has no standing committee on the public understanding of technology (and science). I believe, however, that this solution—at the society level—is not enough by itself. The urgency of educating ourselves and our culture to have a more balanced view of science and technology, with all the ambivalence of their impacts on humanity, demands action simultaneously at two other levels of organization.

First, the government agencies and Congress have a responsibility. Supporting research is no longer enough. To paraphrase Oliver Wendell Holmes' famous aphorism about justice: Research must not only be done, it must be known (by the public in broad outline) what has been done. Congress could require every agency and subagency to devote a fixed percentage of their budget to funding multiple-source interpretation of the results of the work it sponsors.

Second, scientists have a responsibility at the personal level. Asking societies, government branches, and agencies to be responsible will not work unless there is a personal commitment to the importance of this part of a scientist-engineer's profession. We must all do our part to share the meaning of our work. In a speech given in 1931 at Caltech, Einstein said (a quote curiously omitted from the centenary celebration):

> It is not enough that you should understand about applied science in order that your work may increase man's blessings. Concern for man himself and his fate must always form the chief interest of all technical endeavors, concern for the great unsolved problems of the organization of labor and the distribution of goods—in order that the creations of our mind shall be a blessing and not a curse to mankind. Never forget this in the midst of your diagrams and equations.

The Judeo-Christian tradition demanded tithing of one's worldly goods. It would not be unfitting if science and technology, the prodigal children of this tradition, continued that demand by requiring each practitioner to give a tithe of time and resources for interpreting her or his craft to the public.

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