LETTERS

Parapsychology—A Correction

I am writing to correct what I said about J. B. Rhine of Duke University in the question-and-answer period after I gave my paper "Not consciousness, but the distinction between the probe and the probed, as central to the elemental quantum act of observation" at the panel session "Physics and Consciousness" on 8 January 1979 at the annual meeting of the AAAS in Houston. The tapes of that session, distributed under the sponsorship of the AAAS, carried my prepared paper. They also carried the two appendices I prepared for my paper when I discovered to my dismay that the other three participants were speaking on the so-called field of "parapsychology." One of these appendices was called "Put the pseudos out of the workshop of science," and the other "Where there's smoke, there's smoke" (both reprinted in the 13 April issue of the *New York Review of Books*, along with my February letter to the board of directors of the AAAS suggesting that the AAAS disaffiliate the Parapsychological Association).

In response to one of the questions from the floor, I unwisely repeated a secondhand, and as it turned out, incorrect account of the experiments of Rhine and McDougall purporting to show that descendents of "educated" rats do better at mazes than the descendants of "uneducated" rats. Rather than repeat here my inaccuracies, let me give references to the literature (*1*) in which the interested reader may get the story correctly.

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I am glad to see John Wheeler's letter of retraction of the charge he made against me in Houston on 8 January and am pleased to have this opportunity to reply. It is also good to know that his statement of retraction will be sent to all those who have already purchased tapes containing a record of Wheeler's charge against me, and further that the Wheeler charge will be deleted from tapes and records of the symposium being distributed by the AAAS in the future.

As may be seen, however, Wheeler's letter does not identify just *what it is* that he retracts; it could be *any* little thing; he vaguely calls it "inaccuracies." I have therefore to insert here a brief abstract of this missing part of the story, condensed from the official taped record:

After Wheeler ended his critical remarks on the Parapsychological Association (PA), he was asked to be more specific. In reply he gave an account of an experiment from McDougall's rat research at Duke of 50 years ago, work in which I had a part. According to Wheeler a postdoctoral assistant in the experiment intentionally altered the conditions so as to produce spurious positive results. However, subsequent consultation with Dr. S, a distinguished geneticist (whose name was given to the audience), led to the disclosure to McDougall of these false-positive results and in consequence they were never published. Wheeler concluded his story at this point by saying "The only thing I haven't mentioned here is the name of the assistant who did the experiment. It was Rhine . . . Rhine—he started parapsychology that way."

No one was present who was prepared to respond to this unscheduled accusation; so it went unchallenged. It was some weeks before I got it from a transcription of the AAAS tape of the seminar. Dr. S., the witness cited, was the first to respond. He rejected the Wheeler charge against me as wholly untrue. I sent his letter to me (which is necessarily confidential) to William D. Carey, the Executive Officer of the AAAS and received on 19 March a prompt and cooperative response from him. In the meantime, Dr. S., however, wrote Wheeler directly to set him straight. Finally, Wheeler wrote me a note of apology (on 20 February) and, on 12 April, he wrote the letter of retraction to *Science* to which I am now replying.

An acceptance of Wheeler's retraction might be expected at this point to wind up this "Houston affair," but for one more item so far not discussed. This is a letter from Wheeler to Carey dated 12 January in which he pursued his plan announced at Houston to "run the 'pseudos' out of the workshop of science." This letter, only 4 days after the "blast-off" in Houston was, of course, based on the impressive case Wheeler was evidently still confident he had made at the seminar in identifying parapsychology as a "pseudo," and for which I had been chosen as an example. The dates show that Wheeler could hardly have known of his mistake at the time he made the appeal to Carey. The collapse of his plan right on the launching pad, as it were, may reasonably be assumed to have left the "Houston affair" to history.

But in science, mistakes are seldom completely fruitless. No sooner had the PA been "read out of the status of eligibility" for affiliation with the AAAS than the new president of the association, Kenneth Boulding, was asked in an interview by the Washington *Star* (9 January) where he stood on the issue of the attack on the PA by Wheeler. These few courageous words of President Boulding as quoted by the *Star* will I think make the Houston meeting of the AAAS a memorable one long after the controversy over the PA affiliation is deservedly forgotten. This is the "Boulding Declaration," as I would like to call it. "The scientific community has to be kept open." "The evidence of parapsychology can't just be dismissed out of hand." "One has to subject their methodology to something." I am "in favor of keeping them in."

These words put new meaning into AAAS affiliation and give this great organization an added responsibility for the advancement of its more difficult, venturesome sciences, such as parapsychology.

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Drug Safety: Phenacetin

The assertions presented by Johansson and Angervall (Letters, 13 Apr., p. 130) to support their point of view that phenacetin (P) is a carcinogen need further examination. The steps between clinical indication of risk and identification of a carcinogen need to be based on sound scientific evidence.

The case reports in the literature associating abuse of P-containing analgesics with renal pelvic tumors can hardly be classified as sound epidemiologic data. At the time of the initial case report associating renal pelvic carcinomas with the abuse of P-containing analgesics (*1*), the results of a negative 2-year study in the Charles River CD rats (Sprague-Dawley) were available (*2*). Phenacetin was administered (20 to 200 milligrams per kilogram per day) in a meal-form (unpelleted) rodent diet. The results of an additional negative 31-month study in Berlin-Druckery rats (>100 mg/kg per day (*3*) were also available.

The Burroughs Wellcome study, mentioned in Cuatrecasas' letter to *Science* of 5 January (p. 6), was initiated after the Bengtsson and Angervall letter to *Lancet* in 1970 (*4*). In this negative 18-month study, C57BL/6 mice were supplied up to 754 mg/kg per day) of P in meal-form (unpelleted) rodent diet; the drug-diet mixes

were prepared fresh weekly, appropriately stored, assayed for P and also found free of phenetidine. Evidence from our laboratories indicated that the metabolism of P to 2-hydroxyphenetidine by this strain of mouse is similar to that of man. This metabolite has been reported to induce renal damage when administered *intravenously* at 160 mg/kg to the hooded rat (*5*).

The National Cancer Institute (NCI) also conducted studies in Fischer 344 rats and B6C3F1 mice (*6*). In these studies, aspirin, phenacetin, and caffeine (APC) were given in meal-form (unpelleted) rodent diet. These unpelleted drug-diet mixes were prepared fresh weekly, appropriately stored, and the purity of the drugs was determined prior to use. Animals were exposed to levels exceeding 500 mg/kg per day, assuming average feed consumption. These studies also did not indicate P or APC to be carcinogenic. The results of two dog studies (*2, 7*) in which P was administered orally at doses of 20 to 450 mg/kg per day for up to 30 months likewise showed no evidence of neoplasia.

The animal studies cited by Johansson and Angervall as showing P to be a carcinogen (*8, 9*) have problems with experimental design sufficiently serious to question their validity. In both studies P was incorporated into a diet which was then either pelleted (*9*) or made into a "cubic diet" (*8*). Such processing, which does not simulate the preparation of analgesic formulations, involves a combination of heat, pressure, and moisture, usually in the form of steam (*10, 11*). Such processing may produce temperatures within the die exceeding 250°F and hotspots within the mash or meal being pelleted easily as high as 275°F (*11*). The melting point of P (134° to 135°F) is thus exceeded, and at these high temperatures reactive *N*-oxidation products can be formed. Moreover, under these artificial conditions chemical reactions between dietary components and degradation products of P created by the pelleting process must also be considered. It is of concern that the diet used in one of these two studies (*8*) (Charles River Formula) contains fish meal, a product which not only has been identified as containing *N*-nitroso compounds but which also contains relatively large amounts of secondary amines and is sometimes "preserved" with nitrites (*12, 13*). Other reactions might occur with degradation products of P in the acidic environment of the upper gastrointestinal tract. The authors do not state the purity of the P used, whether the drug-diet mixes were assayed, how frequently they were prepared, or if and under what conditions they were stored. The type of tumors reported in these two studies (nasal cavity, urinary bladder, ear duct, and mammary gland adenocarcinomas) have all been induced with *N*-nitroso compounds in rodents (*13, 14*). The use of pelleted drug-diet mixes introduces artifacts. Johansson and Angervall fail to mention the negative 86-week study in female Sprague-Dawley rats which they reported in 1976 (*15*). In this article the authors do not indicate if the experimental drug-containing diet was pelleted but do indicate that the 30 controls received pelleted diet without P.

Johansson and Angervall cite a report (*16*) which they believe suggested P may be carcinogenic through a "nitrosation product." The authors of that study state that only very minimal nitrosation could be achieved under physiologic conditions simulating those in the stomach (*16*). Significant nitrosation was accomplished only under very unphysiologic conditions, with the resultant nitrosation product used for tumor studies being stable only at −30°C. The subcutaneous administration of this compound at 100 mg/kg in oil to rats once weekly for 18 weeks produced severe local necrosis, preventing further injections. The local tumors that subsequently developed at the site of injection are apparently those that led Johansson and Angervall to conclude that P is carcinogenic via its "nitrosation product." The relevance of these data to the potential carcinogenicity of P is obscure.

Johansson and Angervall also cite a report (*17*) of liver tumors in rats treated orally with large doses of *N*-hydroxyphenacetin (*N*-OHP), a trace urinary metabolite of P in humans (*18, 19*). When *N*-OHP is exposed to acid or alkaline conditions, as occur in the gastrointestinal tract, it readily hydrolyzes to form *N*-hydroxyphenetidine, which can react nonenzymatically with itself under such conditions to form azo compounds (*20*), or with oxygen to form nitroso compounds (*21*), known inducers of liver tumors (*13*). *N*-OHP is not exposed to such acid or alkaline conditions under normal in vivo metabolic conditions when P is given orally. Considering the instability of *N*-OHP in the gastrointestinal tract, it is unwise to label it a "potent carcinogen" when it is fed in the diet.

The statement by Johansson and Angervall that the Fischer 344 rat is a poor *N*-hydroxylating strain is incorrect. It is inappropriate to use this as an explanation for the negative carcinogenicity study with APC, conducted by the NCI. This strain of rat efficiently *N*-hydroxylates acetanilid compounds and is the strain of choice for studying acetaminophen-induced nephrotoxicity which is considered to require *N*-hydroxylation (*22*).

Concerning the potential carcinogenicity of analgesics in general, Johansson and Angervall have overlooked reports relative to antipyrine (AT) and aminopyrine (AM). Both drugs have been widely used in those countries from which have emerged the overwhelming majority of the case reports of tumors in humans associated with analgesic abuse. In other publications they identify the analgesic mixture involved in Sweden as a powder mixture of P, AT, and C. Aminopyrine is a known mutagen (*28*), and nitroso compounds of both AM and AT, which are easily produced under physiologic conditions, are also mutagenic (*24*). Coadministration of AM and nitrite at very low levels is a potent carcinogenic regimen in rats (*25*) and AM has been demonstrated to be contaminated with nitrosamines (*23*). Phenacetin has not been demonstrated to be mutagenic (*23, 26*) with or without metabolic activation and, as previously cited, does not efficiently "nitrosate" under physiological conditions (*16*). Curiously AM and AT have not been adequately tested for carcinogenicity, even though Schabert *et al.* (*27*) report two renal pelvic papillomas in patients who had abused AT alone. While AT is usually available in analgesic mixtures and not used singly, the same is true with P. There are no similar reports of cancer with P alone.

In previous reports the carcinogenicity of P has been suggested to occur by metabolic analogy with known carcinogens like 2-acetylaminofluorene (2-AAF). Metabolic data (*18, 28*), including covalent binding studies, reveal the behavior of P to be quite different from that of 2-AAF and therefore much less likely to be carcinogenic "if indeed phenacetin is carcinogenic at all" (*32*).

In summary, experimental data are used selectively by Johansson and Angervall to support their conclusions drawn from poorly controlled animal studies and uncritical clinical case reports. Unfortunately, such an approach serves neither science nor the general public welfare.

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Nuclear Reactor Operation

With all due respect for Kenneth S. Pitzer (Letters, 22 June, p. 1263), I would like to comment on organization for safe reactor operation. As one long associated with the achievement and regulation of reactor safety, I know that an acceptable level of risk cannot be achieved by reliance on reactor operators alone, licensed or not.

First, all reactor safety systems should be, and most are, designed to shut the reactor down automatically and immediately, given a condition that could in any way pose significant risk to the equipment, the operating personnel, or the public. Second, redundant and diverse means always are provided to the operator (licensed or not) to initiate such automatic or manual action. What is different for reactors than for aircraft and ships is that these procedures and actions can be and usually are carefully thought out and demonstrated ahead of time—before incidents occur. While several operational errors appear to have taken place in the sequence of events at Three Mile Island, there probably would have been no accident had the plant been operated in accordance with the technical specifications of its license (that is, the valves in the auxiliary feedwater lines were closed when they shouldn't have been during reactor operation). This situation apparently prevailed for at least several days. Perhaps it can be argued that higher standards for education, training, and pay for licensed operators would have precluded this operating condition, but, in my opinion, they would have been totally irrelevant. The only way that an acceptable level of risk can be achieved to conform with the public (and media) perception of that risk compared to already (much greater) accepted risks, is to demand that this risk level be achieved independently of the actions or decisions of any single operator, licensed or not. This can be achieved only by insisting on a number of things, the most important of which is competent management of the operating organization. Corporate management is responsible for safety, just as it is for return on capital investment. Any competent management knows that safety is good business (look, for example, at duPont's 150-plus-year-history in the manufacture of explosives and toxic chemicals). The violations of the technical specifications of the license that took place at Three Mile Island might be ascribed to operator error, inadequate operator licensing requirements, or inadequate training. This would be unjustified. Complying with license requirements is a management responsibility.

The eminently safe nuclear operations in the United States during the development and application of high-powered reactors was accomplished by the duPont Company (the design, construction and operation of the Hanford and Savannah River weapons materials production plants), Phillips Petroleum (operation of the first test reactors at the National Reactor Test Station in Idaho), and the Navy nuclear program under Admiral Rickover. The one distinguishing feature among these very diverse nuclear activities is that each had an organization devoted to safety and technical matters completely separate from that charged with day-to-day operation and maintenance of the facilities. This concept, and its importance, has been increasingly recognized by the U.S. nuclear utilities in recent years, but its full acceptance and implementation has been inhibited by state public utility commissions (motivated by perceived consumer interest) who want to reduce utility expenses and consumer costs by minimizing the utility staff, a traditional reliance of the utility on its supplier, and the fact that individual reactor operator licensing is required by the Atomic Energy Act, to the detriment of a real appraisal of the competence of the licensee organization and management.

The importance of a strong independent technical staff, if not on site or on immediate call, cannot be overemphasized, compared to the impractical requirement of using highly trained operators to perform routine and boring operations for days on end. Should human ingenuity be required—and I believe Three Mile Island underscored that desirability—the combined expertise of a multidisciplinary technical support group, subject to existing management organization and discipline, is clearly superior to that of a "reactor captain."

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Having also been a member of the General Advisory Committee to the U.S. Atomic Energy Commission, I wish to add a few words to Pitzer's letter.

I fully agree with him—we do need "reactor captains" with a deeper knowledge of the functioning of the reactor. But there is another problem with reactor supervising: for days and days the reactor shows no sign of irregularity, and the captain has nothing to do except watch for the occurrence of some irregularity. He becomes bored and, after some time of boredom, pays too little attention to possible signs of trouble. I can relate amusing stories of such behavior—principally, I admit, of guards, not reactor supervisors. But, for the reasons mentioned, it would be important to keep the supervisors awake. This is not a technical problem and requires an understanding of human nature. I propose that supervisors not be left at the same job for too long; that they be asked, quite frequently, to review their experiences to a group of colleagues; and that they participate in regular get-togethers with colleagues and others. I believe such measures would help keep them interested in their functions and also keep them more awake.

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