α2μ-Globulin Nephropathy in White Ravens

In a recent article in *Scientific American*, Woodward and Goodstein (*1*) discussed the handling of data that do not support a given hypothesis. They illustrated their point as follows:

> an investigator might inductively infer, after observing a large number of black ravens, that all ravens are black. According to the inductive approach, good scientific practice consists in recording all that one observes and not just some selected part of it. The guiding ideal is to avoid any error that might slip in as a result of prejudice or preconception.

Later, the authors discussed the falsificationist ideas of Karl Popper in relation to the black ravens: "the observation of a single nonblack raven will falsify the hypothesis that all ravens are black."

Huff (*2*) recently discussed the role of cell proliferation in chemical carcinogenesis. At one point he discussed the ability of certain putatively nongenotoxic chemicals to induce renal cancer in male rats. The section in question is worth quoting in full.

> Meanwhile regulators and administrators should continue to be considerably cautious before embracing a purported mechanism—even a reasonable proposed hypothetical mechanism of carcinogenesis—as being pivotal to public health decisions. One example still garnering considerable debate centers on whether chemicals that induce cancers of the tubular cell epithelium of the kidney in male rats, concomitant with an increase in cell proliferation and testosterone-mediated α-2μ-globulin protein are relevant or useful to overall hazard identification for humans. The U.S. Environmental Protection Agency (for example) has embraced the concept that these experimental carcinogenic responses are not important to the human situation, whereas others (e.g., the Interational Agency for Research on Cancer) appear properly cautious, or have proposed equally reasonable alternative hypotheses. For example, and yet to be clarified, there are several chemicals known to induce this specific nephropathy syndrome that do not cause kidney cancers, and may or may not produce cancers in other organs; this lack of consistency must be explained.

Huff has seen some white ravens, but he has not identified them for other interested parties to study. I too have heard similar rumors, but I have yet to see a convening of the chemical structure, genetic toxicity, hyalin droplet data, and adequate rat cancer bioassay data for such a chemical. Given the importance of the issue under discusion, it would be valuable if Huff were to identify the chemicals to which he referred and present the relevant data for them in a focused paper. This would enable the commissioning of research to elucidate whether the α2μ-globulin male rat renal cancer hypothesis should be retained or abandoned. Equally, when the available data are scrutinized, and perhaps extended, it may be possible to retain the hypothesis for use under qualified conditions; for example, it may be concluded that the persistence or magnitude of the nephropathy, as opposed to its presence, is the critical parameter.

The surest way to make progress in assessment of the hazard posed to humans by rodent carcinogens is for exceptions to current models to be clearly identified and made the subject of active research. In the absence of a range of valid models, there will be only one: namely, that the rodent carcinogens dibenzanthracene and sodium saccharin present the same intrinsic carcinogenic hazard to humans.

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References

1. Woodward J, Goodstein D. Conduct, misconduct and structure of science. Sci Am Sept-Oct:479–490 (1996).
2. Huff J. Mechanisms, chemical carcinogenesis, and risk assessment: cell proliferation and cancer. Am J Ind Med 27:293–300 (1995).

Response: α2μ-Globulin Nephropathy, Posed Mechanisms, and White Ravens

In our zest to discover the holy grail(s) of chemical carcinogenesis—read mechanism(s)—we seem to have short circuited the time-honed pattern of Koch's path of finding/proving scientific truth. As I understand the scientific paradigm of discovery, one must exhaust and counter all possible exceptions to the purported hypothesis before accepting the conjecture as truth. Further, if one exception to the rule persists—white ravens—then the hypothesis is either untrue or, at the most, must be modified to accommodate the uncertainty introduced by the exception. If several and varied exceptions exist, then the putative mechanism must be abandoned or be considered very limited in validity or application. Ashby (*1*) proposes that "it may be possible to retain the hypothesis for use under qualified conditions." Ideally, I have little difficulty with his suggestion; however, in practice, the workability of such nuances is nearly impossible. Recall that "as it happens often in science, a timid suggestion at the end of a discussion, a carefully worded hypothesis, become transformed in the next paper (often by other authors) into a fact" (*2*). Perhaps this is what happened to the α2μ-globulin hypothesis, without the attendant necessary search for white ravens. Some have associated this testosterone-mediated protein with tumors of the kidney in male rats. Importantly, a plausible rationale has yet to be offered to explain why certain α2μ-globulin-provoking chemicals fail to systematically induce renal tubular cell tumors. Early on, in fact, several of us have raised basic issues about this purported mechanism (*3–5*).

Hence, from my personal perspective in the sensitive area of human health and life, one must ignore the scientific urge to retain such tentative and "footnoted" hypotheses because proof, acceptance, and utilization for public health purposes must remain sacrosanct and on a firm foundation, especially when the use of said limited proof allows greater potential risks to be propagated or perpetrated. Nonetheless, the search for mechanisms of carcinogenesis—likely to be chemical specific—must continue.

In this vein, Ashby (*1*) urges me to identify the white ravens in the α2μ-globulin story. As that earlier paper, from which Ashby generously quotes my writing, was a more broadened view of the visible white ravens in the overall hypothesis of chemically induced cell proliferation and cancer (*6*), I did not identify the specific chemical exceptions to the α2μ-globulin hypothesis. I had given the names of those chemicals in previous papers (*7,8*) and did not think them particularly relevant in the cell proliferation paper quoted by Ashby. Further, I certainly believed that those professing the strength of the α2μ-globulin hypothesis would have been aware of these exceptions—aware of them and either explained the discrepancies or simply discounted them. In this communication, the chemicals that disobey the α2μ-globulin hypothesis are given.

I am pleased for the opportunity to list these chemicals, together with brief explanatory passages for each. So far, there are at least four chemicals that instigate the α2μ-globulin-syndrome yet do not induce tumors of the kidney in male rats: gabapentin, an antiepileptic drug; lindane, an insecticide; decalin, a solvent; and trimethylpentane, the prototypical α2μ-globulin inducer present in gasoline. Additionally, another chemical induces the α2μ-globulin sequela but causes two different cellular types of tumors of the kidney (dimethyl methylphosphonate). One