CANCER'S UNCERTAINTIES AND PUBLIC POLICY

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An unusually intractable policy problem of environmental pollution and toxic waste disposal is how to deal with the risk of chemically induced cancer. Many features of this issue make this policy task inherently complex, such that decisions must *necessarily* be made in the context of uncertainty and incomplete knowledge. In other words, analytically "perfect" solutions, of the sort beloved by scientists and engineers, cannot usually be found. Instead, one or another strategy for coping with uncertainty must be employed.

Why *must* science be uncertain about the causes and prevention of cancer? Why, indeed, is cancer a matter of such unique public concern in the first place? And what policy alternatives might be entertained to handle the peculiarities of this problem? This paper will be devoted to these questions.

I. Cancer's Causes: Proofs and Evidence

First a few facts about cancer. It is not a single disease but a large collection of them, which differ one from another in causes, in the particular organ and tissue giving rise to it, in the most effective form of therapy, and in prognosis. Any organ of the body may become cancerous, but the large majority of lethal cancers involve the intestine, the lungs, the breasts, and the sex organs (chiefly the prostate and uterus). Common to all of them is an uncontrolled growth of altered cells that have arisen (some think by mutation) from normal cells. Such malignant cells can invade surrounding normal tissues,

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exerting physical pressure and competing for nutrients. Cancerous growths can also spread, or metastasize, to areas of the body remote from the primary tumor site, repeating their deleterious effects in these multiple new locations.

The salient fact about cancer that accounts for the high degree of public concern is that it is a common and, with some exceptions, largely incurable disease. About one in four or five of us will develop cancer of one type or another at some time in our lives. This is a much larger fraction than used to be the case, although this increase is *not* due to there being a sudden epidemic of cancer attributable to our industrial society. Rather, it is a consequence of the great reduction in mortality from infectious diseases (tuberculosis, diphtheria, pneumonia, smallpox, polio, and others) which public health measures and modern medicine (especially antibiotics and vaccines) have achieved in this century. Now almost everyone can expect to reach the age where cancer, which is largely a disease of the elderly, can develop. Cancer-incidence figures that have been corrected for the larger numbers of people living into old age (called "age-adjusting") show that, with one exception, the overall incidence of cancer has been rather steady or slightly decreasing since 1933, the first year for which all states had to centrally record the causes of all deaths.[1] The exception has been the large rise in respiratory cancer, for which smoking, not "modern industrial pollution and chemical exposures," is by far the largest cause.

Proof of Causation

What is known in general about the cause of cancer? As a chronic disease, cancer is particularly difficult to deal with. The criteria for proof of causation in this case are less rigorous than for infectious diseases, but involve a number of concepts that intuitively strengthen

There are five general principles concerning proof of causation. Often not all of them can be applied to a particular type of cancer, but the more that can be, the stronger is the case for causation. The first criterion that must be met is that exposure to the suspected agent must precede development of cancer. While this may seem obvious, it is often difficult to ascertain when the cancer takes a long time to develop. Over the course of 5, 10, or 20 years, an individual may be exposed to any number of potential carcinogens, each of which could be the cause of cancer. Moreover, once the disease is present, it may

[1]R. Doll and R. Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," *Journal of the National Cancer Institute* 66 (1981): Section 4.1 and Appendix D.

be difficult for an individual to remember what he was exposed to many years ago.

The second principle of causation is that the observed relationship between a substance and a disease in one experiment must be borne out in other experiments. Again, this is difficult to document for humans, because it is not likely that the circumstances surrounding one set of individuals can be replicated. Nevertheless, if the same relationship between cancer and the suspected agent is seen among different, but similar groups of people, it's more likely that the association is real.

Third, the stronger the association between cancer and a particular exposure, the more reliable is the evidence that the agent is responsible for the cancer. This means that as the proportion of those exposed to the agent grows, the more likely it is that the agent leads to cancer. Fourth, to prove causation, the substance should cause cancer in and of itself, without the addition of other carcinogens. It is always easier to prove causation if only one agent, rather than a combination of agents, is associated with the disease. In particular, when more than one agent is suspected, the case for causation becomes obscured by time relationships: We must determine which agents were present first and to what extent each agent is responsible for the disease. With multiple exposures, it may not be possible to tell if one or all of the agents were necessary for cancer to develop. The more specific we can be, the better.

The last principle regarding proof of causation is that a logical mechanism exist by which we can explain how a particular agent causes cancer. A good example of this is lung cancer and cigarettes. The changes that occur in lung tissue exposed to cigarette smoke have been well studied, and the evolution of cancer from this exposure comes as no surprise. The association is further supported by a dose-response effect, where heavy smokers get lung cancer more often than light smokers.

Decisions to ban or regulate the use of potential carcinogens generally rest on how well these five principles of causation can be applied to human data. As fewer criteria are fulfilled, the basis for regulations designed by legislators to control the use of potential carcinogens becomes less rigorous. Scientists can rarely collect human data that fulfill the five principles of causation. Thus, instead of saying that an agent "causes" cancer, we normally say that an agent increases the *risk* of cancer. For example, if a substance is shown to increase the incidence of cancer in humans, this is evidence that the substance is a true cancer-risk factor. On the other hand, if a substance has been

shown to cause cancer only in laboratory animals, it is classified as a hypothetical cancer-risk factor for humans.

The decision about the carcinogenicity of a substance to humans falls on legislators, who must answer three questions: Is the material carcinogenic? How carcinogenic is it? And, how carcinogenic is it to humans? It is well established that our chances of getting cancer are highly influenced by "environmental agents" (see footnote 4). This insight is deduced from the fact that the incidences of particular types of cancer vary greatly from place to place around the globe, and also from time to time. Liver cancer, for example, is common in parts of sub-Saharan Africa, but rare here. Breast cancer is common here but rare in Japan, whereas stomach cancer is common there and uncommon here. That this is not due to a genetic difference is shown by the fact that Japanese immigrants develop within one generation the cancer patterns typical of the United States. Lung cancer, seldom seen at the turn of the century, is now the leading cause of cancer death among men, and is rapidly on the rise among women as well, reflecting the historic smoking patterns among the sexes. Persons of Scandinavian and Celtic descent do not have high rates of skin cancer when living in Northern climates, but do when they move to the tropics (where they are exposed to more sun). By a careful comparison of such variations, the World Health Organization concluded in 1964 that "the majority of human cancer" was influenced by "extrinsic factors."[2] This early estimate has been updated and confirmed: Currently the best estimate is that 75 or 80 percent of human cancer in the United States is influenced by environmental factors.[3] This fact raises the hope that cancer, if not curable, might be preventable, and it has led to extremely diligent attempts to identify the causative agents.[4] It has also resulted in a vast expansion of the regulatory apparatus set up to deal with these hazards.

[2]World Health Organization, "Prevention of Cancer," Technical Report Series 276, Geneva, 1964.

[3]Doll and Peto, p. 1205.

[4]These agents are by no means to be equated with "chemicals" or "pollutants," a common misinterpretation. Instead, the estimate refers to the *total* sources of environmental differences, which are in the main related to cultural and personal practices. Whether or not one smokes, chews betel nut, chooses to reside in sunny climes at high altitude, eats fibrous or fatty or pickled foods or moldy peanuts or corn, drinks alcoholic beverages such as Calvados, is sexually promiscuous or abstemious, or bears one's first child at an early or late age are all factors that have been shown to be correlative with, and in some cases causal to, particular cancers. Only a small fraction of all cancer in the U.S. is presently thought to be attributable to workplace chemicals (4 percent) or to general environmental pollution with manmade chemicals (2 percent). Doll and Peto, pp. 1245, 1251, and Table 20.

Despite the diligence of the effort to find causes, only limited (though extremely important) success has been achieved. Consensus has been reached on the main cause of lung cancer and on a variety of occupational cancers,[5] but in these cases the proportional increase caused by single factors has been quite large. This does not seem to be the case for many common cancers (e.g., breast and colon), which makes it hard to tease out particular causes in these cases. Another difficulty in identifying causes is the stochastic, or statistical, nature of cancer; that is, among a group of similarly exposed persons only some of them, seemingly at random, will actually develop cancer. Not every smoker of high-tar cigarettes contracts lung cancer (in fact, only about one in five does), and not every worker who worked with asbestos comes down with mesothelioma (a rare form of cancer associated almost exclusively with exposure to asbestos). An even greater problem in connecting causes with effects is posed by the long latency of cancer, where a period of one or more decades passes between the commencement of exposure to a causative agent and the manifestation of symptoms.

Types of Evidence and Problems of Uncertainty

There are three main kinds of evidence that are used to try to establish whether or not a chemical poses a cancer hazard to humans: epidemiology, animal bioassays, and short-term tests. Each has advantages and disadvantages.

1. Epidemiology

The first of these, epidemiology, is the study in humans of the patterns of occurrence of disease and of exposure to various suspect agents. This tool has the great virtue that it directly identifies human-risk factors; once a carcinogenic agent has been identified, there are no further problems of fundamental interpretation as there are with animal and short-term tests. But it suffers from several inherent limitations. For one thing, it is not a very sensitive technique, which means that it is difficult to establish small effects with statistical confidence – "small," of course, means proportionally; this could still translate into many thousands of cases annually for a sizable population. This is due, in part, to the difficulty of assembling reliable information on large numbers of people, whether this is by means of interviews or examining medical records. It is also due to the difficulty of eliminating "confounding variables" from the comparison

[5]Doll and Peto, Tables 11 and 19.

groups (i.e., eliminating all differences between the groups to be compared that may be spuriously generating, or concealing, a causal relationship). This can be a problem even when the carcinogenic effect under investigation is large. However, when it is small (such as the suspected effect of saccharin on bladder cancer, or of hair dyes on breast cancer), the problem can be insuperable. The use of large numbers of subjects and great care in matching up the comparison populations can reduce the problem

Epidemiology's usefulness is also reduced by the difficulty of assembling true, zero-dose control groups. For example, if we wanted to test the hypothesis that caffeine was carcinogenic, it would be hard to find a sizable group of people with *no* exposure to caffeine since it is a constituent in coffee, tea, Coke, and many other commonly used foods. One would have to look at groups like the Seventh-Day Adventists; but these individuals' habits differ in so many other ways from those of ordinary people that confounding might occur.

Complicating the limited sensitivity of epidemiology is cancer's long latency, which means that conducting a study among people who currently have cancer entails asking questions about their personal habits and occupational and medicinal exposures two or three or four decades in the past. People's memories that far back are not usually very accurate, and estimates of dose tend to be even less reliable. Multiple exposures to suspect agents are common (diet pops, hair dyes, chlorinated water, X-rays, cigarettes, etc.), so that attribution of a particular instance of cancer to any one of them is difficult. The picture can become even more complex because of the possibility of interaction between suspect agents. (Smoking, for example, greatly increases the already elevated chance that asbestos workers will develop lung cancer, so should we attribute it to the smoking or the asbestos?)

A final, serious limitation of epidemiology is that it cannot help us with new chemicals to which humans have never been exposed, or to which exposure has been occurring for only a relatively short time. (The latency period may not have had sufficient time to pass, so negative results cannot be conclusive, and even a positive finding may underestimate the full effect.) About a thousand new chemicals are introduced into commerce each year, so that this is a significant circumspection.

Despite these shortcomings, epidemiology can be used, even when it has yielded a negative or equivocal result, to set an upper boundary on the risk to humans of substances to which they have been exposed for adequately long periods. For there would be certain levels of carcinogenic activity that *could* have been seen in the study with

statistical confidence had it been present. Not seeing this activity, then, at least says that the suspect substance is not a "strong" carcinogen; it is at most "weak" (the actual numerical meaning to be attached to the words, "strong" and "weak," would, of course, depend on the details of the particular study).

Finally, it must be noted to epidemiology's credit that every human carcinogen now known has been identified by means of epidemiology; this tool has established the very phenomenon of human cancers resulting from environmental exposures commencing many decades before clinical symptoms were evident.

2. Animal Bioassays

Because of the limits of epidemiology, other means are used to identify the human cancer hazards from chemicals. The predominant surrogate currently in use is animal bioassays. These are studies where the suspect chemical is administered to laboratory animals, usually rats or mice, and the animals monitored for the growth of tumors. Typically, the chemical is given to the animals in their food or water (or by stomach tube if the substance is unpalatable) for long periods, often their entire lifetime. The key advantages of bioassays are: Rodents live only about two years so the time required to observe a tumorigenic effect is reduced from decades to two or three years, and one can deliberately test any specific chemical of interest. This is especially important for new chemicals that are being considered for the marketplace. The disadvantages of bioassays, however, are substantial. In particular, these tests are expensive – a thousand dollars an animal for a lifetime study is a typical cost. Thus, a standard-sized test on a single chemical involving an untreated (control) group and low- and high-dose groups with 50 animals of each sex, at each dose (300 animals in all), would cost well in excess of a quarter million dollars. Even such a test, however, would have a limited sensitivity, since it would probably never pick up a chemical that caused a one percent incidence in high-dose males. And, such a chemical might well be declared "safe" even though it would be capable of causing many tens of thousands of cases of cancer a year in humans.

It is to compensate for this limited sensitivity that high doses are commonly employed in animal bioassays. In general, the incidence of cancer will rise as the dose increases, up to the point where the animals are dying off prematurely from simple poisoning. Hence, to make a bioassay as sensitive as possible, a dose will be included that is the maximum the animals can tolerate over their lifetimes without succumbing early from poisoning. This is the so-called "maximum tolerated dose" or MTD.

While this procedure undoubtedly maximizes the chance that even a weak carcinogen will be picked up, it introduces other sources of uncertainty. Perhaps the physiological events taking place in dose-stressed animals do not occur at all, or at least not in proportion, in normal animals. So the outcome observed in highly-dosed animals would not be valid at the much lower doses common in human exposures.

This reasoning leads us directly to the problem of dose response; specifically, to the question of whether the risk at low dose can be estimated by simple extrapolation downwards along a straight line from the risk observed at high dose. Such a risk/dose relation is called a "linear" dose response. And while this may be a reasonable guess when the extrapolated dose is not very far from the experimentally observed dose, one is very uncomfortable with relying on such an estimate when extrapolating to doses 100 or 1,000 times smaller than the experimental dose, as is often the case. The critical question is whether one or more inflection points (or a threshold) exist in the dose-response curve, in which case the true low-dose risk could be much smaller than under the linear assumption.[6]

In theory, one can readily design experiments to find out what actually happens to the cancer rate at low doses comparable to human exposures. However, the incidence of tumors will get small, and so much larger numbers of animals would have to be used in order to detect these tumors with statistical confidence. That would mean doing a test with thousands of animals and multiple doses ranging down to the dose of interest. This would be prohibitively expensive,

[6]There are many theoretical reasons for thinking these must frequently exist. For one, the human organism has evolved in a sea of naturally occurring carcinogens, and has likely developed defenses for coping with these in normal circumstances. In fact, we have direct evidence of such a defense in skin pigmentation, whose level determines sensitivity to UV (sunlight-induced) skin cancers. Another defense is DNA repair, which many identified enzyme systems can accomplish. One genetically caused defect in DNA repair, xeroderma pigmentosum, leads, in fact, to much higher susceptibility to sunlight-induced skin cancer. Other enzymatic systems in the liver are constantly at work cleansing the blood of toxic materials. Any of these systems can be saturated or overloaded by sufficiently high doses, and there is little reason to expect that cancer effects seen only in animals whose normal defense mechanisms have been overloaded by high doses must necessarily be predictive, either qualitatively or proportionately, of the results to be seen at physiologically normal doses. In addition, it is known that some enzyme systems that metabolically *activate* carcinogenic substances are inducible by those same substances. For these, the dose response must be non-linear, curving upwards at high doses. Finally, many apparent carcinogens may be acting by means of "promotion" rather than by "initiation." Practically nothing is known about the dose response of promotion; there is not the slightest theoretical reason for thinking its dose response might be linear in general.

not to mention logistically difficult (e.g., acquiring thousands of animals of identical genetic background and age at more or less the same time, labelling them and maintaining records, and so forth). And, in any case, the test would pertain only to the chemical of immediate interest, so that it would have to be repeated for every chemical investigated. This is clearly impractical on a regular basis; thus, we are reduced to making extrapolations (guesses) about the expected risk of cancer at low doses.[7]

Many thousands of words have been devoted to the problem of estimating low-dose risks from limited high-dose data, and some highly sophisticated statistical models for extrapolation have been advanced. The hard fact remains, however, that the verifiable dose effects are similarly compatible with all of them (not surprising, since the models were developed to fit the available data), and so cannot distinguish between them; yet the models differ by factors of hundreds or thousands in their estimates of the size of the risk to be seen at very low doses. Of all the various models, the linear one is not only by far the simplest mathematically, but it also has the virtue of being the most "prudent"; that is, if its estimates are in error, they are virtually certain to err on the side of *overpredicting* the true risk. This means that if a low-risk estimated by means of the linear model is considered to be negligible, then one can feel quite secure in this judgment. For this reason, the linear model is often adopted as a prudent way of dealing with this profound uncertainty. However, when the estimate yielded by the linear assumption is not so negligible (as is the case with saccharin, where the FDA estimated an annual incidence of about 1,200 cases of bladder cancer per year[8]), the procedure leads to dispute.

The other intractable problem with animal bioassays concerns whether rats and mice can be regarded simply as "little men," or whether there can be, in any specific instance, an important physiological difference in the way rodents and higher primates handle a

[7]Only one such "megamouse" test has been carried out. In brief, the chemical used induced tumors in only two organs, the liver and the bladder. For liver tumors, the incidence at the lowest dose (which was only five times less than the highest dose) was excellently predictable from the incidence seen at the higher doses by a linear model, but for bladder tumors, there was a clear inflection point, and the low-dose risk would have been overpredicted many-fold by linear extrapolation from the higher doses. N. A. Littlefield, J. H. Farmer, D. W. Gaylor, and W. G. Sheldon, "Effects of Dose and Time in a Long-Term, Low-Dose Carcinogenesis Study," *Journal of Environmental Pathology and Toxicology* 3 (1980): 23, 27, and passim. Nature is not yielding her secrets easily!

[8]Office of Technology Assessment, U.S. Congress, "Cancer Testing Technology and Saccharin" (Washington, D.C.: U.S. Government Printing Office 1977), p. 88.

carcinogen. This uncertainty affects both the qualitative outcome (is this chemical a carcinogen in humans?) and the quantitative outcome (can we infer the degree of risk to humans from the degree of risk seen in rodents?). Again, arguments run on both sides of this question and science is not able to offer a definitive judgment, since we are limited to unwitting, and hence almost always unmeasured, exposures for practically all of the human data. The fact that all but one of the proven human carcinogens (the exception is arsenic) have been found also to cause cancer in laboratory animals favors the "little men" argument, at least qualitatively.

The crucial question, however, is: Can we expect, just because we have found conditions under which a chemical will cause cancer in rodents, that it will pose a true risk in man? This question becomes even more unsettling when one cogitates upon the peculiarities of the experimental conditions under which carcinogenicity in animals has often been established (e.g., high dose regimens, or, as in the saccharin experiments, *in utero* exposure). Hundreds of chemicals have by now been shown to cause cancer in animals under one or another set of experimental conditions, including table sugar, pepper and vitamin D.[9] Is is really reasonable to assume on this basis that these substances imperil mankind? One would feel more confident in making such a prediction if a chemical had been tested in several mammalian species and was carcinogenic in all of them (that is, if the qualitative results in any one of them could be used to predict correctly the results in the others). But it is uncommon to have results on the same substance tested in more than two species (usually rats and mice), and even for these two species, discordant results are often seen.[10]

Even with these weaknesses, animal bioassays are the best means we have for assessing a chemical's carcinogenic hazard in those

[9]On the cancer risks from sugar, pepper, and vitamin D, see the following studies.

On sugar: "Tumorigenicity and Carcinogenicity Study With Xylitol in Long-Term Dietary Administration to Mice," Study no. HLR 25/77774, prepared by the Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, for Hoffman LaRoche Co. Ltd., Basel, Switzerland, January 30, 1978. Available from the Food and Drug Administration, Rockville, Md.

On pepper: J. M. Concon, D. S. Newburg, and T. W. Swerczek, "Black Pepper (*Piper Nigrum*): Evidence of Carcinogenicity," *Nutrition and Cancer* 1 (1979): 22–26.

On vitamin D: G. H. Gass and W. T. Alaben, "Preliminary Report on the Carcinogenic Dose Reponse Curve to Oral Vitamin D_2," *IRCS Medical Science* 5 (1977): 477.

[10]In fact, in the famous saccharin rat studies, males but not females developed tumors (of the bladder). Thus, even within a single species under uniform test conditions, males failed to predict the outcome for females. Office of Technology Assessment, pp. 50–60. This weakens the basis for predicting human risk from these results.

instances where we have only poor epidemiology data, or none at all. Some chemicals are such strong and reproducible animal carcinogens that there is consensus among scientists about their hazards. But in general, there is a continuity of results grading smoothly down to situations at the margin of statistical significance, or where there is reason to believe the MTD has been exceeded, or where there is dispute among pathologists whether the observed growths should be classified as tumors or not.

One highly important fact to come out of animal tests, which has not yet been incorporated into routine regulatory decision-making, is that the relative carcinogenic "potencies" of different chemicals – defined as the dose needed to give half of the test animals cancer – vary over a million-fold range. In other words, a dose of aflatoxin (the strongest carcinogen yet known) would cause a million times as many cases of cancer as the same dose of saccharin (the weakest carcinogen so far detected).[11] That chemicals' intrinsic carcinogenic hazard can vary over this enormous scale is a fact of central importance for sensible policymaking, since it forces one to set priorities and to pay attention to considerations of cost-effectiveness.

3. Short-Term Tests

In the last few years a new group of human surrogates has been under development, the short-term tests. These use bacteria or cells in tissue culture, and examine the capacity of test substances to induce mutations or other genetic damage. These have a vast advantage over animal bioassays in that they take only a few days or weeks to carry out and cost only a few thousand dollars per chemical. By far the best known and best validated of these is the so-called "Ames" test (named for its inventor, Dr. Bruce Ames), which seems to detect about 90 percent of chemicals that have been shown to cause cancer in animal bioassays and to have a low incidence of "false positives" (i.e., the obtaining of positive Ames test results for a substance that has been adequately tested in animals and found not to be carcinogenic).[12]

Still, certain classes of chemicals are missed by the Ames test, such as hormonally active carcinogens like diethyl stilbestrol (DES), and some chlorinated hydrocarbons (which include many pesticides such

[11]L. S. Gold, W. R. Havender, N. K. Hooper, C. B. Sawyer, and B. N. Ames (manuscript in preparation).

[12]J. McCann and B. N. Ames, "Detection of Carcinogens as Mutagens in the *Salmonella* Microsome Test: Assay of 300 Chemicals: Discussion," *Proceedings of the National Academy of Sciences (U.S.)* 73 (1976): 950–954.

as DDT), that are proven carcinogens in animal tests or humans. Dioxin, for instance, which is the highly dangerous contaminant in Agent Orange, and the herbicide, 2,4,5-T, is an extremely potent carcinogen in rodent tests, but is Ames-negative. Some short-term tests detect substances missed by others, so that a carefully assembled "battery" may be the best way of utilizing them; but just what the best composition of the battery should be is a matter still under discussion.[13] Currently, the prime utility of short-term tests is in the preliminary screening of large numbers of chemicals for exceptionally mutagenic (hence, presumptively carcinogenic) ones, particularly those contained in complex mixtures of chemicals (such as urine, cigarette smoke, drinking water, air pollutants, foods, or cosmetics). Once suspicions have been raised by such a screen, full-scale animal tests can be scheduled.

These are the main kinds of evidence that are used for inferring whether a chemical poses a carcinogenic risk to humans. Currently, short-term tests are in use in thousands of industrial and university laboratories, and the National Toxicology Program/National Cancer Institute has a vast testing program in rats and mice underway, with a hundred chemicals placed under test each year. In addition, industry is carrying out a large number of animal tests, as marketing approvals are sought for new drugs and other consumer products. And, of course, a great variety of epidemiology studies are in progress at any given time. Thus, decision makers are faced with a large and steadily growing volume of information (generating the "carcinogen-of-the-month" phenomenon), with only some of it capable of unambiguously establishing human risk (namely, positive epidemiology findings) and the bulk of it raising questions about, but not clearly proving, the imminence of human risk.

This evidence forms a seamless continuum, without clear decision boundaries. It ranges from chemicals that show strong carcinogenic activity in several species to disputed results in others. Frequently it reveals discordant results between species or sexes or strains, or between animal tests and short-term tests, or between suggestive animal results and decades of safe use by humans. The evaluation of such varied data, and the inferring of the degree of human risk therefrom, is what goes by the moniker, "risk assessment." And while it sounds fancy and as though its practitioners know what they are talking about, I think it is apparent from the foregoing discussion that

[13]M. Hollstein, J. McCann, F. A. Angelosanto, and W. W. Nichols, "Short-Term Tests for Carcinogens and Mutagens," *Mutation Research* 65 (1979): 289–356.

this is far from the case. Rather, science is really at its limits in most instances and cannot yield a single, consensus verdict concerning human cancer-risk factors from chemical substances. Decision makers must cope with this reality. In a word, with the uncertainty surrounding cancer's causes.

It may be that the best use of the scientific evidence will not be for yes/no decisions or for predicting absolute degrees of hazard (e.g., "*x*" cancers per year), but for *ranking* hazards. One might use uniform assumptions for the dose and species extrapolation problems, assign weights to the various kinds of available evidence, and then rank chemicals in terms of intrinsic hazard. This could then be combined with estimates of current human exposure to get a rough sense of the *relative* human health hazard posed by different chemicals. Uncertainties would exist, of course, even for this limited interpretation of the evidence, but one's chances of establishing sensible priorities would probably be greater than by ignoring these relative differences altogether.

II. Coping with Cancer's Uncertainties: Alternative Policy Responses

The Misuse of Prudence in Regulatory Policy

Given that science can raise many more questions about the potential causes of cancer than it can answer, what do we do about it? One response, the one that has dominated regulatory developments in the last several decades, goes by the name, "prudence." It is a way of coping with unknowns, and its practical prescription for regulatory policy is that if it is to err, it should always err "on the side of safety." Thus, the Delaney amendment (a food safety law) obviates all debate about the appropriateness of animal test procedures (such as testing at high doses, or *in utero* exposure) and species specificity (do results in lab animals truly tell us how humans would respond?) by mandating an automatic ban on any food additive that causes tumors in animal tests. (Certain food additives, such as those on the GRAS, or Generally Recognized As Safe, list, are not governed by Delaney.)

Another example of "prudence" carried to an extreme is OSHA's "generic" carcinogen policy, which was set forth in the *Federal Register* early in 1980.[14] Here, OSHA tried to deal with the fact that it had to relitigate certain of the same scientific issues over and over again in different rulemakings. These issues tended to recur because they *were* uncertain, particularly as they applied to specific cases.

[14]OSHA, *Federal Register*, vol. 45, January 22, 1980, pp. 5001–5296.

These included such questions as the appropriateness of high-dose testing, the existence of thresholds, species specificity, how to reconcile conflicting evidence in different species, or between rodents and humans, how to count in benign tumors, and what to do about "promoters" (substances that are not capable of causing cancer by themselves but that can increase the cancer-inducing effect of other substances). All of these questions are still in active dispute within the scientific community. Nevertheless, OSHA's policy has been to declare them settled in such a way as to minimize the chance of harm and, thus, to err on safety's side. OSHA officials, for example, refuse to recognize an overdose in animal tests; they presume that safe doses (e.g., thresholds) for humans do not exist (or at least are not estimable from animal data); they consider rats, mice, and other laboratory animals comparable to humans in their response to carcinogens; they view a single positive test in any species as outweighing any amount of negative evidence in other species or in people; they assign equal weight to benign growths and malignant tumors; and they regulate substances that merely "promote" cancer in the same fashion as dangerous, totipotent chemicals.

There was a time when such "prudence" seemed to be a feasible and unproblematic way of dealing with these uncertainties. Chemicals capable of inducing cancer were thought, after all, to be quite rare. Tracking them down did not seem insuperable, and most of them were thought to be artificial, manmade chemicals. Ending human exposure to them would therefore be a simple matter of stopping activities for which we ourselves were responsible. But such has not turned out to be the case. As a result of the active search programs described above, hundreds of chemicals have by now been identified as carcinogens under the conditions of animal tests, and many more have been shown to be mutagenic in short-term tests (and hence are presumptively carcinogenic). Moreover, most of them have turned out to be of natural origin rather than by-products of industry.[15] Virtually any food or other consumer product (which usually are complex mixtures of many chemicals) will contain some carcinogenic or mutagenic compounds, or at least substances capable of being metabolized by the body into such (e.g., nitrites can be converted to the highly carcinogenic nitrosamines). It is now clear that trying to identify and eliminate every proven or presumptive carcinogen is a daunting and – if the item is to retain its utility at all – a frequently impossible task.

[15]Bruce N. Ames, "Carcinogens and Anti-Carcinogens," in *Mutagens in Our Environment*, Proceedings of the 12th European Environmental Mutagen Society Conference, June 20–24, 1982, Espoo, Finland (New York: Alan R. Liss, Inc., 1982).

Compounding this is the fact that modern chemical analysis makes it possible to detect extremely low levels of trace components, as low as the parts-per-billion and parts-per-trillion range. Thus, what would have been considered "pure" with the techniques of one or two decades ago can now be seen to be teeming with infinitesimal contaminants. Attempting "prudently" to remove all detectable amounts of trace carcinogens is proving to be far more costly than originally envisioned.

Moreover, using the term "prudent" to denote these policies is misleading, since the term is not so much a description of a true attribute of a particular decision as of its wished-for result. In practical terms, regulators operate under restricted mandates; what might appear "prudent" to them in their confined view may not in fact be prudent when viewed from the perspective of consumers. The Delaney clause, for example, focuses narrowly on the cancer hazard that might result from the use of a food additive, but consciously ignores the *overall* health risk that might ensue from *not* using it. Banning nitrites would therefore be prudent in Delaney's circumscribed view, but would not truly be prudent from the perspective of the wider public facing the danger of botulism with no adequate substitute for nitrites. A ban on saccharin might similarly seem prudent in Delaney's view, but it would not appear prudent to those members of society who successfully use saccharin to avoid gaining weight (with all the associated health and psychological problems) or to manage diabetes.

Likewise, requiring that the chemical trichloroethylene be replaced in the decaffeination of coffee might have been prudent when it was learned that this chemical was a carcinogen (even though it is one of the weakest carcinogens ever detected in animals, on a par with saccharin, and only trace residues ever reached the public). But this step does not seem particularly prudent now that its then-untested replacement, methylene chloride, has also been shown to be a carcinogen. And lest it be forgotten: It was the Delaney-based ban on cyclamates in the late '60s that forced a great increase in the public's consumption of saccharin, a step whose wisdom is clouded now that we have learned that saccharin, too, is a carcinogen.

Complicating this issue even more are some perverse animal test results (alluded to earlier) that are hidden from the public in the technical literature or the files of the FDA. The following animal test results are noteworthy: a lifetime diet of egg yolks mixed with milk induced liver cancer in rats;[16] pepper applied to the skin of mice

[16]D. Nelson, P. B. Szanto, R. Willheim, and A. C. Ivy, "Hepatic Tumors in Rats Following the Prolonged Ingestion of Milk and Egg Yolk," *Cancer Research* 14 (1954): 441–445.

induced a high incidence of malignant internal tumors; table sugar caused stomach cancer in mice; and vitamin D, a standard additive to milk to prevent rickets, caused cancer in laboratory animals (on the pepper, sugar, and vitamin D cases, see footnote 9). Clearly, no regulator would be so intrepid (especially after the saccharin fiasco) as to try to ban eggs, milk, pepper, sugar, and vitamin D. Some technical objection may, of course, always be found to rationalize not taking these findings as the basis for bans. But the fact that such pesky research results get interpreted away rather than taken at face value casts doubt on the reasons why mitigating interpretation is rigidly ruled out when the item in question is more in accord with the fashionable bogeys of the *Zeitgeist*, namely, manmade chemicals.

Aside from breathing life into the troublesome regulatory rule of "prudence," the uncertainties surrounding suspect carcinogenic chemicals have engendered another phenomenon. Uncertainty about the cancer potential of a given chemical means that one can neither prove that it is safe nor conclusively demonstrate that it is dangerous. As discussed above, this is a very common situation in cancer testing. No persuasive proof has been adduced that saccharin causes cancer in people, nor DDT, nor hair dyes, nor the agricultural use of 2,4,5,-T, nor water pollution, nor New Jersey air. But few scientists would feel comfortable in declaring them absolutely safe, since grounds can be found for criticizing any negative study. For instance, had it been larger, or longer, or had it checked out high-risk subgroups, or investigated the possibility of interactions with other environmental agents (e.g., promoters), or controlled for more confounding variables, or whatever, a hazard might have been identified.

The practical consequence of this indeterminacy is to magnify greatly the significance of deciding which side of a given proposition shall bear the burden of proof. The essential unprovability of either position puts great discretionary power in the hands of the side not needing to prove its position, which side can simply keep generating new speculative scenarios of hypothetical risks that its opponent must rule out. One side releases the hares, and the other must chase them all down. Thus, we can easily understand the crucial strategic utility of such regulatory tools as "rebuttable presumptions," and the determined efforts by virtually all regulatory agencies to require applicants for new products to supply *proof of safety*, rather than for the agency to have to advance evidence of probable harm before denying an approval.

Private Alternatives to Government Regulation

"Prudent" regulation, then, is far from a faultless method of dealing with the irreducible uncertainties associated with cancer. But is there

any practical alternative that can handle cancer's uncertainties and act effectively to protect people from dangerous carcinogenic substances? Certainly. Three factors that *already* sharply constrain the risks that manufacturers can impose on consumers are: bad publicity, leading to loss of markets; the sobering prospect of being sued; and the oversight practiced on business by casualty insurers. It may be helpful to review a few cases illustrating the effect of each of these factors.

Concerning the first of these: When a few years back two people who had dined on vichyssoise produced by the Bon Vivant Co. (then a leading manufacturer of gourmet foods) died of botulism, the company went out of business. When the Bellevue-Stratford hotel in Philadelphia was found to be contaminated with the bacterium causing Legionnaire's disease, the hotel, despite being a venerable name in that city, was forced to close its doors. When Rely tampons were implicated in toxic shock syndrome, Procter & Gamble quickly withdrew the product from the market. When a DC 10 crashed in Chicago, there was a prompt response by air travellers to avoid DC 10's until there was assurance the problem had been identified and corrected. Thus, whenever hazards are clear-cut and imminent, consumers can be expected to react rapidly. This response supplies a strong incentive not only for companies to avoid actions that put the public at risk, but also to take swift measures to eliminate recurrences of those accidents that, in the context of ineluctable uncertainty, will occasionally occur.

Those accidents that do occur will expose the companies to the threat of being sued. It is worthwhile to refresh the reader's memory by reciting some of the tort cases currently in litigation or lately settled involving major corporations. An Oregon woman recently filed a $1 million suit against Dow-Corning Co. over a defective silicone breast implant, and a Brooklyn, N.Y., woman filed a $7.5 million suit against the same company for a similar mishap.[17] A woman who contracted cancer from her mother's use of DES filed a $10 million suit against Ely Lilly & Co.,[18] and another women won $1.75 million in damages from E. R. Squibb & Sons for the same complaint.[19] Firestone Tire and Rubber is facing 200 suits totalling over $100 million in connection with defective tire rims.[20] American Motors Corp. recently settled for $5 million with a man disabled in a rollover

[17]*San Francisco Chronicle*, April 28, 1982.
[18]*San Francisco Examiner*, October 14, 1981.
[19]Ibid., March 25, 1982.
[20]*U.S. News and World Report*, June 14, 1982.

of one of its Jeeps.[21] General Motors settled in June with a Napa, California, couple for $17 million as a result of burns they received when the gas tank of their G.M. car exploded in a rear-end collision.[22]

At least 83 lawsuits totalling more than $2 billion have been filed in the Hyatt Regency hotel disaster in Kansas City.[23] A $1.5 billion class action lawsuit has been filed in California for health damages sustained by residents in the areas sprayed last year for control of the medfly.[24] At least $2.8 billion in compensatory and punitive claims, spread among 3,500 lawsuits across the nation, is pending against the A. H. Robins Co., the maker of the Dalkon Shield birth control device.[25] Procter & Gamble currently has over 400 suits outstanding against it in connection with its Rely tampon, totalling over $3 billion.[26] The Hooker Chemical Co. is being sued for more than $12 billion in connection with Love Canal.[27] And at least 10,000 asbestos cases are pending against the Manville Corp., the largest producer of asbestos in the United States, and more than 400 new cases are being filed each month. In one of these cases, a widow won a $2 million award.[28] Estimates are that asbestos lawsuits across the country may total more than $40 billion. In fact, on August 26, 1982, it was announced that Manville had filed a bankruptcy petition under Chapter 11, citing the overwhelming costs of the asbestos lawsuits filed against it.

This sampling is by no means exhaustive. What it establishes beyond a doubt is that the business of suing corporations for torts, including cancer torts (e.g., DES, asbestos), is seething with vitality. It also illustrates the important watchdog function (although some might prefer a metaphor based on vultures) carried out by lawyers in seeking to discover and to gain restitution for consumer harm. Finally, it highlights the fact that the sums at stake are stupendous, so large that even the dimmest profit-oriented management will get the message that *it pays* to identify in advance and to reduce public health hazards. Even if they don't get the message, their insurers will.

This brings us to the third powerful, non-regulatory force acting to reduce business-caused risks – the oversight role of casualty insurance companies. Such companies have a direct interest in monitoring

[21]Ibid.
[22]*San Francisco Chronicle*, June 14, 1982.
[23]*San Francisco Examiner*, August 28, 1981.
[24]Ibid., May 8, 1982.
[25]Ibid., June 18, 1982.
[26]*Wall Street Journal*, December 8, 1981.
[27]*Newsweek*, September 14, 1981.
[28]*Wall Street Journal*, June 9, 1982.

and reducing the level of risk involved in the commercial activities of the companies they insure, since it will lower the likelihood they will have to pay off claims. Identifying risks, particularly novel ones, and supplying information on ways to reduce risks to their insurees or to responsible authorities, is a crucial part of their normal operations. For instance, insurance companies support the Insurance Institute for Highway Safety, an organization that identifies road hazards that contribute to the frequency and seriousness of highway crashes, and supplies the information to the state and local officials responsible for maintaining roads and highways. Clearly, reducing the occurrence of road accidents, and lessening their severity when they do occur, benefits the auto insurance industry by lowering payouts. There is also industry support for the Underwriters Laboratory, which inspects and certifies electrical equipment. Other insurers directly inspect their own insurees. The Hartford Steam Boiler Inspection and Insurance Co., for example, undertakes to inspect steam boilers and to insure those that pass muster against explosions.

Established non-regulatory mechanisms and entities do exist, then, to identify dangers and to foster business behavior that protects the public. In fact, there are swarms of beady eyes and brains out there scrutinizing innumerable local situations, restlessly watchful for the earliest signs of peril. Given the multiple layers of monitors that are active (the public, corporate management, contingency fee lawyers, and insurance companies) and the intensity of their motivation (one's own personal safety, enormous liability awards, and legal fees), these forces are probably far more pervasive and effective in promoting safety-conscious conduct than the slow pace of government regulation.

"There is only one way that you can get societal safety and that's out of liability – making it more expensive to do it in the unsafe way .... the Federal Government's efforts in getting a safe society are infinitesimal compared to what we do. It's the difference between a million-dollar verdict and a $500 fine," says Harry M. Philo, past president of the Association of Trial Lawyers of America.[29] "[L]awyers for the plaintiffs may come to be regarded as regulators without portfolio." This, says San Francisco lawyer Peter Weinberg, is already happening. "If you didn't have trial lawyers bringing suits," he says, "it would be hell getting manufacturers to provide protection."[30] And says Bernard Spring, president of the Boston Architectural Center, with reference to the Hyatt Regency collapse: "Litigation and insur-

[29]*New York Times*, July 30, 1981.
[30]*Newsweek*, March 1, 1982.

ance premiums. That's a tool that works like crazy. I don't think we need much more than that to insure that people will be careful."[31]

III. Conclusion

Nevertheless, the special features of cancer pose unique problems for existing institutions which still need resolution. Of particular importance are the following.

1. Statutes of limitations vary from state to state. In New York, for instance, a victim has only three years from his last contact with a toxic substance to file a claim, a time period that is obviously inappropriate for chemically induced cancer where induction periods of two to three decades are the rule. This clear defect in the law reduces the incentives of companies to be alert to health hazards with long latencies. Statutes of limitations should, where needed, be remedied to take account of such hazards.

2. The statistical nature of cancer's action, where only a few out of a group of similarly exposed people will actually contract cancer (e.g., only one in five two-pack-a-day smokers of high-tar cigarettes develops lung cancer), can make it difficult to establish causal proof in a courtroom and hence pin down liability. For instance, if five workers out of a group of 100 come down with a rare form of cancer that normally is found in no more than one person in 100,000, this would be considered persuasive by an epidemiologist, but a jury or judge might wonder why the other 95 workers did not also get the cancer. To the extent that courts will not accept epidemiologically convincing (but not traditionally causal) evidence, the effect of potential liability on structuring decision incentives will be less than it should. The standards of evidence deemed acceptable by courts in these novel cases should therefore be examined and updated in the light of modern knowledge.

3. The long lag involved in the manifestation of cancer makes it difficult to document exposure. Memories have faded and records may have been lost. This is a major problem in the current litigation about DES. In this unusual instance, it was the *mothers* of the women stricken with cancer that were exposed to the carcinogenic agent during pregnancy. Dozens of drug companies have manufactured DES at one time or another, and a pharmacist may have pulled any of several manufacturers' DES off the shelf in filling a particular prescription. Failure to be able to document which particular manufacturer supplied the drug in a specific instance is in most states grounds for dismissing the case. However, California courts have

[31]*Wall Street Journal*, February 18, 1982.

recently given standing to an innovative legal doctrine in an effort to remediate this situation: *All* the drug companies supplying DES at the time of a mother's exposure are being held jointly liable in proportion to their market share, unless a company can definitely prove that it had not supplied the doses in question. Clearly, the difficulty of precisely documenting sources and amounts of exposure that occurred two or three decades earlier is a common problem in cancer cases. This, of course, will diminish the effectiveness of liability as an incentive favoring cautionary steps against such long latency diseases. The California doctrine is at least an attempt toward correcting this problem, although whether it is the optimal solution is arguable.

4. A tremendous legal battle is now brewing over yet another aspect of cancer torts that is attributable to cancer's long latency. Is it the insurer whose policy was in effect at the time the exposure occurred that should pay off, or the insurer whose policy is in force when the disease first becomes manifest? This question is deeply involved in the present litigation over asbestos, and as yet there has been no final adjudication. Until this is cleared up and responsibility unambiguously assigned, the monitoring role that insurance companies should exercise over decisions affecting carcinogenic hazards will be blunted.

There are, then, original problems rooted in cancer's singularities and existing institutional rigidities that bear importantly on the capability of non-regulatory mechanisms to minimize the hazard to the public from chemical carcinogens. But that such mechanisms are in place and already operating is clear, and they are rapidly evolving and adapting to accommodate cancer's unique features. Thus, with these improvements our legal institutions will become more effective.The existence of these additional layers of protection should, therefore, permit some relaxation in regulatory "prudence." The burden of proof could, for instance, be shifted to the regulatory agencies by requiring them to demonstrate a reasonable probability of public harm before a product could be denied marketing approval. Such a major step may not be politically feasible in the near term. At minimum, however, regulators should pay more attention to assuring a company's financial capacity *to be responsible* for whatever harm its product might cause (for example, by requiring minimum levels of insurance coverage). Then they could be less concerned with requiring that every last residuum of speculative doubt about a product's safety be eliminated in advance of marketing. Once a company has demonstrated that its product is *reasonably* safe and that (concerning the remaining, inherently unresolvable uncertainties) it is

able to respond to potentially large lawsuits, then it ought to be allowed to proceed. For it is likely that when the actors in the economy are operating under rules that unambiguously assign responsibility (subject to the incentives and constraints of possible loss of markets, potential liability, and insurance oversight), simply letting those "beady eyes and brains" loose will result in a better balance between the public's need for innovation and its competing need for safety, than the practice of boundless "prudence" that has taken form in our current laws and regulatory customs.