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For about 15 years, I have been thinking and writing about what I see as a very dangerous and portentous collision between the different interests of innovation and advance--particularly in the biomedical sphere--on the one hand, and the rise in ecological-environment risk averting consciousness and the profession of environmental hazardry that has been emerging on the other side. This was fueled by many forces and one must say they included the somewhat thoughtless and unstructured over-application of a wide variety of chemicals introduced into our environment, far beyond the core of indubitable benefit and value and without very serious regard to their subsequent health effects. You only have to think about the polychlorinated aromatics, both as pesticides and PCB, to have a very clear example of what I am talking about. I will expose my own concerns, for example, about the quantities of lead that continue to be used and where I think we do not have a cost effective balance between their obvious advantages and fuel economy and their potential health dishazards.

The point is that for a very long time there has been little concerted concern with, and no single institution devoted to, trying to rationalize the trade-offs that are involved in the economic and health advantages of various introductions and their corresponding disadvantages. And so we have been in a headlong collision of these kinds of interests. I do view this as a major crisis in the technological development of our economy. As the world tends to follow behind us, I don't know what the final outcome will be particularly since there is now a politically-articulated demand for verifying the safety for human populations of essentially every new introduction of chemicals into our environment. While the specific regulatory procedures of TOSCA may appear to be fairly mild--

after all, they are merely a reporting activity at this stage and the administrator must use some discretion and is obliged to take account of the economic tradeoffs in reaching his conclusions--I don't believe a word of it. I think the same psychological and political forces that have fueled the zero-risk ideology, which is of course essentially unachievable, will be very difficult to resist when it comes to chemical introductions where one can always argue for substitutions of other products, for wide dissemination, for worker hazards and so on and so forth.

My own political judgment, for what you think it is worth, is that industry caved in and gave away a great deal, perhaps inevitably so, in the adoption of that Act, far beyond the actual language of that particular legislation. Just imagine any confrontation where there ends up being a retrospective determination that a compound had been allowed through the filter, that there then did arise some human risk, and you could imagine a sort of Kefauver Amendments coming in, fueled by a public crisis--in that case thalidomide, even though it was essentially irrelevant to the actual issues of the legislation that then followed through.

So I think we are in a fundamental crisis about some of the most important elements of innovation in a technological society. We are operating without guidance, really groping quite blindly with essentially random shots on the particular issues that come to a fore at any particular point. One should be alarmed at the inherent irrationality of the process. I don't see anything in the present mechanism of exposure of compounds that suggests that that roster of

candidates is arrived at by any rational procedure of priorities that has sorted out which agents are the ones that are most worthy of immediate attention and which may be subject of deferred action and so forth.

Of course there are many reasons for this situation. It may be that the ones that, as technical people we can do something about, are such a small part of the whole story as to suggest trends that have a kind of inevitability as a religious phenomenon rather than one that can be influenced by laboratory investigation. I will come back to that a little later on. But, obviously, I think we are under severe compulsion, both as a matter of public policy and also as a matter of what it is that drives private enterprise to try to discover what can be done to ameliorate the situation, to find some guideline that offers some reliability to an industry like this in its further development.

I am well aware that, as long as regulations are applied with some reasonability and predictability, a large company can do very well regardless of the level of bureaucracy that it has to cope with. In fact, there are many respects in which a company like Roche might want to encourage the bureaucrats, since the selected impact of a tight regulatory system is much greater, as against market entry, for your small, potentially innovative competitors than it would be for you. That is, there would be a deadening of the overall process, but I am sure this company would be one of the last actually to get hurt with respect to what it could deal with with new innovation.

But I think the country will suffer, I think our people will suffer, I think the world will suffer if that innovation comes to a grinding halt, as there are many signs of it doing.

Now most of the content of what I have to talk about is probably less expertly known by me than it is by some of you here. If you were to collect your own sources of expertise and wisdom, I am sure that you would be able to add up to far more than what I can offer. What I think I can present is a generally sympathetic but basically detached perspective. I am not owned by you. I can argue with you. I can talk back to you. I can complain when I think you do wrong. On the other hand, I am not a zealot trying to put corporations out of business. I'm simply trying to find out what makes good and sensible public policy. I think that there are not that many earnest but reasonable critics of your own activity and operation that you ought to dispense with me lightly.

In a certain sense, the bottom line of the process that I am going to advocate to you is to use not just me personally but but the whole network of my colleagues at academic institutions for this purpose, and I hope in some way the Rockefeller University in particular. We do have a group of very skilled, very specialized investigators in the biomedical research area who are not making the kind of contribution that they potentially could in areas of public policy determination, wherein those skills might be most useful. So it's not for me and it's not for my friends that I am speaking. I think there is a public interest that needs to be addressed and that some better community between our respective sectors might help. I will come back a little later with some specific proposals.

Now the tragedy, along with benefits of an action like TOSCA, is that these dampeners on innovation are coming along at a time when the capability of poisoning our environment is very, very great, usually with inadvertent by-

products of many other things. One really ought to think of the tobacco industry and the automotive industry as perhaps the prime sources of environmental hazards today in contrast to what you are likely to do from your perspective. Here, at least, no compound gets out of these laboratories without having been investigated for at least some of its biological effects. You will have some interest in the mechanism of action of these agents. You will have some rationale for the disposition within the human body, whereas most environmental changes that are very comprehensive are more indirect than that and no attention whatever is given to those concerns.

We are beginning to learn a little better. Thus, there is some thought when coal is advocated as against nuclear power as the necessary alternative to the oil that we are not going to get. We think a bit about the environmental side effects of the utilization of coal. But it should take just a moment's thought that whatever such effects are going to be, the use of coal on a large scale again as an energy source is going to have an enormously greater effect on the chemical pollution of our environment than anything this company could ever do or the rest of any specialized chemical industry. Yet somehow those matters are relegated to the bottom of the list. There is a list here of chemicals known to be carcinogens in man and only a sort of side reference to soot, tars and oils, which encompass a great deal. I think if one looks in quantitative terms, introduction of these latter materials into our daily environments and our indigenous consumption of them is far more pervasive, and in my own view far more important, than saccharin or a large number of any specific additives that one can think of. I am not saying that you shouldn't worry about

saccharin from any of a variety of perspectives. There certainly is however, a lack of balance, or no sense whatever, of priority in terms of addressing important problems first in our present context.

The other side of that concern though--and the reason that I call it a tragedy since TOSCA was formulated because of the unprecedented capability of industrial activity to modify the human environment--is that we are also facing a time of equally important pervasive innovations for beneficial purposes. The one that looms the largest in my mind are the oral contraceptives. They have had a tremendously important, beneficial and in fact indispensable impact throughout the world in dealing with the very important issue of population control. And one has to face it, they have been a very important element in the liberation of the majority group in this country. But I think it is fair to say that if the present climate of regulation and concern prevailed 20 years ago, it might never have been possible to introduce oral contraceptives into routine practice. They might still have been available for high risk situations where an individual life might have been at stake. But the ground rules have shifted very, very sharply and I myself am totally persuaded, and I think the current climate of work and research bears out Carl Djerassi's arguments about the non-existence of birth control innovations after 1985 because the cycle of introduction and regulation becomes longer than the steps needed in order to catch up with it. That is to say, it takes longer to do a test that would satisfy particular criterion than it does for some new hazard or new concern to be discovered or invented that will invoke still some further regulatory procedure.

The situation is aggravated, as Dr. Djerassi points out, in cases where you are dealing with a very large scale introduction of a compound that wouldn't be used if it didn't have potent effects on human physiology but in essentially healthy people at the time of introduction. There would be none of the argument whatever about the steroid sex hormones with respect to life saving applications. But even low levels of risk that are very difficult to predict and ascertain with any assurance loom very, very large when the whole population of the world is the target group that is involved with such introductions. Of course, it is for comparable benefits that such materials are introduced. I think we are on the threshold of discoveries which could have a similar impact in the prevention of atherosclerosis and it would be very difficult to introduce them on any reasonable scale because the benefits will take 20 years to discover, the risks will take 30 years to discover and the cycle of invention of new hazards will of course be much quicker than that.

Now in some situations you may be able to glide in from some very high risk medically-indicated situation into more general use. But you can well see how the de novo introduction of such derivatives for which there have been some very exciting developments recently would probably have been impossible if they had to stand on their own feet admissio.

The fact is that even now I think there is a sleeper in the very large scale program to encourage the prophylactic use of anti-hypertensive agents in people that are essentially healthy. Now the 20 percent of the population that is at that quintile of blood pressure has been defined to be at greater risk, although

why one defines that particular percentage isn't at all clear to me. There have been aggressive efforts to try to promote the use of diuretics and other still more potent approaches to blood pressure control. And I must say, in my own view, no thought has been given to the possible side effects of very large scale applications of these agents in such large populations with all the possibilities of genetic idiosyncrasies, environmental interactions with other agents and so forth. And it's been possible to even think of those because of ones already established with drugs whose validity had been certified in a totally different framework than large scale prophylactic use. So I would be willing to bet a dollar to a nickel that there will be a major scandal in that area, whether it has any real substance or not, some few years from now. And we will wonder why there hadn't been much more attention to concerns about side effects in that arena.

To say that these substances are safe for such use when it is based entirely on clinical studies for high risk individuals is open to the same criticisms as we've seen over and over again in the past with other agents that have gone through such transition. I am not saying that these are real hazards. I am predicting, however, that there will be a backlash on this question and that it might be well advised today to begin some studies in this direction, even though I don't think such studies are going to get funded. We tried out of our department and found that it was such a dull subject--to try to interest anyone on the effects of diuretics on hyperuricemia, for example, with the possibility of picking up some genetic polymorphism--that we weren't even able to get started in getting such programs going.

You can all have your own pet theories on where chronic uses of new chemicals may be most exciting. Just beyond the horizon are agents that would be quite centrally involved in the fundamental process of aging. You can see how in dealing with that issue we face the question of how to determine whether substances that are given over periods of 50 years are safe for their intended application. We may be in an unsoluable dilemma.

At the same time, there are going to be other large scale interventions that, because they don't fall into the environmental or additive framework, are not going to be regulated but may be far more drastic in their implications for human health on a chronic basis. I think of all the abstentions that people argue about, for example, the most primitive method of birth control. I've yet to see any carefully conducted clinical trials on a large scale to determine whether or not abstention is or is not safe from a hygienic standpoint. I don't think that is a non-issue. I don't think that trial will ever be done. You can understand the difficulties in organizing that experiment. But if I approach other areas of abstention in the dietary realm, for example, we already know of some acute effects of strict vegetarianism regarding B-12, and who knows whether that is going to be the whole story. There are many other areas of changes in life style where things that may appear to be beneficial have just as much risk of insidious hazard as do any of the chemicals that we are now talking about. We ought to be at least thinking about how we would answer those questions even if we know they are not going to be in the same bureaucratic framework as the conscious use of new chemical introductions.

To get to a more substantial concern that I happen to have, I don't know how many people share it, I am frankly quite worried about the long term implications of the high level of hygiene. The facts that we work very hard to cleanup our environment from bacterial and parasitic insults and provide vaccinations against every conceivable viral infection--these are all obviously highly beneficial from a short term standpoint. However, I have no idea of what that is doing to our immune systems, speaking fairly globally. We may be setting the stage for potential explosive epidemics by having clean populations which have not seen a variety of infectious agents for some period of time. We may have very large naive herds for the reintroduction of poliomyelitis, more virulent strains of influenza and perhaps the re-emergence of smallpox, although I have no specific criticisms to make of Dave Henderson's wonderful campaign and very careful controls and concerns as far as can be done in that area.

But I am just pointing out that there are several ways in which we are changing the environmental context of the human organism on a very large scale and in ways that have been virtually unexamined, in part because we don't have the techniques and in part because we don't know that we should worry about them. And I do think they belong in the same bag as our concerns such as risk assessment of specific chemical introductions. The latter are easier to study and they may help to overweigh what to do with respect to other changes in the chronic human condition.

Now there are some policy implications of this perspective that I think are only beginning to seep in. For example, people at WHO were deeply shocked at the Depoprovera decision in this country essentially banning it for all but

high risk uses. This of course puts quite a serious wrinkle in efforts to have a depo injectable, long-acting steroidal contraceptive that might be a very useful technology for population control in other contexts, such as where taking one pill a day might be simply unrealistic from the point of view of the particular cultural and social framework. And while Don Kennedy and the FDA were very careful to state that they did not wish to impose our standards of risk-benefit assessment on other countries, and in fact requested legislation that expressly permitted U. S. manufacturers to export drugs not permitted to be used here to other countries, there is no question about the explicit impact of such findings elsewhere. That was a rude shock and one has to sympathize with the dedicated efforts over many years to set up a framework for the trials of such agents on an international basis. I think, however, you also have to fault the population control research executive of WHO in the same way that one must now fault any drug company that would believe that risk problems are a side issue to be dealt with when they arise or met in a defensive way when some opposition arises to them.

I think it is perfectly plain that in the current climate it is essential that an anticipation of risk assessment be a central part of every chemical development program from its very inception. And if you can't figure out how you're in fact going to accomplish a useful demonstration of safety in the context of a particular agent, then there is no point doing the rest of the research which is necessary to bring it to validation. These kinds of chronic public risks are no longer side issues. They are becoming the central question that has to be answered before a new compound can be introduced into general

practice. Unfortunately, you also have to anticipate by at least 10 or 15 years both the scientific and public and regulatory climate of the context of a new compound's use. That is very, very hard to do. Imagine yourself in the position of distributing diethylstilbestrol in the early 40s. What could you have done to anticipate the kind of reaction and the legal sanctions that may indeed still be available on a very large scale?

It seems perfectly obvious to me that far more than the specific regulatory restrictions that FDA imposes on an industry like this, the doctrine of implied warranty and the very large target that a successful and thriving company will be at sometime in the future if anything, however unanticipated, goes wrong are major obstacles to having some spark in innovation and enterprise. Frankly, I think any drug company, whenever it introduces anything, is taking risks that I wouldn't dream of incorporating myself. I wonder how the institution ever manages it because it is perfectly clear that, in our present technical context, it is impossible to anticipate not even all but simply many of the potential hazards that may arise with respect to any chemical.

At the same time, we have not gotten over the point that the beneficiaries of such introductions, the people who profit and did not have the side effects of a given drug, should share in the load, should share in the burden. I am very much in favor of schemes for the compensation of victims of vaccination programs. There the distribution of public good is rather more obvious since the person who submits himself to vaccination is benefiting the community in the first instance at least as much as he is benefiting himself,

as regards the spread of infection. But I think the person who benefits from a new drug is benefiting the community as well by having provided the incentives, the framework, the stimulus for development of those agents as well as his own personal benefit. There is, however, obviously no place in our present ideology for the explicit inclusion of insurance against hazard to others in the pricing structure of a given agent. Perhaps that is something which ought to be thought about as an approach to that problem.

The one thing I have not seen FDA do is assume its own responsibility for warranty, that it will pay the bill if a drug that it has approved in fact incurs some later hazard. You better hope they don't, because if that doctrine were ever to be established, obviously no drug would ever be approved.

Well, the specific substantive issues in this field today are very largely in the area of carcinogenesis. I wonder a little bit why that is the case. Why is all the action with respect to unanticipated risk in the field of cancer, since there are so many other hazards that have a very long time delay? That's the obvious first reason, that with cancer you are dealing with time bombs in terms of the very long latent periods. I suppose above all, however, is that we have such a profound mystification about its detailed etiology. It is also the disease most feared by a large majority of the American people. I think most of us would prefer to die of a heart attack than of a variety of cancers that we might possibility be subjected to. Another reason is that a few links in the chain of etiology have been established and it is possible to use an adjective carcinogenic and attach it to a chemical and perhaps stop thinking after that point in terms of further implications of that attribution.

I don't think that that pride of place is going to last forever. My own candidate, if you are willing to pay a nickel for prophecy, is that the greatest problems will be in the area of behavorial toxicology. Something that happens to all of us is that our thinking apparatus goes awry at some stage in our lives. Some of us become alcoholics, some of us will become psychotic, all of us will become neurotic and depressed and unable to work at some stage in our lives. And some of the same things that I've said about cancer I am sure are going to apply to the invocation of the history of chemical exposure as a basis for such events. I have been saying this for about ten years and there have now been two or three symposia that has been dedicated specifically to these problems. They will be the most insidious because plainly there are essentially no animal models whatever that could or could not corroborate the psychotogenic effects of long-term exposure to whatever you name it. But there will be plenty of actors very willing to look for culprits of this kind. You can be sure that they will exist. I guess MSG is the first example I can think of where there was in fact a major campaign directed against such effects of a given substance. The talk about excessive doses of salt in baby foods would be very much of a kind. So there already is some groundwork for that level of concern.

It is not at all clear to me what we are going to do about this in the absence of animal models, except to say that we will not be bereft of these problems until we have achieved a much more fundamental understanding of the diseases in question. I think we will face these impossible dilemmas on carcinogenesis until we know enough about cancer that we have a rational model for fitting the role of environmental additives. And the same will eventually have to be true on the behavorial side and probably be very much more difficult.

Now I would have spent more time and detail on the scientific basis for regulation of chemical carcinogens except that three days ago there appeared a remarkable review article in Science magazine by Thomas Small. Some of you have already seen it and for those who have not, I have left a few copies for your further pondering and perusal. This news report by a Science journalist is the broadest statement of the problem of extrapolation from laboratory sources to human risk that I have seen so far. I am sorry that I have to say that because, for a subject of such fundamental importance, I would have expected risk assessment models would have been developed in much greater analytical detail than has been the case up to this time. It has taken the journalists to put it together, to get the controversial views of a variety of participants in the process and to bring the level of dialogue to the scale that it now is. The author says exactly what I would have, almost point by point with some elaborations. So I am going to confine myself to some critical remarks on what Small states about this issue.

However, let me also say that the matter is too important to be left to scientific specialists and they haven't dealt with it. The reason it has taken a journalist is that it takes a very broad inter-disciplinary perspective to approach these problems. Many of the questions are essentially unanswerable at the present time. Respectable scientists don't go into important problems; they go into answerable ones. And that's basically what we've got to do. But social policy is still left hanging in mid air in those circumstances. We are becoming a race of greater and greater specialization, knowing more and more about less and less at a time when we have ever increasing needs for a broader point of view.

Not only are there very few individuals who can provide such a view, there are almost no institutions that are devoted to doing so. And that's going to be the final point of my remarks with an obvious appeal to try to create some unit that can do a better job than we've had so far.

The one point that I would take the sharpest issue with is his central stance and that is that "the scientific basis for regulation of toxic substances probably exists now" and there is merely the problem of the controversial character of regulations that emanate from it. I believe we have to take a much more critical view of that scientific base right now.

The general issues discussed here will be rather familiar to most of you. He reviews the current guidelines of the National Cancer Institute for cancer testing in animals, pointing out that each chemical should be tested in two strains of animals and in both sexes. Chemicals should be administered by a route that approximates human exposure. I guess he means that the route is that of human exposure but at the maximum dose available at which the animal will survive. The point that emerges from that is that if you want to design a compound that will be most likely to get by the regulatory procedure, build in enough acute toxicity so that you are only able to test it at doses that are a small multiple of its human exposure. Then you will be unable to do the animal experiments at levels enough higher to discover the dose at which that compound does in fact become carcinogenic.

I am not suggesting that every compound will be found to be carcinogenic in some system. I will be very much surprised, however, if one can't find

some condition, some circumstance and some dose in interaction with other substances at which you could make a case for enhancement of carcinogenicity for almost anything that you chose. So the limiting factors are the side issues of how much you are able to pump in, whether that is acute toxicity or a mass that can be introduced into the diet or whatever. Those of course are really quite irrelevant to the thresholds involved for human application.

My main concern about such tests is their feebleness in the detection of chronic hazard. It is very easy to see that compounds that might have very serious effects on one percent of the exposed human population over a period of 15 to 20 years would pass muster very readily in animal experiences of this kind and vice versa. I am not at all persuaded by the existing empirical evidence based on past experience that this is either an efficient or credible way in which to approach the problem of safety testing in the future. And of course we are reaching the situation where the cost of trying to fight the hassle when carcinogenicity indices are reached at fairly early stages of development of a compound just aren't worth it. Most development programs are likely to be stopped pretty early in the game, even if the FDA were to let you proceed with further clinical testing, under those circumstances.

So we will never know, and one might say greatfully may never know in some cases, what the potential toxicity is of a number of substances that have failed to pass this particular hurdle. With all their inadequacies, these tests take 3 1/2 years or more and cost at least $250,000 per substance. One can also say that they reveal absolutely nothing about mechanism, whether the results are negative or positive, since they say are simply a tabulation of the number

of bumps that appear in the animal in different organs. They tell you nothing about the etiology of the formation of tumors, nothing of the biochemistry, the distribution of the drug, further transformations and so forth. As a research-oriented scientist, I can't help but be appalled at the money that is going down the drain in this kind of road-testing when, in the long run, a fraction of that sort of investment might be so much more productive in going after fundamental mechanisms of toxicity and of carcinogenesis.

I gather some 7,000 chemicals have been tested in this way. That comes out conservatively to an investment of the order of $2 billion in this particular kind of safety testing cumulatively. This is a lot of money compared to what goes into basic investigations along these lines. What one gets out of these kinds of assays as well as others is a label carcinogenic or non-carcinogenic, as attached to a given chemical. I can't imagine anything more simplistic than trying to give a one word answer to a highly multi-dimensional problem. I just don't believe that that can begin to describe the multiplicity of ways in which a compound can interact with the physiology of the organism in producing a deleterious effect.

It is just beginning to be appreciated at this level, as the cancer research people have known for a long time, that many substances operate in at least a two-phase fashion. The well-known is known for 50 years and, therefore, some of our modern molecular biologists don't know about it. Interactions of croton oil with carcinogenic hydrocarbons, where croton oil by itself is virtually without visible effect in production of skin cancers and where there is an enormous potentiation of the action of some of the familiar carcinogens,

is just the beginning of that kind of analysis. As soon as you say that, you realize you cannot put a simple, single label on a chemical and say it's carcinogenic or not.

I would have thought that much more pause than has been the case would have been given the fact that the plain of nutrition is an extremely important factor in the determination of the levels of tumor genesis. That, to my mind, has been one of the most important findings of cancer research of the last 50 years and has been almost totally ignored. But pure calories could be defined as being carcinogenic in experiments that follow that particular model in ways that would be simply embarassing to these kinds of discussions. We have substances that are very clearly carcinogenic to man, like asbestos, although possibly through quite complex interactions with other environmental inputs, they simply don't fit our chemical models at all. These agents, like plastic films and other physical additives, when introduced in particular locales, have an action that seems to be essentially independent of their chemical structure. Put a little differently, the same chemical substances are totally inactive in other chemical forms. Thus, you are not even talking about a carcinogenic chemical; you are talking about a carcinogenic state of matter in those circumstances. There plainly must be a very complex interweaving of different etiological factors coming into the story.

Well, I am just reciting the obvious, perhaps in a slightly different context. The whole conception of labeling substances as falling into one category versus another is one that should be much more vehemently attacked. We need a far

more sophisticated approach to the problem, in order to have good public policy (not just to rescue your favorite drug or food additive) and to discover those influences in our environment which involve very serious interactions. As a most elementary example, the hazards of asbestos interact so strongly with those of cigarette smoking that one would have thought that the most immediate public health measure involved in that sphere would have been education about the hazards of smoking in that context and some fairly severe regulations about occupational exposure to tobacco where asbestos is present in the environment. I think one could also have expected other important side benefits from that equal to those of the immediate involvement. I am sure we are going to discover equally important interactions in the future which will be covered up if we talk about classifying the white hats and the bad hats in the world in terms of individual compounds.

There are many other elements of the process of carcinogenesis that defeat this simplistic characterization. There is an observed phenomenon called "the malignant transformation" of cells often seen in cell culture which is quite orthogonal to the abrupt DNA-mediated changes that alkalating agents and so forth induce. We don't really know how to relate these two. I would assume that malignant transformation is probably an epigenetic alteration. But any number of hypotheses could be introduced. I simply point to the need to complicate one's thinking in this particular area.

Well, there seems to be some admission about these points. There was an argument that is discussed in this article about nitrulo-triasedic acid which was proposed as a counter-measure to the pollution of the environment with

phosphates, which of course were serious sources of eutrophication of lakes. Then came findings that large doses of NTA, completely predictably, would cause some problems, followed by argument about the dose-effect relationships in that particular area. Then the president of the new chemical industry Institue of Technology, Dr. Leon Goldberg, maintained that the use of the maximum tolerated dose is completely inappropriate. Instead, he and others argued, the complete spectrum of absorption, distribution, bio-transformation and excretion of the chemicals should be considered before determining the maximum dose for bio-assays. Dr. Rawl, who is the director of the National Institutes for Environmental Health Sciences, says that he cannot disagree with this viewpoint but notes that such studies would probably limit the number of chemicals that could be assayed to about four per year.

The rest of the article goes on to how you are going to evade that issue and do it "on the cheap." "On the cheap" means setting up some fairly arbitrary standard, using one parameter of toxic hazard like the Ames test. This is a perfectly legitimate and valid designator. Many of the compounds that produce a strong positive on that test are very clearly agents that will alkalate DNA and some of them are hazards that you and I would unquestionably avoid in our daily lives if we could possibly do so without going into further complications.

However, I think the bottom line is that we are going to get "on the cheap" what we pay for. If we think we can substitute one simple test for a deep understanding of the mechanisms of interaction of a new chemical substance with the physiology not only of a single organism but of the whole population of

organisms with its genetic variability and with its co-exposure to other environmental agents, we are going to get what we deserve. And that is roughly the present situation.

Obviously, we have to do better than look at four compounds a year. We do have to find other answers to the question. But the rote examination of compounds in a standardized pathology assay, on the one hand, or the simplified laboratory test, on the other, is simply not going to accomplish the task.

Nor are they going to result in the capability of looking at the very serious trade-off problems, which is really the second chapter of any book that one would write here. There is always a trade-off. There is probably always some possibility of a disbenefit even from the cleanest compound that one could imagine. We have to find some framework in which that can be measured against the costs and effects of alternatives in an economic sphere which also intersects with our health sphere. We have a finite number of dollars to put into other health preventive measures and so on and so forth.

There again the only institutions that we have today that do anything about it are the regulators. And I have to say that the more I observe a bureaucracy, the more I believe in Parkison and that they have a life of their own. Perhaps it is just as well that they do. I don't envy the bureaucrat's life in as much as all of us share a certain exasperation in having to deal with it. But the regulator today increasingly must be viewed as a self-interested adversary, not as a neutral judge. That is a point which has to be understood. He is an adversary because he has to protect his neck. No one else is going to do

it for him when there is some nonfeasance on his part, and something gets through that could arouse large public outcry. Why complain, if bureaucrats behave in that self-protective fashion when no one is going to watch out for them when the ax does fall?

You have to recognize that as a fact of life. Every one of us is attached to self-interest. I am attached to the promulgation of a neutral scientific attitude and a successful career for my graduate students and myself in doing public good in a certain respect. The consumerist is self-interested to the extent that he or she can arouse public excitement over a particular issue; that person is also in business to do public good. Every one of us here has some stance in those circumstances that we really ought to be very honest about.

But this also suggests that the single elements in these adversary processes are really not to be trusted for the whole story. I don't think we can trust the regulatory bureaucracy for making the value judgments that are involved in these tradeoffs because the life of the individual bureaucrat is too much involved in the way that those decisions are reached. I don't have to give all the reasons why industry can't be trusted, although in many respects it is the most publicly-exposed party. The academic side has its own biases that I have also indicated. Somehow, though, I think we have to put these together.

The specific proposal that I would like to see some more thought about is a consortium in which academic institutions can play a regulated role in

holding the bag in the study of these questions. Now they already do. Most of the tests and assays and arguments and so forth about these different procedures have come from academic sources. But it's very hard to pin a professor down to working on a problem that is of particular interest in a particular locale. In a way, it's not his business to do so. If you are talking about the central core of basic research and if you want the highest level of creativity--which is the discovery of new problems--you really don't want to tell that cadre of individuals what to do.

We then have a vacuum. We have a vacuum on a number of axes of applicable science. Where the yield is immediately potentially profitable, industry will do it. We know what drives private enterprise. But there is a large zone where knowledge that is part of the commons, that is part of the common social good, falls between the responsibility for problem discovery of the academic laboratory and the proprietary interest of the industrial laboratory. I used to think government was the place to do that and indeed it has to a large degree. But, one, it is increasingly hard to get money to do anything new and different these days, regardless of its merits. So we have a status quo problem against us. Two, for all of the bureaucratic reasons that I indicated before, I think industry in particular ought to have reason not to trust government to be the only source of wisdom with respect to risk assessment of environmental chemicals.

There is getting to be some cross-talk between the regulatory side and the research funding side. As enthusiastic as I would be in principle about an

agency like FDA having a very strong scientific base, including a grants and contract mechanism and so forth, I really wonder how that agency would be able to live continuing to support outside activities that were in immediate and direct conflict with its existing regulatory policies. Frankly, I don't think it could. I just don't see the dynamics to make it possible. And I think we do need some agency segregation.

Well, there may be many versions of what is needed here. The CIT is one I have only recently heard about. It's the chemical industry's consortium for the study of industrial toxicology at Research Triangle. It seems to me that it is too close to industry to be completely credible. I don't see where in its governance, its direction or problem choice, it has the neutral ground which is required for an effective operation. This may be largely a problem of public perception that hasn't emerged yet, although it's predictable that it will.

There is also bound to be some reality to it, however. I found myself once at a discourse on cost-benefit analysis involving a particular additive. Believing myself to be a fairly calm, detached person sympathetic to both sides, I found a consumer advocate inappropriately criticized during the discussion. I wondered how come, how come I couldn't do the job myself of assimilating his views. I thought I was as honest a person, as much involved in public interest as that individual was. I wasn't as rash as he was. And that was the point. We need people in the system who are protected in making outrageous allegations, outrageous assumptions and hypotheses, but

rebuttable ones. If we don't have that element in the system, you can be sure that it will also inevitably be co-opted to the fundamental interests of law and order, in other words, to the prevailing mores of the group rather than necessarily the long range public interest.

Very concretly, I think that there would be a place for a universities-industrial consortium to manage laboratories oriented in the general direction of CIT but at a more fundamental level. I think CIT is dedicated primarily to the testing of particular compounds and in part to the development of new testing methodologies. I think we need a further place for the development of applicable science where the emphasis is a little on the other side, where there are tasks that originate from industrial requirements which do require new methodologies, new insights, and where very careful and critical academic oversight is also important. Such an institute should embrace the examination of fundamental issues of toxicological hazard from a very new perspective, much more applied than the Roche Institute of Molecular Biology (which I think is somewhat to the left of the Rockefeller University in the purity of its academic objectives) and, of course, much more fundamentally oriented than the research and development laboratories of this particular corporation. I think that within that framework, we might also be able to get a discourse which is almost totally lacking between the people who know something about the toxicology of a compound and people who can say something about the techniques of cost-benefit evaluation in public application.

Having said all of that, I have to revert to one theme that is somewhat discouraging. I am not sure that it will make the slighest difference. The issue

that has shaken me to the core, because it does have deep religious overtones, is recombinant DNA. Here I was a protagonist. I was not sitting on the sidelines. I was an investigator who devoted all of my scientific life to laying the groundwork for these investigations. I can hardly claim a purity of motive in wanting to see the effective utilization of that particular technology. But I have been very reluctant to get into the middle of that fray because, to be very frank with you, I couldn't find a way to bring a cost-risk benefit analysis into that picture. I had no way to estimate the risks. I got off on my own intuitions. I can offer all kinds of reasons why there are many, many other things going on in the world that are far riskier than what is involved here. But I had no way to articulate that in a clear-cut, rational analytical framework. I haven't heard that very much from my colleagues either. I think we have to own up to that. Also, one thing that was never stated clearly enough was the benefit side of these kinds of investigations. And there I have gone "gung-ho" to try to articulate the very important fruits of research in that particular area.

I honestly and earnestly believe that the risks have been vastly exaggerated. I indeed can point to many many things far more consequential, like letting anyone in this auditorium who shows signs of sneezing. There is always the possibility of some epidemic disease being initiated by such an individual. You have no way to estimate the risk if that will happen tomorrow and that the world's population will be decimated as a result of your carelessness in letting that person come into the room. I am quite serious. I think you can

make just as strong a chain of argument about those possibilities and historical precedence about the Great Plague and so forth as you can about any of the other areas of discussion.

However, they defy rigorous analysis at the present time and I think we have to be getting on to a somewhat different track in dealing with them. That track, I suppose, has a great deal to do with instilling public confidence in the integrity of your motives and your approach and a great many other things, some of which have been very badly fumbled by my colleagues in this particular arena. For example, you don't start out an honest effort in this direction by making it a media event to begin with. That has predictable consequences of the kind that in fact have come to fruit.

Well, I have offered some propositions, not very strong on substance, but I think at least I have conveyed the notion that we are all on the same leaky boat, a notion I think we need to share with the much broader community.