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(Applause.)

9 DR. KENAGA: Now, we come to that point in our
10 morning where we are peeking at our famous speakers. We have
11 all famous speakers this morning, of course, but today we
12 have with us Dr. Joshua Lederberg who was educated at
13 Columbia where he received his bachelor's of art and
14 Yale University where he received his PHD in microbiology.
15 He received his honorary doctorate degrees from both of
16 those alma maters as well as several other universities.
17 He has taught and chaired departments of genetics and
18 medicine at the University of Wisconsin, Stanford University,
19 is now President of Rockefeller University in New York.

20 While at Yale where he received his PHD in
21 1947 he discovered the mechanism of genetic recombination in
22 bacteria, demonstrating for the first time that a form of
23 sexual reproduction occurs in these microorganisms. Prior
24 to this discovery scientists had known little about
25 bacterial genetics, and many had even doubted that bacteria

1 possessed a genetic mechanism similar to that of higher
2 organisms.

3 Because of their simple structure and rapid
4 growth, bacteria now afford geneticists a field for study.
5 Later at the University of Wisconsin Dr. Lederberg and his
6 then student Dr. Norton Zinder, now a professor at the
7 Rockefeller University showed that bacterial genetic material
8 was exchanged not only by conjugation when the entire
9 complement of chromosomes is then transferred from one
10 bacterial cell to another but, also, by transduction where
11 only fragments are transferred.

12 They did this by introducing bits of genetic
13 material into the bacterial body and found that they became
14 part of the genetic material of the bacterial cell, thereby
15 altering its constitution.

16 This was among the first demonstrations of the
17 manipulation of an organism's genetic material. Eleven years
18 later at the age of 33, he was named co-recipient with
19 Dr. Edward L. Tatum and George Beetle of the Nobel Prize
20 in Physiology and Medicine for his work in bacterial
21 genetics.

22 In addition to being an outstanding research
23 scientist, Dr. Lederberg has been active in numerous
24 government and advisory boards dealing with problems of mental
25 health and retardation, a member and chairman of the

1 President's Cancer Panel, played an active role in the
2 Mariner and Viking missions to Mars sponsored by NSA, was
3 a consultant to the Arm Control and Disarmament Agency
4 during the successful negotiation of the treaty in
5 biological weapons disarmament, as a Director of the Center
6 for Advanced Study in Behavioral Sciences at Stanford and
7 the Institute for Scientific Information at Philadelphia.

8 He is especially interested in comparative
9 toxicology and hopefully in organizations like SETAC.

10 His continuing interest in improving communication
11 amongst scientists, the general public and government
12 policy makers has led Dr. Lederberg to write extensively
13 for lay audiences and includes a series of columns
14 distributed by the Washington Post syndicate on the social
15 impact of scientific programs.

16 If I continued to list his many achievements
17 and events of his illustrious career, I will be encroaching
18 on the time allotted for his message which we are all
19 anxiously awaiting to hear today, entitled Comparative
20 Toxicology, Environmental Health and National Productivity.
21 I am pleased to present to you as our founding lecturer
22 Dr. Joshua Lederberg.

23 DR. LEDERBERG: Thank you, Dr. Kenaga. I noticed
24 walking in the room that the placement of the lecturn on one
25 side was making it rather difficult for people to see and

1 perhaps even to hear down at that end, although the latter
2 does not make much sense.

3 I must confess that when Eugene Kenaga first
4 approached me about attending this first meeting of SETAC
5 I was more than a little bit skeptical. My first question
6 was who needs it? Did we really need another scientific
7 society? Would we end up contributing not only some further
8 pollution along the lines of hot ~~hair~~, as well as the
9 depletion of those important natural resources like airplane
10 fuel and human energy? Did we need another clarion call
11 to action and further rationality in public affairs based
12 on scientific and technical judgments?

13 To be very frank with you, I did not fully
14 appreciate the unique thrust of the society until just a few
15 days ago when I carefully scanned the program and the titles
16 of the papers that were being presented here and then the
17 full impact of what it is that you are trying to accomplish
18 finally did reach me, and in my observation from that
19 program of the combination of deep concern for environmental
20 conservation and rigor of scientific analysis in reaching
21 conclusions in that field, I am certainly a firm convert
22 to both the uniqueness and the necessity of this kind of
23 organization.

24 It is, if anything, long overdue, and I certainly
25 wish you all success in that enterprise. Yes, there is a

1 need.

2 In my own perspective on toxicology, it has been
3 founded more on the specific threats to human health that
4 are embraced by human toxicology, and so in my observation
5 of your program I was led to reflect on a couple of elements
6 by which these perspectives might be contrasted and what it
7 was that was really especially unique about this meeting.
8 These may be platitudes to you, but one person's platitude
9 is another person's illumination, and let me share some of
10 that with you.

11 First of all, the ramification of ecosystem
12 responses which is your immediate preoccupation seems to me
13 to embrace even deeper complexities and uncertainties and
14 perplexities than asking specific questions about the
15 encounter of one particular species, the human with defined
16 quantities of a particular environmental exposure.

17 The ecosystems are, if anything, more intricate
18 than the physiology of the single organism. You must be
19 vulnerable to issues of balance amongst competing species
20 in a given niche. You must be concerned not only with
21 toxins, but with nutrients, alterations of habitat, the
22 actions of other species, and they may be prey or predators
23 or parasites and these, of course, must lead an outsider, and
24 I do not count myself a professional ecologist, to wonder
25 at the audacity of establishing a theoretical system in which

1 not merely to understand and explain observed phenomena
2 but to attempt some prior prediction as to what the
3 consequences for the evolution of an environmental system
4 will be on the introduction of a new substance.

5 Secondly, ecosystems, if they, in fact, can
6 survive other natural perturbations must already have some
7 degree of adaptive robustness. Therefore, there is certainly
8 a threshold of environmental insult that such systems can
9 tolerate, a non-linearity of response which is far less
10 controversial than is true at the present time in human
11 toxicity, but this is a double-edged sword.

12 On the one hand it does offer some latitude
13 with respect to what may be regarded as insignificant
14 exploitation of the environment but may, also, be beguiling
15 because most systems are far too complex for us to anticipate
16 the consequences of human intervention before the fact.
17 The ease with which a biocommunity responds to our taking,
18 let us say, 1000 tons per year of a given species of fish
19 may delude us into believing that 100,000 tons will be
20 likewise acceptable and when the fisherie collapses we may
21 not then know whether it was a pesticide runoff or over-
22 fishing or some even more complex interactions that were
23 responsible. So, whilst there is some comfort in the view
24 that yes, indeed, there must be insignificant levels of
25 insight that can be applied to something as huge and as

1 diffuse and sometimes as self-protecting as the biosphere.
2 It may, also, deprive us of advance indicators of major
3 collapses of those systems. It is my own belief as an
4 outsider that ways to detect indicators of major collapse
5 may be one of the most important challenges, both at a
6 practical level and in the development of the theory of
7 environmental toxicology.

8 The other branch of your preoccupation and
9 especially today is an explicit concern for risk hazard and
10 how it is perceived by various communities. The last
11 30 years has seen the maturation, perhaps even the decadence
12 of an environmental movement of major proportions. What was
13 an exciting awakening of public consciousness after a very
14 long era of neglect and indifference has now become itself
15 one of our major industries, contributing its own pollution
16 as a side effect of some of its activities and invoking the
17 clamor of public attention to compete for power with the
18 technocratic sector of our society, and a system that was
19 strongly out of balance 30 years ago on one side has in the
20 perception of many, many people, swung far in the direction
21 of paralyzing almost every initiative on the technological
22 side.

23 This has two hazards; one, and the most material
24 is that the invocation of delay, delay in every project that
25 one can see as the last ditch resort of resistance in the

1 confrontation of these groups has left everyone far poorer
2 and highly frustrated. The environmentalists on the one
3 hand see continued encroachment on the environment, can have
4 little optimism that there will be significant improvement
5 over the next decade or two decades over the present status.
6 They can speak in many areas at best to having held up the
7 initiation of this, that or another project but from their
8 prospective that they are always in a losing battle, that
9 the major interests, the strength, the financial and
10 advertising and public relations and sometimes political
11 strength of industry will, in the end, override them, and
12 on the other side we have the exasperation and frustration
13 that we have run out of alternatives, that whereas from a
14 broad national perspective it did not matter much to give
15 in on one pesticide on the abrogation of one food coloring,
16 on the delay of one particular drug in its introduction, in
17 the construction of one powerplant in a particular area,
18 in the exploitation of one particular form of energy supply
19 we have reached the point where these are not vulnerable
20 merely point by point but are in a totally pervasive network
21 of confrontation and opposition to where there is scarcely
22 an industrial project of any magnitude and particularly one
23 of any innovation that does not have to anticipate public
24 confrontation and considerable delay in its further
25 implementation, and plainly something has to give in this

1 context. Besides the immediate and obvious economic costs
2 that are involved in this phenomenon, there is in my view
3 even the more serious one of the stultification of
4 initiative. In many areas people have given up trying to
5 develop or to introduce technological innovations regardless
6 of their merits, because they know there will be such a long
7 struggle before they can, in fact, be introduced that the
8 likelihood of the original investment, both in dollars and
9 in human initiative and in individual careers and that whole
10 texture ultimately founded on individual greed but tempered
11 by the mandates of the social contract begins to falter in
12 efforts at initiative, and I am afraid this is not too far
13 from being a description of the tenor of society today.
14 But the other cost which could be even more serious is the
15 backlash which I believe we are seeing emerging in full swing
16 against regulation of every kind and if one could contemplate
17 the extension of the public psychology that has led to the
18 legitimization of Laetrile and in other areas beginning to
19 emerge very strongly and perhaps some element of the
20 testimony of the last election is really all I need to
21 remind you of very sudden and rapid swings of public concern
22 on major issues not unrelated to what we are now facing.

23 So, I think there is a real sense in which the
24 concern for environment of the eighties must take stock, must
25 look for realistic objectives and above all must find ways

1 for the more constructive conciliation of these motifs, of
2 the very necessary concern for the protection of environmental
3 amenities, environmental necessities, both from the standpoint
4 of public health and for our ability to enjoy life as we
5 would like to see it in this country and that if we do not
6 find better ways to reach some sensible accommodation,
7 important values on both sides are very seriously at risk
8 and the best that we can hope for will be a variety of
9 highly irrational, often mutually contradictory and
10 inconsistent decisions that are likely to leave us all far
11 worse off than we are today.

12 There are some indications that there is still
13 a residue of accommodative thinking in the public will as
14 expressed both by the Congress and by some elements of the
15 Executive, although these are often no more consistent here
16 than they are in other spheres of national life. One way to
17 offer the statement of what we must achieve may seem like
18 a brutal one, but I think it better than we confront the
19 necessity of certain facts than shilly shally about them,
20 and that is that we must embrace ways to identify and then
21 accomplish some optimal level of environmental pollution and
22 to understand that this optimum is often not zero.

23 This may appear to be like some new diabolistic
24 ritual, maybe appear to be embracing the devil. We all hate
25 pollution in some form or another as it appears to our lives,

1 and the notion that we will find some optimal level of being
2 sure that our environment is contaminated with such and
3 such dosages of various toxins or other insults to us may
4 seem bizarre and the difficulty of understanding that there
5 is an optimum of evil in a world that has to run along some
6 practical principles is one of the chief difficulties that
7 we face, not only in our own understanding of the problem,
8 and I think an audience like this is sufficiently sophisticated
9 that one can at least discuss it, but even more so in trying
10 to reach what is all too often a highly confused public.

11 It may end up putting people in the posture of
12 being proud of having found mechanisms whereby they can
13 guarantee that a certain number of people will die, but for
14 the benefit of socially distributed goals which should, also,
15 guarantee that a larger number will be protected, and this
16 can sometimes be expressed in direct trade-offs with respect
17 to health opportunities and sometimes through the vehicle of
18 other economic advantage.

19 One wishes one lived in the world that it was
20 impossible to discuss trading off lives for dollars, but that
21 is not the world that we live in today. We are constantly
22 making decisions where we reach some limit with respect
23 to the expenditure of public funds, with respect to our own
24 personal investments, in protecting our safety as against
25 some statistical expectation of a reduction of death hazard

1 having come to an equilibrium with the level of social or
2 personal investment in that sphere.

3 How many of you have guaranteed the electrical
4 safety of your home by investing some few thousands of
5 dollars in a ground fold interrupter circuit? That gives you
6 a particular example. How many of you have installed
7 filters in your air ventilation system to guarantee against
8 the dissemination of potentially infectious microorganisms
9 as against other chemical insults?

10 We all draw the line at some point on matters
11 that we do know might afford some level of protection with
12 respect to our personal health. I don't feel that in this
13 audience I need to argue the point, but it is one that one
14 needs to have some illustration of.

15 But this is a rather brutal confrontation not
16 only to have to express but to have to internalize. It is
17 a very uncomfortable position to be in, to be even thinking
18 about these kinds of trade-offs, and if there were ever any
19 way to evade the moral dilemmas that are involved in that
20 kind of trade-off, I think we would eagerly seek them.

21 I do not believe they are evaded by the asserted
22 doctrine that there can be no trade-off, that risks must be
23 reduced to zero, that no matter what the cost, chemical or
24 physical pollution of an environment that might bear some
25 hazard to human health should be driven down to zero. That

1 is simply looking at a problem in a very narrow sphere,
2 examining only the single transaction that is at issue at
3 that point and failing to recognize the spillover of the
4 invocation of those costs into every other sector of our
5 economy and the immediate health consequences that will flow
6 from that neglect, to the extent that after a fair
7 consideration of the overall framework in which such
8 trade-offs occur we can verify that we can reach zero
9 pollution as not only an optimum, not merely an optimum but
10 even an acceptable level of investment which is fair to the
11 competing demands for health, as well as for other purposes
12 in other spheres, then that zero level might be acceptable
13 in a rational framework. I am not aware that that can ever
14 be done.

15 Those who deny it, those who look for zero
16 pollution are in my view living in a world I would like to
17 inhabit myself but which I believe is one of fantasy. Above
18 all it denies Avogadro's number. It suggest that this is
19 a small finite indenture, that we can obtain absolutely
20 pure preparations of materials that we take in that can
21 guarantee that there are zero molecules of undesired
22 pollutants in them.

23 To a degree it denies that the natural world
24 itself is already free of predators, of toxins, of infectious
25 microbes and other hazards which require measures that have

1 environmental costs of their own in order to provide our
2 protection against them. One need only invoke the trade-offs
3 that are involved in both public and private policy with
4 respect to the use of vaccines to illustrate that point.
5 There is no vaccine which is totally free of risk and if one
6 were to invoke that as a principle for the introduction of
7 a health saving measure in that sphere the human cost would
8 be absolutely enormous and sometimes has been.

9 Once one accepts that zero pollution is a fantasy
10 at least from the standpoint of the informed chemist who
11 knows about Avogadro's number, then it is plain that some kind
12 of quantitative standard must be set by some principle in
13 the regulation of affairs that may influence the entry of
14 a substance into the environment.

15 Once one has done that, once one has agreed that
16 a standard is what must be applied because zero is an
17 undefinable in chemical terms as against Avogadro's number,
18 then the question is no longer whether a trade-off analysis
19 is going to be done, but the procedure by which it is
20 accomplished, and I would submit that every decision that
21 has mandated a standard, even those where the number zero
22 was used but in a real world where analytical methods are
23 capable sometimes of identifying only a few molecules of a
24 given substance and that that has been used as the standard
25 of application that there has been some kind of implicit

1 trade-off analysis made in the mind of that administrator,
2 and our main purpose in speaking for cost/benefit/risk
3 analysis, it seems to me must be to attempt to expose in
4 detail, to lay out on the table for public examination the
5 full process of reasoning by which any such conclusion is
6 made, and I will make the rather harsh statement that in the
7 present state of the art I do not believe this can be done
8 by a rigorous mechanism of cost-risk/benefit analysis as it
9 is commonly put on, but there is someplace in between in which
10 the mind of the regulator must not allow to be a black box,
11 must not allow to be insulated from examination and
12 criticism where the arguments must be exposed and exposed
13 in some kind of technically sensible, quantitative rationale.
14 There will still be an extraordinary latitude of judgment
15 that must be invoked at a time when almost none of the
16 variables that are involved in an explicit cost risk/benefit
17 analysis can in fact be stated with any high degree of
18 precision.

19 We have seen circumstances where predicted costs
20 of environmental improvement have failed to materialize
21 sometimes very drastically. I can think of by factors of
22 100 in either direction, where engineering improvements
23 that were asserted to be very difficult to apply have resulted
24 in fact, in savings and other circumstances where engineering
25 improvements that were mandated on industry have proven to be

1 essentially impossible to achieve regardless of any
2 reasonable degree of investment that would be mandated.
3 One certainly wants to encourage a deeper examination of
4 what the costs of an initiative will be than is likely to be
5 conducted in the absence of pressure from a regulator to
6 accomplish a given aim, but here in the one area which
7 should be the hardest, the soundest of the numbers that
8 could be attributed to an analysis we find that there are
9 already grave difficulties.

10 Risks of environmental pollution are, of course,
11 the very meat of the scientific concerns that we have at
12 a meeting of this sort, and I would acknowledge that they
13 are far more difficult in your sphere of concern in terms
14 of the complex responses of complicated ecosystems than they
15 would be even on their intersection with and their
16 involvement with the health of human individuals. Benefits
17 must embrace health improvements, environmental amenities,
18 other elements of production, conservation of resources for
19 future use and those resources include in very large measure
20 that environmental sink which is the place we have to go
21 when we want to get rid of something and which is a very
22 finite number.

23 The estimation of those benefits since they are
24 not fungible; they are not readily translated into dollars
25 is not only a technical exercise of great complexity, but is

1 probably the main focus and legitimate one of value
2 controversies; precisely what trade-offs should there be
3 between having a clear atmosphere around a city and the
4 costs of improvement of its factories? That is not something
5 that can be settled for the rest of the community inside of
6 this room. That is something where the basic issues have
7 to be presented for public determination on a far broader
8 sphere, but they must be presented far more clearly than
9 they have been up to the present time.

10 One the risk side, we know we face many
11 dilemmas, and here I am going to speak mainly from the
12 perspective of the human toxicologist. The question of
13 linearity of response, the absence of tresholds of human
14 responses to toxic substances remains and will long remain
15 one of the most controversial issues that we have to face.
16 The fact is there are theoretical arguments that would allow
17 for any of the numerous models that are proposed abstractly
18 in this sphere; as against the notion of mandating a threshold
19 one could invoke sunlight, one of the best proven carcinogens.
20 Would we suggest that exposures to this carcinogenic
21 entity be subject to governmental regulation in order to
22 reduce the risk to zero? And while we may wish to refrain
23 from interfering with the personal preferences of recreational
24 sunbathers and believe some protection of privacy with
25 respect to large-scale exposure might, in fact, be something

1 that is a personal privilege, there are, of course, many
2 people who have no recourse but to expose themselves to sun.
3 A considerable fraction of our population not only lives but
4 works out of doors, enjoys it; should we mandate engineering
5 controls in order to minimize their exposure to ultraviolet
6 light which can be guaranteed to cause a certain incidence
7 of skin cancers, and while many of them are quite innocuous,
8 one cannot dismiss the melanomas that will, also, be some
9 fraction of that exposure.

10 For other chemical substances there is a wide
11 range of theoretical argument with respect to threshold.
12 I do not think one can adopt the general and generalized
13 view that since there are indeed repair mechanisms and there
14 are indeed metabolic mechanisms that can dispose of a
15 certain fraction of the insults induced by a particular
16 molecular species that this has anything whatever to do
17 with the existence of a threshold.

18 For either metabolism or repair to be relevant
19 to the question of linearity one must know more about the
20 chemical kinetics of those mechanisms. If there is a cup
21 that can be filled, and only the spillover is toxic, then
22 of course there will be a threshold, but is that the
23 mechanism by which either repair or metabolism of toxic
24 substances occurs? The answer is probably not, in most of
25 the specific circumstances that one can invoke as applications

1 of those particular notions.

2 To the best of my knowledge, and this has been
3 investigated quantitatively only in bacterial systems repair
4 of DNA damage is not a saturating phenomenon but is one which
5 is proportional at every level of the insult. One does have
6 repair of ultraviolet induced injury, chemically reduced
7 injury, but at least in these bacterial systems it is a
8 constant fraction of the primary insults that are subject
9 to repair; a constant fraction even at the lowest doses
10 escapes and under those circumstances one changes the slope
11 of the dose response curve but not its shape, and one will
12 still have a linear response for which no absolute threshold
13 can be determined.

14 These are matters that could be studied
15 experimentally in tissue culture, for example, even with
16 human cells. To my knowledge that has not been done. So,
17 I am asserting a rather, I think, soundly based theoretical
18 proposition in this sphere. If one relies on the metabolic
19 capacity of the organism to provide that cup that can be
20 filled without injuring the rest of it, one faces even
21 greater perplexities. There again, it is difficult for me
22 to invoke systems where I am aware that they are saturated
23 with respect to the toxic substances with which we are most
24 concerned.

25 In fact, for highly toxic materials it is rather

1 unlikely that that will be the case because it would imply
2 that you are titrating out the enzyme molecules responsible
3 for that metabolic conversion, and if we are dealing with
4 toxins that are active at fairly low concentrations, it is
5 rather unlikely that that will ever be the case in practice.
6 There may well be exceptions. There certainly can be
7 differences in the metabolic handling of large quantities
8 of a toxic substance compared to small ones, and I do have
9 some sympathy for those people who are working in bladder
10 cancer and are aware that feeding of very large amounts of
11 particular substances can result in crystallurias and in the
12 formation of stones where this is indeed an example of
13 spillover, where the ability of the urine to remove a given
14 quantity of solute does reach saturation on super saturation
15 and in a very literal sense you have the formation of
16 precipitants and there in principle the possibility of local
17 toxic actions which would be highly dose dependent.

18 These are very interesting theoretical
19 propositions. None of them has been carried to the point of
20 experimental corroboration in ways that they would be useful
21 for regulatory purposes. I just wanted to give one or a few
22 examples where it would be possible for those people who are
23 most deeply concerned about what they would call the
24 premature application of general principles of limited
25 rationality like the linear response to dose, really do have

1 an opportunity to offer up some concrete and relevant
2 evidence to the contrary. One might be quite optimistic that
3 one will discover exceptions to the linear rule, but they have
4 not as yet been forthcoming, and I think that there is a gap
5 that can only be filled by further scientific investigation.

6 We do, of course, suffer in many, many ways
7 from the historical development of toxicology as an orphan
8 science. It is a field which until very recently was neither
9 a very great public or national importance, nor one that had
10 achieved a considerable degree of academic respectability.

11 I think we are all very pleased that this
12 situation is changing, changing quite rapidly at the present
13 time on both counts.

14 It was not helped by the fact that for the past
15 15 years the market for toxicologists has been dominated by
16 the demand of the regulatory agencies to perform tests that
17 had to be, I stress had to be conducted in the most routine
18 way imaginable because they were testing protocols for
19 safety of materials that in the way the bureaucracies must
20 run had to be applied fairhandedly to all comers, had to be
21 written down in a book in advance and had to be applied without
22 favor or exception or reasonable accommodation or any
23 approach to the acceptance of real scientific insight to a
24 given problem in order to meet the regulatory demand.

25 No wonder a profession, the market for whose

1 product was dominated by the need to staff laboratories to
2 perform these very routine tasks that went contrary to
3 common sense, as well as scientific reason for so many years
4 had great difficulty in establishing itself as an attractive
5 setting for the most aggressive, energetic and enthusiastic
6 of young minds and even when they would go into it would find
7 themselves in circumstances where, guess what, they had to
8 kill 10,000 mice next week in order to meet their quota.

9 This is something that must change, and it must
10 change in the direction of bringing toxicology firmly into
11 the mainstream of modern biology.

12 There are a number of ways in which this can and
13 must be done. The relationship of toxins to the general
14 evolution of ecosystems which is the main focus, I believe,
15 of the scientific interest of this organization is an exciting
16 illustration of how to build a bridge to a major arena of
17 modern biology, and it is not only in this field that in fact
18 I think we will find that not only does that modern biology
19 offer a good deal to toxicology but that the converse may be
20 true even more deeply.

21 There were dozens of papers in the program that
22 I looked at today that involved close analytical examination
23 of the responses of an ecosystem to an intended or inadvertent
24 but in any event manmade intervention that involved
25 experiments with the environment that could never have been

1 done and would never have been analyzed were it not for the
2 toxicological framework of that examination. I believe that
3 in general principles the physiology of individual organisms
4 and the responses of communities are going to profit
5 enormously not only from the general attention and support
6 but from the provocation of the findings of these kinds of
7 experiments that can bring that field as well to a state
8 of development and excitement that it would be unlikely to
9 have achieved in its absence.

10 In fact, I rather suspect that by far the major
11 effort that goes on in ecological analysis during the next
12 decade is going to be in the context of environmental
13 toxicology.

14 The same is true of other aspects of biology.
15 One route that would be of particular pertinence would be to
16 try to generate more excitement for toxicology about the
17 application of the comparative method which is one of the
18 fundamental routes of biological analysis. It is one that
19 runs so deep in my own consciousness and the way that I think
20 about how to ever design experiments or to look for general
21 principles in biology. I guess it was mentioned that I was
22 on the Mars Viking team, and of course, that had no other
23 motivation than an attempt to go beyond the bounds of our
24 own terrestrial biosphere to see if there were something else
25 that that rather limited evolutionary framework that we had

1 here could be compared with. So far it looks as if the
2 answer is negative, but that has been far from exhausted as
3 a matter of examination.

4 This runs so deep that I was rather startled to
5 find that to my own knowledge there really has not been a
6 careful historical examination of the way in which comparative
7 thinking has pervaded biology since its roots. So, I can
8 offer a few observations only as an amateur in my examination
9 of the history of ideas in this field.

10 I was quite intrigued to see how deeply
11 Aristotle used judgments based on comparisons of a range of
12 organisms to make a wide variety of generalizations about
13 what was and was not pertinent, what kinds of correlations
14 would be available, animals that had more teeth in their
15 lower jaw had certain properties compared to animals who
16 had more teeth in their upper jaw and so on and so forth.
17 I am sorry I did not bring the text to read to you on these
18 matters, but it is plain that from the very beginnings of the
19 scientific examination of living forms that the variety with
20 which these forms present themselves was the most immediate
21 provocation to the development of theories of life, of its
22 nature in general, obviously the segregation of living
23 organisms from other aspects of the organization of matter
24 and in much greater detail.

25 We find in 1628 the founder of physiology,

1 the founder of physiology, William Harvey, conducted his
2 examination of the function of the heart by the most
3 meticulous and detailed comparison of the circulatory
4 systems of a variety of species and that this set of
5 comparisons comparing hearts with two chambers with those
6 of four chambers and so forth was of crucial importance in
7 his development of the physiological theory of circulation,
8 and he must have been very much on the defensive for looking
9 at organisms other than man. He apologizes for this at many
10 places in his discussion and in particular he inveighs
11 strongly against those who feel that the only sphere of
12 observation relative to humanity is the examination of the
13 dead human being. That must sound a little bit familiar
14 in today's context.

15 The comparative approach is, of course,
16 fundamental to our understanding of the evolution of life.
17 We have a framework of what we generally now believe the
18 monophyletic origin of all living forms based on that kind
19 of comparison and through the mechanisms that Darwin and
20 the neo-Darwin in evolutionary theory has dwelled upon in
21 very great detail.

22 More recently comparative biochemistry which
23 reached its culmination, I would say, in Beetle and Tatum's
24 work on the laboratory production of specific genetic
25 alterations that then have specific biochemical consequences

1 has been absolutely invaluable in the analysis of biochemical
2 pathways.

3 One wants to reflect a little bit why that tool
4 has been so important. I think it can be summarized in large
5 measure to the very complexity of the individual biological
6 organism. This is so complicated that it is until the point
7 when one knows the pathway and can isolate the enzymes hard
8 to grasp in all of its detail. One has two organisms that
9 differ in respect to one gene, therefore one primary function.
10 It is far easier to dissect out the specific differences
11 between two complex systems which are highly circumscribed
12 and which then cast out a lot of the commonality as being
13 totally irrelevant.

14 If you have one form of an organism that makes
15 no pigment, is white and another form that makes a yellow
16 pigment, you find in trying to chase out the pathways that
17 there are some enzymes that differ between these two strains
18 and others that are common. You can discard the common
19 elements immediately as being irrelevant to the difference
20 in pigment formation and therefore like to be immaterial
21 to that pathway. It is a method that has been used over and
22 over and over again, and it may be one of our most powerful
23 ways of dealing with systems as complex as the organism.
24 You use it as well in your ecological studies. It is far
25 more difficult to do there, to form two bions that differ

1 in only a limited number of initial conditions from which
2 to then try to dissect what the consequences of those will
3 be.

4 I would like to invoke that history of comparative
5 biology as being one of the most powerful potential tools
6 that we have for working out the mechanisms of toxicity of
7 new substances. There are several paradoxes about that.
8 First of all, in the way that toxicology has been mandated
9 to develop as a regulatory discipline the discovery of the
10 toxicity in a single species out of a panel that may be
11 prescribed is usually not the starting point for an
12 investigation of why one species differs from another one
13 but the closure of development of that particular substance,
14 because there is a prima facie argument that if a substance
15 is toxic in any species whatever, that it is likely to be
16 toxic in man. This is sometimes rebuttable, sometimes in
17 practice not but almost always makes the game hardly worth
18 the candle for the further development of that particular
19 chemical and from the standpoint of the developer and producer
20 it is likely to be more economical to abandon one's efforts
21 at the study of a particular substance once it exhibits
22 toxicity in any interesting species that might be thought
23 of as a model for man than to pursue the question of why
24 it kills rats and not mice and try to go on from there for
25 whether it is likely to be a good predictor of its behavior

1 in the human.

2 So, I am convinced, and I have been told that
3 there is, in fact, a vast amount of information on differential
4 responses of different species to potentially toxic substances
5 which has never been followed up, which has never been
6 published. It was in no one's apparent interest to do so,
7 and therefore those kinds of anomalies, those kinds of
8 surprises or discrepancies or paradoxes that are the very
9 meat of scientific inquiry in the academic laboratory are
10 the closure of further developmental study in the industrial
11 laboratory, and we must find some way in which that can be
12 broken out.

13 The other side of comparative toxicology is that
14 in fact it is the theory of prediction as far as human risk
15 is concerned.

16 The one way we do not wish to become the
17 canonical method of determination of human toxicity is by
18 the explicit discovery of human injury after a substance
19 has been introduced into the environment. In order to
20 prevent that from happening, in order to keep our environmental
21 introductions from making unwitting guinea pigs and in the
22 real sense that people have been injured for lack of adequate
23 foresight, we, of course, must develop far more robust and
24 reliable methods of prediction based on laboratory assays
25 on a variety of other species and so on, but there unlike the

1 circumstance in clinical medicine where the final test of a
2 new drug is a clinical trial in which human beings are
3 empirically exposed to a substance that has had some prior
4 testing, some prior validation but where your decisions about
5 its value, positive or negative are based on human exposure,
6 we are obliged to try to prevent those tests from being done
7 where there will be significant physiological responses of
8 humans to a substance.

9 Therefore in environmental affairs, far more even
10 than in therapeutics we need a robust theory of prediction.
11 We need a set of principles, of validated procedures, of
12 methods of analysis and extrapolation upon which we can
13 place some faith and reliance so that when we do these
14 studies in the laboratory we can make confident predictions
15 as to the nature of the human response.

16 That puts a load on comparative biology, including
17 the biology of the human and that of the other test systems
18 far greater than it has had to bear in any sphere up to the
19 present time, but I believe it is one of the greatest
20 challenges both to toxicology as an applied science and to
21 toxicology as a mainstream element of the development of
22 general biological theory that we can look forward to at the
23 present time.

24 At stake in this is not only some straightening
25 out of our national posture in this respect but I must say

1 even to the credibility of our scientific effort itself.
2 I do not know how long the public is going to stand for the
3 uncertainty to which it is subjected, the assaults which
4 it hears, statements that something may be risky, but we
5 really don't know on the one hand and demands for the
6 continued support of basic science for its own sake on the
7 other.

8 I think there is going to be an increasing
9 demand to scientists in the basic biological disciplines
10 to put up or shut up, to provide some effective contribution
11 to what is becoming an ever more urgent confrontation
12 between scientific uncertainty and the needs of public
13 policy.

14 I congratulate the organization of this group
15 for what I believe is a major step towards the bringing about
16 of a dialogue and a forum for critical inquiry of the
17 discipline of scientific investigation criticism and
18 comment in a field that needs it ever so badly.

19 I wish you well.

20 (Applause.)

21 DR. KENAGA: Please don't leave the podium.

22 Dr. Herbert Ward has proposed an award of our society, a
23 single award for your being our very first lecturer and our
24 first award, and he has a citation here which we want to
25 present to you in honor of this occasion. It is a very

1 nicely lettered document which says, "The Society of
2 Environmental Toxicology and Chemistry awards this to you
3 as our founder lecturer," and you can maybe find a place
4 on your wall amongst all the rest of your awards for that,
5 and we thank you very much.

6 (Applause.)

7 DR. LEDERBERG: Thank you. It is really my
8 privilege.

9 DR. TUCKER: You are all anxious to go to lunch
10 I know. Just one brief announcement.

11 (Administrative announcement.)

12 (Thereupon, at 12:20 p.m., a recess was taken
13 until 1:30 p.m., the same day.)