RECEIVED
CSHA
JUL 16 19

PLAINTIFF'S EXHIBIT
DOW-1782

Dedication Address

Northwestern University Cancer Center

by

Philip Handler
President
National Academy of Sciences

18 May 1979

921001 RowVerK .0656

It is a high privilege to be with you this morning to participate in the Dedication of the University Cancer Center. We do so at a time that appears to be particularly felicitous for such a venture.

Neoplasia -- cancer if you prefer -- is a problem of immense human concern. At this time in the history of our country, approximately one quarter of the American population may be expected to succumb to cancer in one or another form. This rate, as a percentage of all deaths, has risen slowly over the years, not because of an actual increase in cancer incidence, stated on an age-corrected basis, but rather because of improved sanitation, because of our history of success in dealing with bacterial infections, because of an improved food supply and an economy that has abolished nutritional deficiency diseases, because of our success in immunizing against viral diseases and in treating endocrine disorders. Moreover, for the last few years, the death rate due to cardiovascular disease and stroke has also been declining. All of these welcome circumstances have freed us to fall prey to the ravages of cancer.

To be sure, viewed statistically, cancer is not a great threat to the human life span. Because, in the main, it is a disease of our later years, were all cancer to be instantly abolished, as it were, the mean age at death of the American population would increase by only one and a half to two years. Nevertheless, we are here for very good reason. Our purpose is not to extend the human life span indefinitely but to join in the intensely human endeavor by which this great cruelty may be relieved or, better yet, to so arrange that it not be visited upon us.

When, some months ago, I accepted Dr. Berlin's invitation to speak today, I agreed to discuss the general circumstances of biomedical research in our time and the public policies necessary to facilitate the progress of such research, to review the areas of greatest progress and adumbrate what may lie ahead. But, in so doing, he set me to thinking about "the cancer problem" in its boldest outlines. In short order, I found myself puzzled.

921091 Rowley 065.1

Accordingly, and with no little trepidation, I would like, instead to share some of my puzzlement with you in the hope that it may give some direction to future research.

Two themes dominate present literature concerning the etiology of cancer: (1) The primary event is a mutation, viz., a permanent alteration of the genome but of unstated nature and (2) the mutation is occasioned by a physical insult to the genome from without, i.e., by the action of a chemical carcinogen or by radiation. These are linked by the fact that, after exposure to the external agent, cell transformation occurs and the succeeding generations of cells proceed along their unheeded course in the absence of the original injurious agent. My examination will be concerned with both of these considerations.

Last week, on the Mall in Washington, several speakers, Jane Fonda among them, inveighing against nuclear energy, urged their huge audience to join them in attempting to shut down the nuclear energy industry so as not to exacerbate further what they referred to as "our current epidemic of cancer." There is no such epidemic. The age-corrected incidences of only two forms of cancer have altered significantly in our lifetimes. Bronchiogenic carcinoma due to cigarette smoking has risen sharply and the incidence of primary gastric carcinoma has declined dramatically for entirely unknown reasons. These two have more or less offset each other and the age-corrected incidence rate for the total of all forms of cancer has remained approximately constant for a half century.

The epidemiology of cancer has been intensively scrutinized. The principal finding has been that the incidence rates of different forms of cancer vary quite significantly among countries and, less dramatically, among regions within our country. In the U.S., there is no correlation between the incidence of any form of cancer and the ethnic origin of any subgroup of our genetically heterogeneous population. These circumstances underlie current belief that observed geographic differences in cancer incidence rates do not reflect differing genetic constitutions of the affected populations but, rather, arise from differences in local cultural patterns and from some unstated aspects of their environments. The most dramatic evidence usually cited is the present

very high rate of gastric carcinoma in Japan, the significantly lower rate in first generation Japanese in the United States, whereas second generation Japanese in this country show no more gastric carcinoma than do the rest of us. And that is even more significant in view of the fact that, 50 years ago, the rate of gastric carcinoma in the United States was approximately what it is in Japan today. We have been doing something right and don't even know what it is.

The sum of such analyses has fostered the frequently stated notion that as much as 80 to 90 percent of all cancer is of environmental origin. That conclusion, however, seems to me to have been improperly coupled to suggestions that the myriad synthetic chemicals, made by American industry and utilized in so many ways in our economy, are major contributors to the current rate of cancer incidence. This idea has gained currency in consequence of several isolated episodes such as experiences with vinyl chloride, asbestos, and a few other substances, for each of which, one should note, the first intimation that it is carcinogenic derived from limited but disastrous human experience, not from animal testing procedures.

In turn, this has led to a now sizable national program in which tentatively suspect chemicals are tested for carcinogenicity in various species, usually rodents. The, by now, compelling evidence that almost all demonstrated carcinogens are mutagenic when tested appropriately has led to the development and use of preliminary, relatively rapid, screening procedures in which suspect chemicals are first tested for their mutagenicity in various relatively simple and rapid test systems, for example, those using bacteria such as Salmonella or a mold such as Neurospora. To this battery of tests has recently been added the technique of assaying for transformation of an animal cell line in culture, confirmed by determination of whether the transformed cells will give rise to a viable tumor when transplanted back into a host animal.

Several hundred specific chemical compounds have been thus examined in the last few years and a considerable fraction found to be both mutagenic and carcinogenic. Nevertheless, we should lay to rest the idea that it is

these man-made compounds, abroad in the land, that are responsible for the fact that 25 percent of Americans die of cancer. They are not. The possible effects of all known man-made chemicals, when totalled, could contribute only a minuscule fraction of the total of all carcinogenesis in our population. As I noted earlier, current age-corrected incidence rates are much what they were before most of these chemicals were introduced into our surroundings. They certainly cannot account for the even higher age-corrected cancer rates in some, more primitive, countries which do not yet enjoy the benefits of a diverse chemical economy. This conclusion can also be supported as follows:

In a general way, the levels of environmental chemicals in various societies may be presumed roughly to parallel the rate of energy use in those societies. That is analytically helpful since acceptably accurate data are available for energy consumption for almost every country in the world. But, as noted by Totter, there is no form of cancer whose incidence in any way correlates with the rates of national energy use; nor does the total rate of all cancers combined so correlate.

If then, carcinogenesis is largely due to environmental factors as the epidemiological data generally suggest, we are left with the conclusion that the environmental culprits remain to be identified. Conceivably, aflatoxin, the product of a mold that grows on peanuts and corn, for example, may be a model for others; it is among the most potent carcinogens known, effective in quite small dosage. A few other, naturally occurring, carcinogens are also known, but none are sufficiently widely distributed or powerful to be regarded as significant, quantitatively, in cancer causation. If the environmental cancer hypothesis is valid, it seems strange that the major naturally occurring carcinogens have so successfully escaped our attention.

I am in profound sympathy with those who are vigorous in the pursuit of environmental mutagens and carcinogens; surely it is far more desirable that we prevent cancer by eliminating carcinogens from our environment than that we wait to attempt to cure or extirpate the resulting cancers.

I trust that their activities will continue apace. But from what I've already said, if the environmental carcinogenesis thesis is valid, our principal task is to identify the real environmental carcinogens that we must assume to be hiding in the natural-, not the man-made environment.

Nor do I mean to deprecate concern for man-made carcinogens. The extraordinary growth of the chemical industry and our reliance on its products is a post-World War II development. It is not inconceivable that a cancer time-bomb has already been planted and will only become apparent after a 20 to 30-year lag time. We should be prepared to recognize this phenomenon should it occur and to undertake the epidemiology required to establish more precise causality. That is not easy. Remember the long uphill fight to so establish cigarette smoking despite the fact that it should have been more readily demonstrable because there was a built-in experimental control group -- the non-smokers.

I must confess that I am dubious of the reality of this proposition, but not because I doubt the reality of chemical carcinogenesis. Epidemiologically, carcinogenesis due to a low potency carcinogen can only be demonstrable and certain if (a) it occurs in a discrete group of occupationally heavily exposed workers or (b) involves some otherwise rare and unusual lesion. If the carcinogen is extraordinarily powerful and very low exposures can occasion a high frequency of lesions, a statistically meaningful increase in cancer occurrence should be unmistakable. For an overwhelming fraction of the carcinogens identified in recent years by laboratory screening procedures, these criteria rarely obtain. The lesions are usually similar to those inducible by a variety of agents. Very heavy doses have been necessary to obtain statistically meaningful results. The argument that "there is no threshold" may or may not be true -- but, epidemiologically, does not matter in the sense that even chronic exposure to very low doses will, according to the theory, engender so small a number of cancers that, unless the lesion be unusual -- and most are not -- the total numbers will not detectably alter the statistics of cancer occurrence.

That is not to make light of the problem. An exposure level for a hypothetical carcinogen that places the entire population at a risk of 10^{-6} could, in the steady state, engender 200 new cases of cancer per year -- this is the tyranny of multiplying even a very small number by 2×10^8, the population of the U.S. -- but these 200 will not be noticeable or identifiable among the 350,000 annual deaths due to cancer. Whether the societal benefits associated with the use of such a hypothetical, low potency carcinogen may warrant such risk is an entirely different subject -- to be dealt with on a case-by-case basis.

Moreover, that hypothetical risk estimate of 10^{-6} is usually obtained by an immense extrapolation from the actual data. What is painful to recognize is that there is no chemical carcinogen for which the medium dose, much less the very low dose end of the dose-response curve has been reliably examined. There are seemingly valid arguments both for and against the linear response, no threshold hypothesis -- in which most investigators now seem to believe. Given the degree of national concern, and the fierceness of the argument, one would think it time that we go to the expense and trouble of a few such major experiments.

Allow me a digression concerning the national debate about how, wisely, to regulate the use of very low potency carcinogens of significant economic value. It is facile to suggest that each case be determined on the basis of a formal risk and cost/benefit analysis. But the environmental problems of our day involve risks and benefits that usually accrue to different groups and costs, risks and benefits that are incommensurable. Costs are reckoned in dollars, benefits in esthetic or material values, risks in human lives. It is for this reason that while risk/benefit analysis can certainly inform the decision maker, his decision must necessarily still turn on a value judgment. The acceptability of a given level of risk remains a political, not a scientific question. When scientists enter these lists but fail to recognize the boundaries, unspoken ideological or political beliefs easily becloud seemingly scientific debate.

Difficulty arises in the scientific community from confusion of the role of scientist qua scientist with that of scientist as citizen, confusion of the ethical code of the scientist with the obligation of the citizen, blurring, therefore, the distinction between intrinsically scientific and intrinsically political questions. And yet that need not happen. In the mind of the scientist there need be no conflict between science and human progress. The scientific ethos itself should compel the behavior of the scientist when he contributes to evaluation of the social value of a specific technology. Unfortunately, when presentation of his analysis and recommendations is also suffused with a social or political ideology, the scientist/advocate can all unconsciously become a partisan -- and leave his ethos behind. And we have seen that occur.

What seems lost on some who would participate in the debate on the place of technology in our society, particularly those concerned with possible environmental carcinogenesis by radiation or chemicals, is that the necessity for scientific rigor is even greater when scientific evidence is being offered as the basis for the formulation of public policy than when it is simply expected to find its way in the market place of accepted scientific understanding. Science itself can benefit by early publication of properly documented preliminary findings. But surely public policy should not rest on observations so preliminary that they could not find acceptance for publication in an edited scientific journal. And yet that has happened repeatedly.

Political decision makers have no choice but to rely on the validity of what seems to them to be the findings of rather recondite science thereby placing a heavy onus on scientists who bring such matters to attention. Announcement in the press of each experiment, in turn, generates public alarm that can neither be justified nor assuaged. Once a compound has been publicly called into question, however meager the evidence, decision concerning its use becomes unavoidable. The sensible guide would be to accept substantial hazard only for great benefit, minor hazard for modest benefit, and no hazard if it can be avoided without penalty. But in most cases to date quantitative assessment of risk is entirely lacking; accordingly, the current guide -- as given expression in

the Delaney Amendment to the Food, Drug and Cosmetic Act -- appears to be to place a value of minus infinity on any possibility of carcinogenesis -- a position that cannot be indefinitely sustained.

For most environmental pollutants that have recently been called to attention we are concerned with potential but as yet undemonstrated hazard. Statistically speaking, relatively few persons are known to have been seriously damaged by man-made chemicals. The absolute number is, of course, meaningful and deplorable. But as a percentage of total mortality it is very small indeed.

In any case we have become highly conscious of environmental health problems. A host of institutions, public and private, are alert and vigilant. The result has been a stream of regulations each well intentioned, most indeed commendable. But in the absence of persuasive data concerning the magnitude of risk to humans, the sum of such regulation can engender public cynicism, ensnarl life in the work place, and slowly paralyze the economic life of the nation. I applaud the evolution of the Clean Air Act, from 1970, when it mandated reduction of risk to zero irrespective of cost, to 1977 when it asked that decision be based on comparison of marginal cost with the marginal benefit of pollution abatement. That returns to the scientific community the burden to identify and quantify risks and relate health effects to exposure levels, as it leaves to all of us the responsibility for developing a meaningful risk/benefit calculus which is now so drastically lacking.

A decade ago it may have been desirable to flag public attention to potential hazards and proceed as if each were a clear and present danger; it is time to return to the ethics and norms of science so that the political process may proceed with greater confidence. The public may wonder at why we don't already know that which appears vital to decision -- but science and technology will retain their somewhat diminished place in public esteem only if we steadfastly admit the magnitude of our uncertainties and then assert the need for further research. And we shall lose that place if we dissemble or if we argue as if all necessary information and understanding were in hand -- whether the question be the health effects of air pollutants, food additives or microwaves, the economics of solar energy,

the properties of a radioactive waste disposal system, the social consequences of electronic mail systems, or of linkage between large data bases. Scientists best serve public policy by living within the ethics of science, not those of politics.

These considerations reveal a painful dilemma. All of us cherish the democratic ideal, i.e., that matters might be so arranged that persons affected by public policy could have a voice in framing that policy, even an opportunity to vote on that policy. Implementation of that ideal with respect to public management of technology and applied science has a less than noble history. Unless opposed by major economic factors understood by the polity, scare tactics prevail all too readily. Witness the outcomes of plebiscites concerning fluoridation of communal water supplies. It is facile to suggest that a more scientifically literate population could more readily and successfully make such decisions -- but the issues that must be factored into decisions concerning nuclear power, coal combustion, automotive emissions, some food additives, etc., are complex even for the practicing scientist. We need no wholesale demonstrations that "a little knowledge is a dangerous thing." Accordingly, we require institutions and procedures that are democratically accountable while informed decision making itself must be left to those to whom we have temporarily given that authority on our behalf.

#

I would not for a moment pose as an oncologist or cell biologist. But there are questions that give me difficulty in my casual acquaintance with this literature. Let me share some with you.

While I am grateful for the long lag that can ensue between exposure to a carcinogen or to radiation and its subsequent expression as cancer, I find myself decidedly puzzled thereby. Just what is happening during all that time? It is certainly not the mere time required for a sufficient number of divisions of a cell that has gone out of control. The early appearance of leukemia after exposure to radiation is sufficient demonstration thereof. Is it because, for many cell generations, the

cells of solid tumors continue to remain under substantial control? If so, why should a mutation behave so? Is the growth and spread of the cancer linear throughout all that period and simply very slow? That does not appear to be the case. Are most of the aberrant cells scavenged by an immune surveillance mechanism which ultimately fails? Perhaps. But if not, what does happen during the long lag period? How can one reconcile the long lag time with the idea that cancer is the result of one or more dramatic mutations of a cell's genetic apparatus?

Almost everything one knows about neoplasia is in accord with the idea that it is an aberration induced in the genetic apparatus of such character that the affected cell(s) dedifferentiates in greater or lesser degree and thereafter divides as does a more primitive cell. What then is its relationship to its neighboring cells? That question did not loom so important until we began to appreciate how exquisitely sensitive cells in the developing embryo are to their nearest neighbors, to the fact that the final mature form of an embryonic cell, dependent, to be sure, on its own genetic programming is, in large measure, programmed by messages received from its immediate environment. Perhaps the most dramatic demonstration of that concept is the remarkable set of experiments in which cells from a growing teratoma have been inserted into the early blastula stage of developing embryos, taken their place in such blastulas and gone on to participate in completely normal development. How can a teratoma, supposedly the result of a mutation, become ancestor to a normal liver? If that teratoma cell was the result of a mutation, what manner of mutation is it that can be completely overcome by its new surrounding? That is scarcely the conventional description of a mutation!

Even the possible nature of the mutation is puzzling. The single hit mutations in procaryotes are patently inadequate models. Invariably, they result in an altered specific protein or, at worst, a defect in the operator that controls expression of a small stretch of related genes -- an operon. But what manner of single gene or operator can control so much of the life of a cell as is evident in the numerous differences between a cancer cell and its normal, differentiated progenitor? Can one reconcile this multiplicity of alterations with a single hit hypothesis?

However, that may not be quite as difficult as it may have seemed. There is an excellent model -- the carcinogenic effect of certain viruses. The src entity of the Rous sarcoma virus and equivalent elements of human Ad5 virus and of SV40 polyoma virus are all genes that become integrated into the genome of the infected host cell. Each appears to code for a protein kinase (an enzyme that transfers phosphate from ATP to acceptor hydroxyl groups on the surfaces of diverse, unrelated proteins) very similar to a protein kinase normal to the host species. It now seems likely that these are the specific 'cancer-genes' of these tumorigenic viruses and that the multiplicity of changes evident in the neoplastic transformation all result from the chain of events initiated by unrestrained synthesis of the protein kinase and the unselective phosphorylation of a considerable number of different cellular proteins, particularly those involved in formation of the cytoskeleton and of the mitotic apparatus. What one cannot say is whether synthesis or activation of a protein kinase -- or its functional equivalent, inactivation of a protein phosphatase -- is the only pathway to carcinogenesis.

Allow me to return to chemical carcinogenesis if you will. I find it extraordinarily puzzling that there are so many carcinogens and that they come in virtually every conceivable chemical guise. They are hydrophilic and hydrophobic; acidic, basic, and neutral; large molecules and small; highly halogenated and devoid of halogens, etc., etc. One must assume that when introduced into a living cell these molecules exert their effects by first binding to some receptor -- using the latter term loosely and without regard to whether the receptor molecule be on the cell surface or somewhere in its interior; whether the receptor be merely structural or functional. But this biochemist has difficulty imagining a receptor molecule (a protein or a stretch of DNA) or even a small number of different receptors, capable of binding all of this large group of such diverse compounds, much less, that, having been so bound, they can all so affect the receptor that the same consequences are engendered. It seems unlikely, surely, that all of them can directly bind to and similarly affect the structure of DNA. What do they do?

A small group of compounds, saccharin among them, has been identified as "promoters"; in their presence, the carcinogenicity of some weak carcinogen(s) is enhanced. Most cannot similarly promote mutagenesis in procaryotes; it has been difficult even to speculate concerning what such promoters may be doing.

Accordingly, there must be many routes, many pathways to carcinogenesis. Yet if cancer is the expression of a 'mutation' such that a differentiated cell's genetic program is reversed in part, it is difficult to imagine that there is a great number of different genes all of which, if adversely affected, result in essentially identical phenotypic expression of their mutated state. And if that is not so, one is led to seek some other common denominator, some set of diverse events all of which have essentially similar outcomes, giving rise to one, or only a few, products which can then affect the genetic apparatus in identical fashion—if, indeed, it is the genetic apparatus, per se, that is affected, a notion challenged by those experiments with teratomas.

I have no compelling answer to these puzzles but I do have one thought to suggest which is scarcely original.

If carcinogenesis is, indeed, always an expression of environmental mutagenesis, if our 25 percent mortality rate due to cancer -- and a significantly higher morbidity incidence -- is to be explained in this manner, we may then ask, "What must be the magnitude of the insult responsible for these effects?" A model is to be found in that form of carcinogenesis for which we have the most precise data linking cause and effect, the insult for which there is available the most reliable dose-response curve, namely carcinogenesis by ionizing radiation. Great public attention has been directed, recently, to the very low dose end of the dose-response curve, prompted by concern for incidents such as Three Mile Island, for the health of persons who have worked around reactors, whether commercial power reactors or those in nuclear powered submarines, and for the health of the observers at weapons tests in the southwestern desert during the 1950s. But the low dose problem -- at most responsible for a very tiny fraction of all cancers -- is not the question I put

before you today. As you will see -- it is the high dose problem with which we seem to be concerned.

As many of you will know, our most reliable information concerning such matters derives from the events that befell at Hiroshima and Nagasaki. The National Academy of Sciences has been responsible for following the fates of the irradiated survivors of those episodes ever since the end of World War II. Accurate data have been obtained on 117,000 survivors for each of whom there is known, to a first approximation, the radiation dosage that that individual must have received. Based on those and other data, one can state that, in order to achieve a 25 percent mortality rate from cancer of all forms, there is required a single exposure of each individual to a single dose of 1,000 to 2,000 rads -- an enormous figure, of the order of the LD_{50}. Alternatively, each of the affected population must be subjected throughout life to about 35 millirads per day of low-energy transfer ionizing radiation, i.e., more than 100 times background. Such exposure would result in the introduction of 1-2 defects into the DNA of every one of the body cells, each day throughout life! Perhaps I should note that less than 1.0 percent of all cancer is the result of our unavoidable exposure to background radiation.

My point in taking you through those calculations is to indicate, first, that the body is, in point of fact, remarkably resistive to carcinogenesis due to radiation. Since they are entirely silent, the vast, vast bulk of all those lesions in the DNA must be successfully repaired by repair mechanisms, the details of several of which are known. Alternatively, the great bulk of all such damage to DNA is phenotypically innocuous and only extremely rare events trigger neoplasia, e.g., an event that derepresses the synthesis of protein kinase. The point is that an immense external insult is required to achieve a 25 percent mortality rate due to cancer. Although there is no theory of chemical carcinogenesis that would enable one to make the necessary bridge, it seems reasonable to consider that if almost all cancer is due to environmental chemicals, a chemical insult of magnitude comparable to that required for radiation should be necessary if such chemicals are to be held accountable for our 25 percent mortality rate due to cancer.

And if that be true, it may be necessary to rethink the entire matter. How can we have failed to detect environmental carcinogens on so vast a scale? Alternatively, perhaps our conclusion was wrong; could the principal carcinogenic culprit be not an external foreign substance but rather some normal metabolic process or metabolite, the extent or flux of which can be increased -- even, perhaps, occasionally decreased -- by lesser environmental insults such as the diverse materials that we have identified as carcinogens?

If such there be, it has certainly not been identified. But I would like to offer one speculation for your contemplation, a speculation that has been entertained by a few others, notably John R. Totter; namely, that the culprit is the superoxide ion, $O_2^{\cdot-}$, the univalent free radical of oxygen that results from the one electron reduction of di-oxygen (O_2). Let me explain why.

Once superoxide ion has come into being, then, in the absence of supervening events, it must degrade by a pathway which results in the formation of the hydroxyl radical ($OH\cdot$). The hydroxyl radical has long been considered to be the immediate attacking agent that affects the structure of DNA as a consequence of the passage of ionizing radiation through cells. Importantly, there are, indeed, mechanisms for the formation of superoxide ion in normal living systems. In my laboratory, in the early 1960s, it was demonstrated that the formation of superoxide is a by-product of the normal operation of a series of widely distributed, different oxidative enzymes. How many such enzymes there are is not known at this time; nor do we know the actual rate of total superoxide formation in living cells. However, if whole cells behave as did our various purified enzymes, the rate of superoxide formation is a function of oxygen tension -- high at high oxygen tension, low at low oxygen tension.

It was when we were convinced of these circumstances that my younger colleague, Irwin Fridovich, sought a mechanism that could dispose of superoxide before it could damage the cell. I remind you that we have known for more than a half century that our cells contain catalase which catalyzes the harmless decomposition of

peroxide, which is also a by-product of cellular reproduction of O_2 and which would be t--ribly destructive to the cell if it were not removed by this scavenging mechanism.

$$4\,H^+ + O_2^= + O_2^= \xrightarrow{\text{catalase}} O_2 + 2\,H_2O$$

As some of you will know, Fridovich succeeded elegantly; he identified two different superoxide dismutases, one in the mitochondria, one in the cytoplasm of all animal cells. Indeed, such enzymes have been found to be universally present in all living cells that can live in an oxygen environment.

$$O_2^- + O_2^- \xrightarrow{\text{dismutase}} O_2^= + O_2$$

But the presence of that enzyme need not necessarily mean that it succeeds totally. Some fraction of the superoxide ions generated in a cell may always escape and, if they do, they will give rise to hydroxyl radicals that can mutate the structure of the DNA. This offers the possibility that some mutagen/carcinogens might act by inhibiting a dismutase; others might serve as the reducing substrate of an enzyme that is a superoxide generator -- thus, perhaps, accounting for some of the remarkable diversity of mutagen/carcinogen structure.

But, what is the possibility that much of cancer is the simple result of the normal metabolic processes that generate superoxide? Were that the case, cell lines that are defective or deficient in superoxide dismutase should be unusually sensitive to oxygen as a mutagen or carcinogen. Fridovich observed that, of several strains of yeast, those that are most sensitive to the mutagenic effects of ionizing radiation are those which contain least superoxide dismutase. Those which are most resistant contain much of this enzyme. In a similar vein, in an issue of NATURE, last fall, a group of investigators at Oregon State pointed out that oxygen gas is a powerful mutagen in the usual Ames Salmonella assay for mutagenesis. Fancy the EPA considering a ban on oxygen! More pointedly, in a recent issue of Cancer Research, Oberley has reported that cancer cells, generally, seem to be deficient in at least one of the two superoxide dismutases. And there are other, teasing observations.

0673

I have not seen the paper, but I am told that there is a report from a Colombian pathologist, Otero, indicating that the incidence of lung cancer in Bogota, Colombia, is extraordinarily low despite the fact that the population smokes as heavily as do their fellow citizens. But Bogota is at 14,000 feet elevation where the oxygen tension is diminished by more than one half from ground level. As I said earlier, the rate of superoxide ion formation by those enzymes which we tested 15 years ago is drastically reduced at this lowered oxygen tension.

Finally, I am told that, if one eliminates from the total cancer rate at a variety of places at high altitude, the rate of skin cancer occurrence -- which can be occasioned by ultraviolet exposure at altitude -- the resultant overall cancer rate seems lower than at sea level. I've not seen these data and cannot say how real this effect may be.

In sum, I cannot know how much truth there is in the sketchy web of an hypothesis that I have offered. But I leave with you the strong suspicion that, in significant measure, cancer may be the price that animal life has paid for life in an oxygen environment. If so, the simplistic environmental carcinogenesis hypothesis has been seriously overestimated.

I know that you expected me to discuss science policy, to discuss what we need do, politically, to get on with the tasks before us. But not today. I return to what I said at the beginning. It is a particularly felicitous moment at which you inaugurate the use of this splendid facility. The disciplines of cell biology and biochemistry are now one and investigators have acquired an extraordinarily powerful armamentarium of research methods and tools. We are just beginning to understand the normal cell cycle sufficiently to be able to perceive aberrations in that cycle, just barely beginning to understand the biochemical events that are the remarkable orchestrated process by which a fertilized egg differentiates and grows into a complex intact organism, just barely beginning to understand the structure and functioning of the genetic mechanisms of the eukaryotic cell and how much more subtle and complex they are than the genetic

apparatus of the bacteria which we had been studying as models. Somewhere in the future of such studies will lie the secret of neoplasia. And until we have knowledge of these primary processes, of the events that govern the timing of differentiation of the chemical basis, of the chemical basis for cell-cell recognition, we will be unable to understand how it can be that the crude shotguns of radiation, of superoxide formation, or of chemical carcinogens can all elicit the same general sort of change in the control of the genetic apparatus, whatever it may actually be, that is the essence of the neoplastic transformation.

I have not presented matters in this light today so as to discourage you with respect to the hope that, one day, cancer may be preventable -- that is a task with which we must get on with the utmost vigor. But, it may be that the most frequent event that results in cancer may be an intrinsic feature of our own biology. If so, then the alternate approach on which medicine embarked years ago, the search for selective, otherwise innocuous means of intervention once a cancer has been recognized becomes even more imperative if, indeed, one day, humanity is to be relieved of this scourge.

We can all rejoice that this splendid new resource will enable the faculty, students and fellows of Northwestern to make a truly significant contribution to that noble endeavor.

Thank you.