ACCOMPLISHMENTS IN CANCER RESEARCH

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A Biologist Poses Some Questions About Cancer

Joshua Lederberg

The neoplastic cell correctly dominates discussions of cancer research today. My first remarks on the oncogene—we then called it the somatic mutation theory of cancer—date back to 1946.[1] My own proposition at the time was fully borne out, namely, that the most effective progress in understanding cancer required an indirect approach, *i.e.*, the foundations of basic understanding of gene chemistry and expression. The best systems for that purpose were microorganisms, such as *Neurospora* and then *Escherichia coli* K-12. For some years we did well to focus on those foundations rather than insist on studies with cancer cells as the best approach to understanding cancer.

An enormous fount of knowledge has been built in that interval, and largely owing to the revolution of research methodology that comes from recombinant DNA and DNA cloning; for the last decade it has been a fair proposition to look more directly at cancer cells themselves.

The system has been responsive; the decade of the cancer crusade has eventually seen an appropriate balance, in other words, a strong emphasis on the molecular biology of the neoplastic cell as the only way to really understand cancer.

For that reason, I focus my own remarks on what may be left out of that frame of reference, so that they are not overlooked. These few propositions relate not only to the understanding, but also to the management and the prevention of cancer.

UNDERSTANDING

How do we count the cancer cells in a cancer?

I contrast the counting of bacteria in a culture, of plaque-forming units for viruses, *etc.* Just how do cancer cells colonize their surrounding environment? Without systems enabling such enumerations, we either confine ourselves to extreme laboratory exemplars or leave ourselves in the prescientific era of microbiology.

MANAGEMENT

We face a fundamental difficulty in contrast to, *e.g.*, microbial infections. There we have the benefit of natural historic observation of

spontaneous remission, cure, and immunity to further attack—the paradigm that lent high confidence to the development of vaccines for, *e.g.*, polio. In our efforts to deal with cancer we have won, at enormous cost, a few measures of some efficacy by essentially pure empiricism. They have not yet given us the kind of insight that flowered into immunologic science, or to refer to the still harder case of psychiatric disease, where the study of psychotropic drugs has been the main stimulus to more fundamental insight into neurochemical and hence psychochemical mechanisms.

How does radiation (or chemotherapy) cure cancer?

I do not believe the therapeutic indices support the obvious inference that the neoplastic cells are eradicated unless these are a small minority of the cell population. If not eradication, then most of our procedures for evaluating cancer–chemotherapeutic agents are deeply flawed; many more agents should be tested in combination in the first instance. The cytotoxic theories also give little account of the tissue specificity of most chemicals.

Why are cancer patients sick?

Many of them are impaired far beyond the anatomic interferences. This is again being studied, with recent interest in cell products such as cachectin.

Why is cancer so painful (e.g., bone?)

It should also be considered why physicians are so reluctant to prescribe adequately for that pain.

Why is cancer so costly?

Along with other chronic diseases, terminal care for cancer consumes a horrendous part of our overall health care resources; it is not always directed to enhancing the quality of remaining life of the patient. Can this not be managed more sensibly and humanely?

Will we ever be able to make really compelling assessments of modes of treatment?

We have few better instruments than the controlled clinical trial, but we have unwonted faith in what they demonstrate. Can sample populations ever be so well-standardized that they can assure us that the primary treatment variable (say lumpectomy *vs.* more radical removal) is the only one relevant to the outcome? Regardless of the skills and styles of the operators? Of the details of postoperative management? Of the selection of cases and their stages? Of the patients' own morale, compliance, and self-care?

Cancer is often devastating to many more people than the patients; their families and loved ones share many of the burdens. We are just beginning to appreciate the need to manage these psychosocial aspects of the disease and to learn how to help the afflicted mitigate their stress. Meanwhile, the litigiousness of our society leaves little margin for humane and common sense dealing with the personal ethical dilemmas that attend every case.

PREVENTION

We all recognize the imperatives of environmental cleanup, but do we have any rational method for establishing priorities or cost-effective standards? Or do we remain at the mercy of the headlined hazard of the month? It is bizarre to retain the fantasy of *zero risk* from chemicals in the environment when we have little choice but to make tempered choices about the risks we must learn to live with from microbiologic factors.

Does it make much sense to continue rote testing for carcinogenic activity in animals, when (1) we have little grounds for quantitative extrapolation to the human, and (2) we know the complex interactions of categories of initiatory and promoter activity in the actual genesis of cancer? Would not those funds far better be spent on more mechanistic analysis of the chemical carcinogenic pathway? On focussed studies of the ways in which human cells (and organisms) resemble and differ from the animal models?

One fact of observation is populational variation in cancer incidence: what a gold mine still to be harvested for genetic and environmental factors and for their interaction. The single-factor cancers have already taught us an enormous amount about regulation of gene expression in cancer (*e.g.*, retinoblastoma). The rapid burgeoning of gene-marker-linkage technology [restriction fragment length polymorphism (RFLPs)] is already making possible the elucidation of many more complex genic effects.

One environmental variable that continues to be puzzling, and has already been illuminating, is the age distribution of cancer. What protects most of us during youth and middle life? Immunosurveillance is invoked, there are probably surveillance mechanisms and cognate regulatory mechanisms of the tissue environment, but they need not be immunologic in view of the futility of finding adequate specificity handles for every aberrant cell. This can hardly have been demonstrated more directly

than in the behavior of teratocarcinoma, which can be reincorporated in the embryo and sustain normal development. Because these cells have already been initiated, they may be ideal test material for the study of promotion unless we abandon the premiss of nucleic informational (DNA) stability of somatic cells.[2,3]

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Discussion

Malcolm C. Pike: A number of these questions can be answered quite straightforwardly by looking at cancers whose incidence is profoundly affected by hormones. The incidence of breast cancer, for example, is drastically reduced by removing a woman's ovaries. Such an operation does not alter her immunology significantly as far as I know; rather, it just removes the main source of the hormones that cause breast cells to divide.

The great and rapid changes in cancer incidence that hormonal changes can bring is currently being seen on a population scale with endometrial cancer. The rate of endometrial cancer in 1985 in 55- to 64-year-old women in Southern California was only 50% of what it was 8 years before. This is almost certainly the consequence of these women taking oral contraceptives in the 1970s, and effectively (as far as their endometria were concerned) becoming menopausal when they were premenopausal, and of the change to cyclic estrogen–progestogen regimens for hormone replacement therapy.

The various age incidence curves are, in fact, not all that confusing when one thinks about "age" in terms of cumulative cell divisions.

Joshua Lederberg: What is your model of the relationship between hormonal status and age incidence, and further interventions in breast cancer?

Yes, it can be modified by changes in the ecologic background but I do not see a comprehensive model at present.

Pike: Epidemiologists have known about the profound protective effect of oral contraceptive use on the risk of endometrial cancer for many years now. We have also known that oral contraceptives provide no protection against breast cancer. It is therefore obvious that the endocrinology of the breast differs profoundly from that of the endometrium. We still discuss breast cancer, however, in terms of estrogen receptors and the like as if it were endometrial cancer. We urgently need to know more about the fundamental biology of the breast and to achieve this we need more of the best biologists to be working in this area. There is a good chance that such knowledge will lead to the prevention of breast cancer, possibly by means similar to the protection afforded by oral contraceptives to endometrial cancer.

Lederberg: Our plea is the same. We want to exploit nature's experiments, and what they are telling us, to bring them into the laboratory to make more detailed inquiries. We know all of those things. I still ask you to give me a model that predicts the shape of the age incidence curves, not only its general features.

John Cairns: I think it corresponds rather well for many kinds of cancer; for example, the relation between lung cancer among smokers and the duration of smoking.

Lederberg: With smoking, we already know the principal etiologic agents so, not surprisingly, we can correlate the interval of exposure with the final expression of the disease. Another answer is that cancer takes a long time to develop. Those cancers that were not already congenital in some form will not manifest themselves during earlier ages. It just takes X years to get there. But

that does not correspond to the shape of the age incidence curve, with its rather abrupt upturn after middle age.

I am not suggesting that we do not know anything about it. I am saying that there is a phenomenon here that can give us exciting leads for further analysis.

Emil J Freireich: I am interested in your comments about curability of infectious disease as a prototype for approaching cancer biology.

I have long contended that, in the clinical trial area, we can pose critical questions in tumors that have a significant cure fraction. I am referring specifically to leukemia in adults, where approximately 20% of patients are cured with interventions that you described as empiric, and I describe as highly intellectual and scientific at the same level as molecular genetics.

We are beginning to understand some of the mechanisms for the heterogeneity for cure in some of these partially curable maligant diseases. An example, in breast cancer, surgery is curative for a fraction of patients. Lumpectomy contrasted with more radical surgery has given insight into the heterogeneity for cure where there was none before there was treatment intervention.

I thought your comments were very incisive.

Baruch S. Blumberg: I would like to address the question of the age distribution. There will probably be different models for different forms of cancer. In primary hepatocellular carcinoma (PHC) there is a good model consistent with a long "incubation" period. The disease can be conceptualized as starting soon after childhood, but the cancer does not occur clinically until 20, 30, or 40 years later. Shortly after infection, liver cells are gradually destroyed as a consequence of the hepatitis B virus (HBV) infection. This process leads to increasing division of nondifferentiated cells, which increases the probability of a second mutational event. This model fits well to the age distribution curves for PHC in various populations.

Lederberg: Are you saying that the total number of cell divisions that have occurred in the liver as it regenerates itself is the fundamental parameter that predicts the probability of cancer?

Blumberg: There may be an age-dependent trigger point, that is, the start time, that may occur later and in some cases much later than the infection.

Jerzy Einhorn: I agree that there are factors in age incidence that we do not understand.

What puzzles me is the inability to induce cancer in an embryo before organogenesis, by chemical agent or by ionizing radiation. If the embryo survives the carcinogen, there will not be any increased incidence of cancer during its lifetime.

Lederberg: We have other information on the morphogenetic field of the embryo. Teratocarcinoma can be reincorporated into an embryo and the identical clone will engender well-organized, well-regulated tissue, whereas presented in other environments, it has neoplastic potential.

My last remark on aging was just that, a last remark. I did not expect it to be so provocative.

Herman D. Suit: I was interested in your comment on the horrendous costs incurred by cancer patients. I want to know if my perception is wrong that the relative proportion of our total expenditure for health care cost is closely related to the proportion of deaths due to cancer in this country.

Lederberg: I was referring to cancer in common with other chronic diseases with terminal outcomes.

We know that terminal care in the last year of life is consuming something like 20% of our resources in health care expenditure. Maybe there is no way to avoid that.

We do not know whether, or precisely when, a case will become terminal. We cannot abandon patients just on the statistical expectation that the situation is hopeless, but there is still something wrong with the way in which these resources are allocated.

I would not single out cancer from other chronic diseases with terminal outcomes.

Allan H. Conney: You raised a question about diet. Certainly we are exposed to many chemicals in our daily diets and some of these dietary chemicals are carcinogenic in animals, whereas others are anticarcinogenic. In addition, people are exposed to manmade industrial pollutants that are carcinogenic in animals. The relative roles of naturally occurring carcinogen exposure *versus* manmade carcinogen exposure for human cancer is an important issue, as is the question of whether the cancer incidence is going up, going down, or staying the same after correcting for tobacco use and age. Do the epidemiologists believe that the cancer incidence is changing after correcting for age and tobacco use?

Lederberg: Dr. Cairns has had a lot to say on that subject.

Cairns: For that I would turn to Dr. Muir.

Calum S. Muir: This is an impossible question to answer in a general way. The answer must be time-specific, population-specific, and tumor-specific.

Conney: Well, what if we do all of that?

Muir: You want a general ballpark estimate of whether the total cancer incidence is going up or not?

Conney: Yes, total cancer incidence.

Muir: Corrected for smoking?

Conney: Yes.

Muir: It is much the same in most Western populations, but it is changing considerably in Oriental populations. Consider countries like Japan or the People's Republic of China, where several very common cancers, such as breast, prostate and large bowel have been rather uncommon. These rates are now going up sharply, and one can see this trend clearly in migrant Chinese and Japanese populations in this country.

Pike: What one can say is that the increases at certain cancer sites in Asia that Dr. Muir has mentioned have little or nothing to do with "pollution." The cancers that are increasing are associated with a higher standard of living. For example, the increases in breast cancer rates are associated with the changes towards earlier menarche, which are mainly due to the ready availablility of food. In Japan, the average age at menarche was 16.4 years as recently as 1920 and was still 14.4 years in the mid-1950s. This compares to their current average age at menarche, which is close to the US figure of slightly less than 13 years. The same phenomenon is taking place even more rapidly in rural China, where the average age at menarche was 17 years around 1950. We had not seen figures like this in the West for more than 100 years.

In general, carcinogenic pollutants do not appear to be an important cause

of human cancer, and searching there (by animal testing and the like) is not likely to be a fruitful exercise unless such experiments tell us something about fundamental biology.

Lederberg: I certainly agree with your concluding remark. Thank you.

Einhorn: We have since three decades a population-based cancer registry with high reliability: Sweden. During the latest 26 years, we have had a 38% increase in the age-corrected incidence of cancer that we cannot explain. Less than 10% of that increase can be explained by the use of tobacco.

I agree with Dr. Pike that pollution is not an important factor in Western Europe or in the US. The factor is our habits, not the pollution.

Peter Magee: I was interested in the discussion that arose from Dr. Conney's question. He and I are trying to produce a rebuttal of the allegations that a considerable amount of human cancer is related to environment pollution. It is interesting that around this table of, presumably, cancer experts of various kinds, nobody seems to support this theory. Is this correct?

Peter Greenwald: I have another theory: we should keep occupational cancer risks in perspective. We probably agree that 30% or so of cancer in this country is due to smoking and that a broad proportion is due to life-style, including diet.

Pollutants probably contribute a bit and there may be a potential for future harm. We should do what we can to minimize exposure to pollutants.

Thousands of new chemicals were developed after World War II, and industry seeks out active compounds. That is why industry wants them, because of their activity. Thus, prudence is on the side of checking for toxicity.

A second point is that there are interactions that are important. We know that most of the lung cancers in asbestos-exposed workers occur in smokers. Other interactions have not been explored fully.

A third point is that a small proportion of our population gets most of the occupational exposure. We should pay attention to that population. For example, if 5% of the total cancer load is due to industrial pollutants, and if these cancers occur in, say, 20% of the population, then that population would be at high risk.

My view is that we have to give major emphasis to prevention and cessation of smoking. We have to give major emphasis to acting on what we think are important factors in the dietary areas, even while we pursue a vigorous research agenda. But we should not ignore or totally set aside what also may be important occupational or environmental pollutant risks.

Lederberg: I do not think that anyone could possibly question environmental cancers and industrial cancers, as from vinyl chloride. We have had a clear example. We used to have betanapthylamine and so on. My question had to do with the method of seeking out the significant hazards.

We need a mechanistic analysis of what a chemical does. It is a waste of time just to inject a chemical into mice.

John D. Minna: There is a common known carcinogen in lung cancer, namely, smoking. I think that Dr. Lederberg's points are well timed. First, we are seeing a great incidence of lung cancer in young people in their 20s. I think that these patients may be the "experiments of nature."

Second, if a patient is cured of lung cancer, we know that there is a huge, perhaps tenfold, risk of those patients having a second cancer. Also, there is some evidence that relatives of patients with lung cancer have an increased risk of lung cancer.

Finally, in reviewing cancers, there is an epidemic of new lung cancer that we hadn't previously discussed, bronchioalveolar carcinoma. This may be a signal of some other carcinogenic elements that we have not yet recognized.

Tsung-teng Sun: Has cancer increased in recent years? For China, the answer is yes, even if the age is correct. Two main cancers are increasing in China. The first is lung cancer, which is occurring in men in large cities. It is mainly related to smoking, but some effects from other factors, such as air pollution, cannot be ruled out.

The second type is breast cancer in women, also in large cities, and this may also be tied to other factors.

Cairns: I understand that Richard Peto did some calculations as to what will be the annual death rates from lung cancer in China if the steady increase in smoking is allowed to proceed. His answer was 2 million deaths a year. He has been campaigning against this. It will be an interesting battle because China is a potential market for the American tobacco industry. The lines of confrontation have been drawn.

Maurice Tubiana: With regard to the role of air pollution, I would like to remind you that several studies suggest that less than 1% of the total number of cancers in the western world are due to air pollution. However, we know very little about the effect of a low level of exposure to a carcinogenic factor, whether it be ionizing radiation or chemical. In fact, very little available data are found concerning the dose–effect relationship for low doses and whether exposure to low doses is carcinogenic in human beings.

William C. Summers: I would like to reinforce what Dr. Tubiana said.

It seems that the very thing that we do not know how to do very well is assess low-level effects on large populations. In 100 years, people will look back and say how primitive we were. We need new methods, perhaps a whole new concept of how to deal with this problem.

Lederberg: I suggest one way not to do it; that is to do a megamouse study where the agent in question is known to be metabolized to a proximate carcinogen, and totally ignore that instead of looking for dose effects on metabolic outcome.

Muir: The question that Dr. Summers raised will be addressed this afternoon when we consider passive smoking: this is one of the major low-level but widespread exposures.

Tubiana: When somebody is smoking near you, it is not a low-level exposure. The air concentration of carcinogens may become relatively high.

Freireich: I want to follow up on Dr. Suit's comment. Recently in Paris, I heard a talk by a French economist, Dr. Pierre-Jean Lancry, who studied the total amount of money spent on cancer-related care in the public hospitals in Paris.

He asked me what my guess was. I estimated that something like 20% of the total money spent for health was spent for cancer-related illness. My perception, like that of Dr. Lederburg, was that it is very high and possibly out of proportion. I was shocked to hear the actual figure which, as I recall, was 3%. When one thinks about the enormous medical burden on the community, he suspects, as Dr. Suit said, that it is much too low. The amount of funds devoted to health care for cancer-related illnesses may be far too low.

John Laszlo: I just wanted to comment on something Dr. Greenwald said. We are all limited by our methods. Epidemiology, by its very nature, has to use crude methods.

You take a history from the patients to find out what they were exposed to, and you will find that there is very little exposure to anything. You come back the next day and take another history and you find that, yes, they are using insecticides, yes, they use herbicides once in a while. More and more becomes uncovered.

There are no population-wide studies that deal with minor elements in the environment, so I do not know that we have a method to create the information base that you are seeking.

Einhorn: Maybe someone should comment on what Dr. Lederberg said about spending so much money during the last year of life. That is the case, but it does not apply only to cancer. It applies to all kinds of death, except for sudden death. The comment can only be philosophic. The priorities are set by others. We should not forget that it is important how we die, not only how we live.

Jonathan E. Rhoads: I have a theory that I am sure is easily disproved: the most expensive treatment of disease is that which is successful because it could cure some people. Then they have to have another disease in order to die.

I suppose that I have survived three or four diseases that might have been fatal, and I expect to consume a lot more medical care.