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# International Research: Its Role in Environmental Biology

The study of man in various environments is essential for the control of cancer and other chronic diseases.

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The biological sciences have a long tradition of international collaboration, through both formal and informal exchange of information. However, with the recent growth of "big science," the creation of international research laboratories has been proposed as a method of expanding scientific potential. While the value of such centers is accepted for high-energy physics, where the expensive equipment necessary may be beyond the financial resources of individual countries [one such center in the physical sciences is the Organisation Européenne pour la Recherche Nucléaire (CERN)], their role in the biological or medical sciences is more controversial (*1*). The value of collaborative research in the control of communicable diseases has been demonstrated at the international level by the U.N. World Health Organization and similar bodies, but such research has largely been related to the application of known knowledge, predominantly through grants or contracts with established laboratories (*2*).

However, the successful control of communicable diseases and the resultant lengthening of life have led to a marked increase in the incidence of the degenerative diseases. The possibilities for rational control of the latter are unsatisfactory in the absence of adequate knowledge of pathogenesis. At the same time, there has been increasing concern in recent years regarding the potential long-term toxic effects of the chemical environment to which man is exposed involuntarily over long periods in modern industrial and agricultural societies. Cancer, "early aging," arthritis, and teratogenic defects are regarded as among the most important possible effects. It is precisely the treatment of these illnesses that has led to the recent astronomical increase in medical costs.

It is my contention, based partly on experience with an international organization devoted to research in the field of cancer, that environmental research of this type requires multidisciplinary investigations in several different populations, and that such research can most effectively be carried out at the international level. Furthermore, environmental pollution does not respect national boundaries.

## Environmental Pollution and Human Health

In addition to the obvious acute effects of environmental pollution on health and quality of life, the more insidious, long-term biological effects of the environmental changes occurring in technological societies are giving rise to increasing disquiet. It should be remembered, however, that environmental pollution is no new phenomenon, and that man has always polluted his environment. Nevertheless, since the 19th century he has also begun to have the technology to control pollution. Today the infectious diseases that ravaged the slums of newly industrialized England have disappeared, as have many of the Dickensian houses in which they were rampant. Such successes occurred at a time of governmental indifference and often of public and medical opposition. As Medawar has rightly emphasized (*3*), to ascribe only bad effects to technology is unwise.

At present it is the chemical aspects of environmental pollution that receive greatest attention. For practical reasons, public health organizations have largely focused their interest on the possible effects on health of air pollution, specific food additives, or pesticides, rather than on the esthetic or ecological aspects of the problem, no matter how important the latter may be in terms of the quality of life. Unfortunately, however, harmful effects on the environment or on other organisms are often assumed, without evidence, to imply biological damage in man. In fact, there is a surprising dearth of factual data on these relationships. Thus, while there is a general tendency to assume that any chemical modification of the environment is bad and to hold such modifications possibly responsible for a wide variety of ailments, the limited data available do not support such a simplistic view, at least not for cancer and heart disease. Human cancers of known etiology can usually be ascribed to a cultural habit (cigarette smoking in the case of lung cancer) or to occupation (the manufacture of asbestos products, in the case of mesothelioma). Furthermore, no consistent correlation can be shown between cancer patterns in different countries and the level of industrialization, which is often regarded, by association, as an index of environmental pollution. In

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contrast, the cynic might make a strong case for the agreement that the increased use of food additives in industrialized societies is correlated with the recent drop in the incidence of gastric cancer in the United States and certain European countries. Much cardiovascular disease and "early aging" appear to be the result of gluttony, lack of exercise, and other such factors, and not of chemical pollution. There is no evidence that industrialization per se has led to reduced life expectancy in Western countries, nor in fact is there evidence warranting association of present cancer patterns in the United States with those chemical and dietary factors that have entered the human environment recently and that at present receive wide publicity.

Nevertheless, epidemiological studies of cancer do indicate that the present environment in the United States is harmful, since it is estimated that from 80 to 90 percent of all neoplasms in this country are partly or predominantly conditioned by exogenous factors (*4*). Furthermore, although available data on cancer do not indicate that any large-scale disaster has occurred as a result of exposure to chemicals (there are certain exceptions—for example, the harmful effects of cigarette smoking), the demonstration that occupational hazards exist and that relatively short-term exposure of workers to certain chemicals may be damaging does not permit complacency. It should not be forgotten that the patterns seen today reflect conditions experienced over the past 20 to 40 years. There is clearly a need to examine and study quantitatively in man the biological significance of the chemical environment and to determine the research approach most likely to be effective. An ecological witch-hunt is no substitute for sound knowledge as a basis for environmental control.

## Extrapolation from Animals

The health problems associated with long-term environmental contamination in industrial societies are complex, but it has yet to be shown that they cannot be solved, provided sufficient data become available to permit adequate control, and provided the technological methods can be applied without intolerable social disturbance. Many chemicals that are useful socioeconomically or medically are being increasingly utilized in modern industrial and agricultural societies before their long-term health effects can be fully known (contraceptives are an example). While few chemicals of known toxicity are intentionally introduced without careful consideration, many other compounds are widely used in industry and elsewhere before their biological action is adequately known. Animal screening is as yet the only technique available for testing chemicals for potential carcinogenicity or toxicity. Unfortunately, a negative result in animals is no guarantee of safety in man. In fact, only two of the stimuli known to be carcinogenic in man were first identified in animals (*4*). Conversely, a chemical that is carcinogenic in animals may not necessarily be so in man under conditions of normal exposure. It might even be argued that inadequacies in early animal testing were a happy accident in that they permitted the use of DDT, isoniazid, penicillin G, and other compounds of value in special situations. Furthermore, toxicity is not necessarily confined to synthesized chemicals. For example, vitamin A in high doses may be teratogenic in animals, but at lower levels it is necessary for life. To assume, as is sometimes done, that all synthesized chemicals do not have a similar tolerance margin is illogical, and the argument could be extended to the naturally occurring carcinogens—for example, aflatoxin.

The problem is complicated, moreover, by lack of the facilities and manpower needed—even if one is thinking in terms of an international effort—to exhaustively test the potential carcinogenicity, in animals, of the vast number of chemical compounds to which man is exposed. Documentation is almost completely lacking on the long-term effects in experimental animals of several compounds administered in combination at low dosages which would be comparable to levels of exposure in man. Furthermore, few first-class scientists are prepared to undertake the painstaking investigations inherent in long-term testing studies, preferring to leave them to others, believing that such mission-oriented investigations, no matter how essential, are unlikely to provide exciting new information. It is not surprising that the frequent equation of long-term research with bad research is justified. Nevertheless, even if adequate facilities for complete animal testing of all compounds were available, such testing could at best provide only indications as to their toxicity or safety in man.

## The "Calculated Risk"

In the meantime, decisions must often be made in the absence of adequate experimental or epidemiological data, and judgments on whether or not to restrict or ban the use of given compounds will continue to be based on educated guesses by experts—on a "calculated risk." Accordingly, public health officials may be forced to be overcautious and take even unjustified but popular action, especially in situations with political implications. This course has three inherent dangers. (i) The use of certain compounds of potential value to human society may be restricted or banned without adequate justification, simply because absolute safety can never be guaranteed. (ii) Unnecessary and costly banning and restriction will be self-defeating on practical socioeconomic grounds and will lead to social conflict rather than to collaboration. To make a man unemployed in the name of environmental control is not a solution for which society as a whole can avoid responsibility. The dangers of such a situation are obvious in industrial societies whose wealth and well-being are dependent on their industries. (iii) With a poor choice of priorities, limited resources may be diverted from the truly important problems to the less important ones.

It is undesirable to create a type of fashionable scientist with an entirely negative approach, happily collecting environmental data with no concern for the ultimate objectives in terms of human well-being and health.

"There's many a life of sweet content
Whose virtue is environment."

It will always be easy to be wise after the event, and conscientious scientists will always be criticized by outsiders without responsibility, especially as all too often the balance between benefits and disadvantages is not easily established.

The controversy surrounding the alleged carcinogenicity of DDT is a useful example of the complex problems involved. It is one thing to continue unrestricted use of a chemical that might save 100,000 lives for each potential cancer, as might theoretically be the case in Africa or Asia, and quite another to continue its use in a situation where only 10,000 lives might be saved for every 1,000 potential cancer cases, as might be the case in Europe. Nevertheless, while it would appear

wise not to expose man unnecessarily to any chemicals showing toxic, teratogenic, or carcinogenic effects in animals, absolute safety cannot be guaranteed, and, conversely, the possibility that an agent which is harmless will be banned can never be wholly ruled out.

## Environmental Studies in Man

Human experimentation, requiring exposure to potentially toxic agents, is neither permissible nor likely to be permissible in present-day society. Accordingly, so long as our knowledge of comparative carcinogenesis and toxicology in animals and man remains insufficient to allow meaningful extrapolation, it is clearly essential to study the biological effects when man has been exposed—advertently or inadvertently—to a suspected agent, in order either to identify early warning signals of toxicity or to establish the safety of the compound in question. That this is a promising approach is suggested by the wide geographic variations in the incidence of cancer, cardiovascular, and other degenerative diseases in populations who live under very widely differing environmental conditions, whether of the same or different races. Furthermore, whole populations are now exposed to agents that formerly were a hazard only to small occupational groups—for example, asbestos, which is now present in numerous articles in everyday use, such as asbestos tiles and electrical installations.

Some situations known to present a high risk of cancer have been successfully investigated; an example is the threat to dye workers of cancer of the bladder. However, the inadequate studies made on pesticides and food additives contrast somewhat unfavorably with the very considerable epidemiological and experimental studies made in the area of radiation carcinogenesis, where, it appears, criteria for relatively safe operation have been introduced (*5*). In the case of DDT, the tragedy is not that use was first permitted and banning or restriction occurred later, but that, from the beginning, steps taken to monitor the situation at either a national or international level were inadequate, in view of the uncertainty of the results of laboratory studies. Even after 20 years of use the potential dangers to man ascribed to DDT are still essentially based on its ecological effects.

## An International Research Laboratory

*Environmental biology as a science.* It is in the above context that establishment of an international center or centers for multidisciplinary environmental research appears important. Long-term investigations of population groups are a form of observational science which is both more expensive and, in general, less prestigious than other branches of science. Thus, while the desirability—even the necessity—of such studies is continually emphasized, in relation to social needs, few scientists are prepared to implement studies which may be long-term and without prospect of immediate results. However, as biology has moved away from classical biochemistry and genetics to more basic investigations at the molecular level, so the complex etiology of cancer and heart disease has made it essential to approach observational studies in man with the same degree of technological sophistication that characterizes animal experimentation. The mere collection of data ("nose counting") is of no value per se, and descriptive epidemiology, although basic to any monitoring system, should be only one of the many medical disciplines that would be the concern of an environmental center, together with toxicology, pathology, immunology, virology, and others. Furthermore, collaboration with workers in nonmedical disciplines, such as environmental engineering and ecology, would be necessary.

While most workers accept the need for this multidisciplinary attack in theory, practical implementation is not easy. There is traditionally an intellectual barrier between the public health official and the field epidemiologist on the one hand and the medical laboratory worker on the other, and similarly, between medical and nonmedical disciplines. The inclusion of field and laboratory workers within the same institute should help to break down this impediment to environmental research. It should tend to force the laboratory scientist to study the application of his experimental techniques to epidemiological studies in man, and it should keep the epidemiologist aware of recent biological advances in relevant fields and of the results of toxicity testing programs. The value of such collaboration can be observed in recent studies on Burkitt's lymphoma and nasopharyngeal carcinoma, where seroepidemiology in the field has proved to be of basic significance in analyzing the role of viruses in these cancers.

This wider biological approach fully merits the name "environmental biology," which should be regarded as an observational science (such as astronomy), and should provide attractive possibilities as an exciting new frontier of research for young workers. There is thus no reason why well-designed multidisciplinary environmental research should not enrich the academic as well as the biological and physical environment. Nonetheless, in view of the fact that the biological scientist cannot avoid consideration of social priorities and thus some degree of the mission orientation that is implicit in medicine (*6*), care must be taken to maintain intellectual satisfaction at a high level. It was to explore the potentials of this approach that the International Agency for Research on Cancer was set up in Lyon, France, by five industrial nations in 1965 (*7*).

*Value of a multidisciplinary approach.* Multidisciplinary environmental studies of the type described above require that a wide variety of situations be investigated, at both ends of the environmental and disease spectra. Where populations are relatively homogeneous, as they are in most modern states, differences in exposure are difficult to measure quantitatively. A sound environmental program implies a network of centers situated in countries of all levels of economic development and of differing political persuasion, working together. Thus the collaboration of developing countries would appear essential, to permit examination of as wide a range of environments as possible. Moreover, the organization of such studies is becoming increasingly urgent as the mode of life in such countries becomes increasingly industrialized and homogeneous. However, it is unreasonable to assume that developing states will be capable of funding such research, which is of no immediate direct benefit to them, at a time when other socioeconomic matters are more urgent.

Well-planned environmental collaborative studies can be developed on a bilateral basis, and such programs have proved highly effective—for example, in atherosclerosis (*8*)—especially where one institute is the recognized leader in the field. While theoretically there is no reason why such bilateral studies should not be further expanded, an international organization may prove to have

certain advantages, especially where there is a need for continuity and where logistic problems are involved in training local staff, buying equipment, and so on. Furthermore, the need to train more scientists to develop environmental studies on a global basis would help relieve the present worldwide shortage of trained workers in the area of environmental biology. Such scientists might also be in a position to collaborate more readily with local scientists and avoid the possible charge of paternalism that may occur in a bilateral agreement where one member is the dominant partner.

Moreover, an international center would be a neutral source of information on environmental problems on which governments or institutions may require data. Expert committees of the World Health Organization and other specialized agencies of the United Nations working in this field are of great value in providing recommendations based on available knowledge. Too often, however, the group making such recommendations has had to draw attention to the fact that the data available are insufficient to permit a satisfactory estimate of the risk involved. Since these expert committees lack executive power, they are unable themselves to initiate the appropriate research. If mission-oriented international research programs are to be successful, direction should be by competent scientists who alone can develop programs of the type and quality required. It would be reasonable to expect that non-center scientists would prefer to collaborate with a colleague actively engaged in research rather than with a scientifically inactive administrator.

Unfortunately, some governments have generally been unwilling to accept the view that an international organization in the field of biomedicine needs laboratory backup for studies, fearing unnecessary duplication of laboratory experiments and a "brain drain." Experience with the International Agency for Research on Cancer has shown that these fears are unjustified, and that, in fact, laboratory workers have greatly enriched the field programs. The staff have also shown themselves willing to stimulate and initiate, either directly or under contract, long-term animal studies of the type which many workers prefer to avoid but which are essential for any rational control program. Furthermore, its programs have not been competitive with national efforts but, rather, have been complementary.

## Other Problems

While the foregoing discussion has been directed largely toward chemical aspects of the environment, and toward carcinogenesis in particular, it is equally pertinent to other biomedical fields, such as nutrition and aging. At a time when the world's population is outgrowing food supplies and a great effort is being made to reduce malnutrition, there is a surprising lack of knowledge as to what constitutes an optimum diet. This knowledge can be obtained only through field studies. While the ill effects of malnutrition are well recognized, it is sometimes forgotten that undernourished animals live longer than well-nourished ones, an observation that may well be related to the fact that today the life-span of industrialized man over the age of 70 is beginning to level off or even to fall. According to Walker (*9*), in South Africa in the older age groups the expectation of life is greater among the Bantu than among the white population.

The increasing height and earlier menarche due to diet in Western countries are usually heralded as successes of modern nutritional science. It is equally arguable that they represent premature aging and are of no biological benefit. It is interesting to speculate whether we should continue to try to breed larger, and perhaps mechanically less efficient, individuals, as represented by North American or northern European man, or try to breed a possibly more efficient Asian type. Discussions on human aging now tend to focus on cardiovascular disease and cancer. Studies on objective signs of physiological aging are desirable in populations living under a variety of nutritional and stress conditions, to determine whether the longevity of the older age groups in certain nonsophisticated societies reflects a reduction in the incidence of atherosclerosis and its complications or a true retardation of the aging process.

While comparative studies of pathology in different geographical areas have contributed much to our knowledge of the distribution of cardiovascular disease (*8*), the complementary analytical investigations to determine the cause of the geographical variations of disease in man have not received similar intensive support. This is surprising, since cardiovascular disease accounts for two-fifths of all deaths in North America at present, and an increase of some 18 years in life expectancy might well be achieved if adequate control could be developed. The possible benefits of such investigations have been even less thoroughly explored for other degenerative diseases, such as arthritis.

## Practical Organizational Considerations

The view that internationalism in science is a good thing per se, and establishment of an international research center wholly on the basis of that view, will almost certainly lead to disillusionment and ineffectiveness. However, although internationalism per se may be no justification for setting up a research center, an international approach may have certain intangible benefits that are difficult to evaluate quantitatively. Furthermore, if international collaboration fails to develop satisfactorily in relation to problems on whose significance there is general agreement, such as research on environmental contamination, one has reason to conclude that greater success is not likely to be obtained in more controversial areas.

*Objectives.* An international research center must have clearly defined objectives. While the scientific objectives speak for themselves in the case of an organization such as CERN, the objectives of an international biomedical research organization may not be immediately obvious. Thus, critical review of scientific policy from the outset by an independent Scientific Council is required, since the quantitation of input versus output in the biological field is essentially a subjective matter. Evaluation of the role of the environment in relation to human health would appear to be an objective appropriate for such a center.

*Staffing.* Recruitment of suitable staff would not be easy. Ideally, the staff members should be first-class scientists who, additionally, possess the managerial skill and diplomacy necessary for the development of collaborative programs. Individuals possessing such qualities are rare, and some first-class scientists do require training in diplomacy. Today the salaries paid by international organizations are no longer as attractive, relative to those paid by national organizations, as they were when the specialized agencies were first established. In fact, staff members of international organizations may be less well off than those of national institutions in North America and Europe,

especially when problems of education and housing are taken into consideration. Furthermore, the loss of position in the national scientific hierarchy and the feeling of isolation may pose very real problems. It is essential that the participating states make arrangements to facilitate the integration of staff members on their return to their national scientific communities.

The greatest danger, however, is scientific obsolescence. This problem is not resolved by recruiting individuals only on short-term contracts, since continuity is required for certain programs. Moreover, facilities must be provided to permit the development and maintenance of expertise and competence in their research fields. Publication in reputable journals should be a usual practice.

*Funding.* The financing of international research organizations will be a perpetual problem. It is characteristic of governmental-scientific relations in international as well as national life that governments think scientists request more money than they need and that scientists think governments do not fully understand their requirements. So long as funds are limited, it is unlikely that this problem will be solved. However, there are advantages in maintaining the budget at a relatively modest level, since such funding is less likely to give rise to political pressure or arouse undue jealousy in national scientific communities—and the question of fair return will not arise. If the budget remains at a moderate level, the danger of bureaucratic inefficiency should be reduced. It thus may be desirable to create several centers of moderate size rather than one large center. In the field of environmental medicine, with its mission connotation, every effort should be made to maintain efficiency through utilizing the most modern managerial techniques available. Furthermore, a moderate budget tends to avoid catastrophic cutbacks at times of international financial stringency. On the other hand, the budget must be large enough to permit effective functioning. Moreover, for environmental studies of the type described, long-term funding is essential, and inadequate funding will only lead to frustration. In fact, one reason why research has not developed more rapidly in this area is that there has been a general unwillingness to accept the financial implications of an international monitoring program, although the costs in relation to the socioeconomic implications are small.

*Environmental programs.* While, in any such organization, it will be the responsibility of the governments' representatives to control overall policy, it is highly desirable that implementation of the scientific programs by the staff be under the guidance of a Scientific Council. The council should constantly review the programs to evaluate their effectiveness and their success or failure relative to the overall objectives of the organization. It is important that activities should not be maintained solely because they happen to exist. In the last resort, a scientific decision can always be justified, whereas a purely political decision relative to a scientific matter may give rise to problems. The final court of appeal is common sense, and only by maintaining high scientific standards and competence, associated with full publication of results, will an organization be able to maintain the trust and confidence of scientists, governments, and industry.

## Conclusions

To determine the role of environmental factors in human health, studies on several population groups are essential, involving the most sophisticated techniques possible. The logistic and political problems associated with such studies, especially in developing countries, and the high cost of modern environmental biological investigations make it particularly desirable to avoid unnecessary duplication and waste of resources. For certain investigations an international research center would appear to have considerable advantages, provided that the organizational difficulties can be overcome. Not only can such an organization provide the human data necessary for calculating the balance between the benefits and harm of a given course of action but also it may stimulate the long-term routine laboratory studies so necessary as a basis for extrapolation from animals to man.

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