New Dimensions in Cancer Research

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A MANIFESTATION of progress in research directed toward the solution of the cancer problem is that many such research endeavors are increasingly more difficult to define as "cancer research." Consider, for example, chemical carcinogenesis. There are hundreds of compounds with activity to evoke neoplasms in one or another species. This activity cannot be divorced from many other pharmacological and pathogenetic effects of such agents. Or, as another, more recent example: to speak of cancer viruses is passé; obviously, many viruses under certain conditions can be involved in the neoplastic process. The small group of viruses previously considered as unusual in their carcinogenic potential fit nicely into larger groups of such entities. The mountain streams of cancer research, small but discrete, have now entered the broad rivers of knowledge and have lost their identity.

Cancer research has thus gained new dimensions, two of which are described here. One dimension is global, and deals with the distribution of some neoplastic diseases on a worldwide basis, in animals as well as in man; the other dimension is subcellular, and concerns some of the recent findings in virus research.

Distribution of Cancer in Man

Our understanding of cancer is still based essentially on the morphologic observations made by clinical pathologists during the latter part of the 19th century and the early 20th century. Their observations led to several generalizations. One was that neoplastic transformation can be found in every group of human beings and all species of animals studied with any degree of intensity. The other was that the neoplastic process involves any tissue in the body capable of reproduction by cell division. One still hears occasional reports of certain human groups being free from cancer, whether they be Eskimos or some mysterious tribes in South America. Investigation invariably reveals that such reports result from incomplete observations of small populations, inadequately studied and usually dying of other diseases at earlier stages of life.

The same assertion is also true of so-called cancer-free species. No species of animal is "immune" to cancer, although undoubtedly certain species develop relatively few neoplasms as compared with others. Thus, experience is bearing out the early generalization that all human and animal species are susceptible to cancer.

The distributions of various neoplastic entities within human and animal populations differ widely, and these distribution patterns are now increasingly engaging our attention. Many years were required to put sound baselines on distribution observations which were made originally on haphazard collections of pathology specimens. It required the development of the census, of central registries, of studies of whole populations, and of the mechanics of registration to bring to flower the task the pathologists had outlined in essence a half-century before.

Many of the findings were evinced as long ago as 1915, when Frederick Hoffman compiled data on cancer mortality throughout the world

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Dr. Shimkin, associate director for field studies, National Cancer Institute, Public Health Service, presented this paper, based on the Sixth Annual Carle Foundation Lecture (1), in Agra, India; Bangkok, Thailand; and Sendai and Kyoto, Japan, during the summer of 1962.

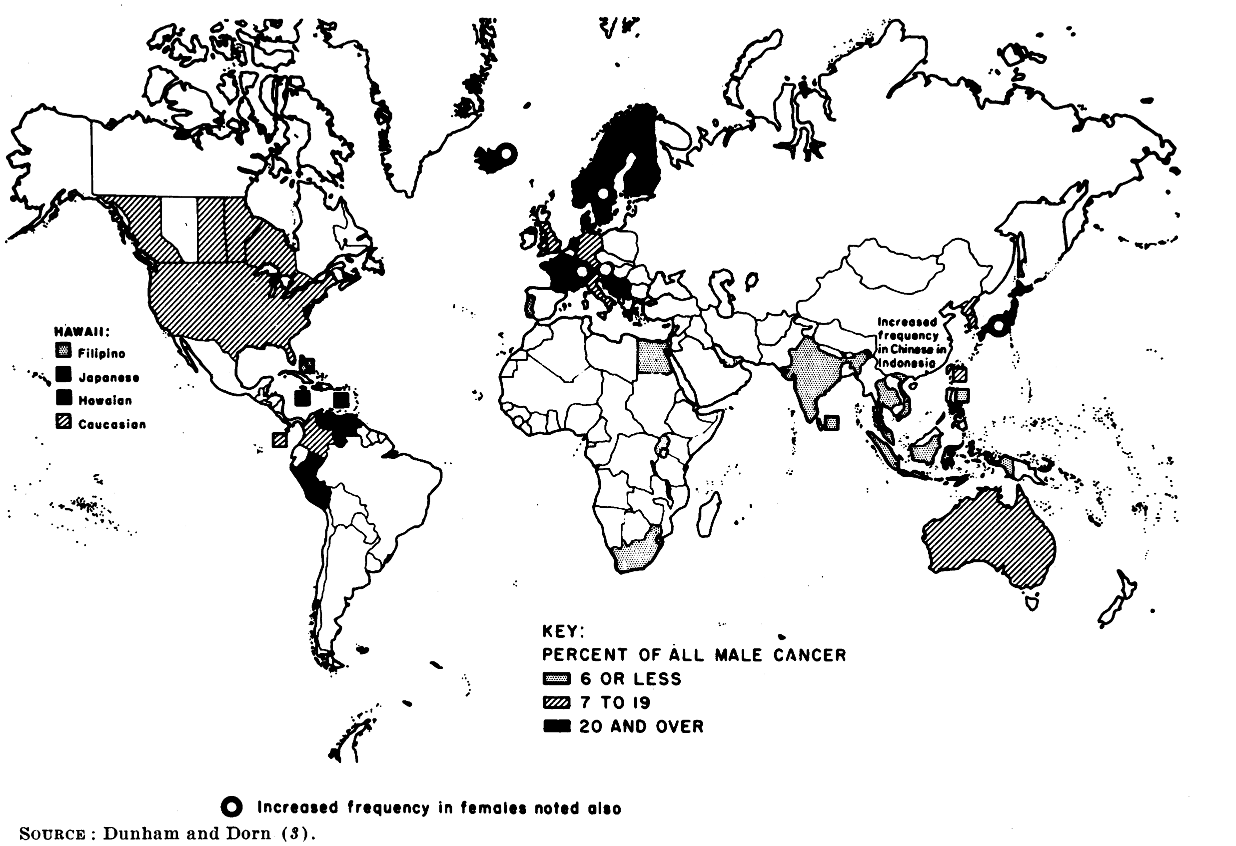
(2). Today, we can speak of these matters more assuredly, on a more reliable basis, and, in turn, we can subject findings to further exploration and exploitation through research methods. Specific situations and differences can be examined in depth through epidemiology, ecology, virology, and other scientific methods which have evolved to full stature only during the past several decades.

The maps on the distribution of cancer presented here were prepared by Dunham and Dorn (3). The orientation of cancer occurrence to political designations of geographic areas requires explanation. Obviously cancer has no political boundaries, but registration systems do. Thus, at present the easiest way to express cancer differences is by countries. In these maps, the areas are represented in solid black where the occurrence of certain types of cancer is high relative to the world average; in hatched lines for approximately normal or average occurrence; and in dotted stipple where occurrence is less than the average for the world.

Gastric cancer. The global distribution of stomach cancer in males is shown in figure 1. This type of cancer is a prominent cause of mortality in the human species, but is rather rare in all animal species. It seems to have a northern belt of distribution which runs through Europe and includes Japan. Recent publications from the Soviet Union indicate that this belt stretches across the great land mass of Russia and Siberia. An area in northern South America also is reported to have a high relative frequency of gastric carcinoma, but the statistics leave much to be desired.

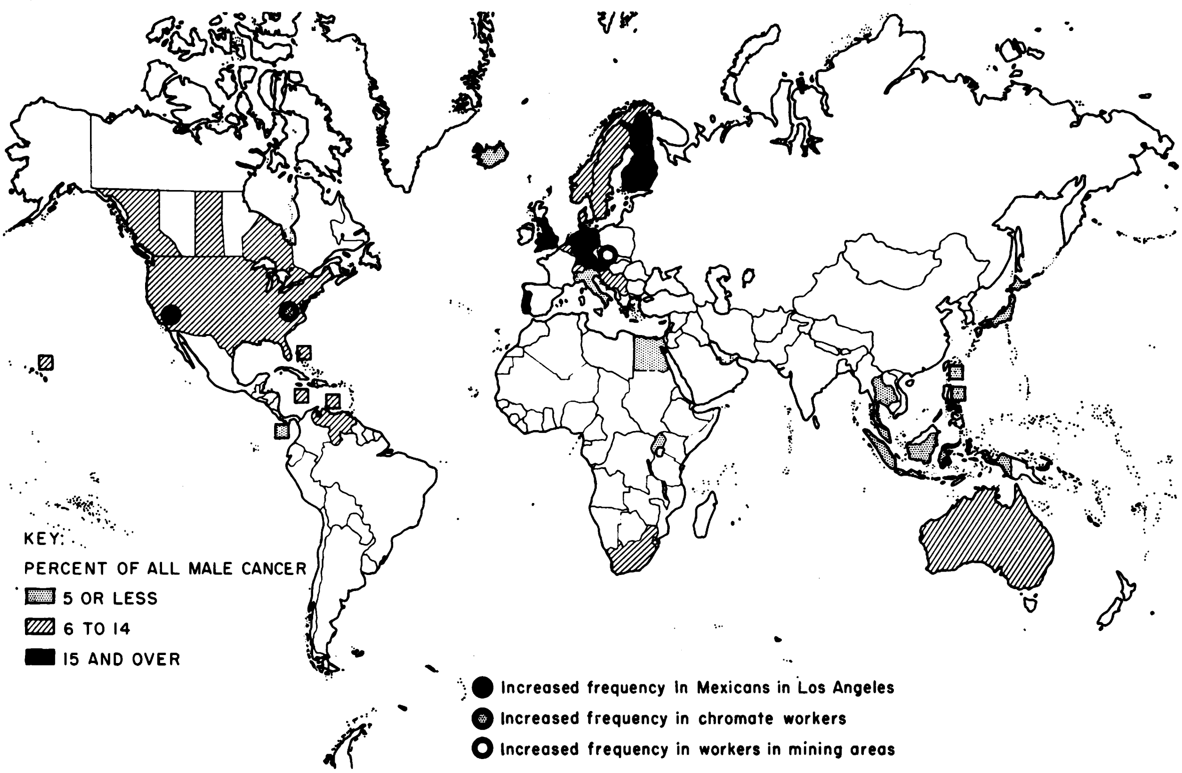
Iceland and the Scandinavian countries, along with Japan, have attracted our attention for further studies because they have populations that have migrated to the United States. We have observed that Japanese or Scandinavian migrants to the United States have a risk to gastric cancer comparable to the country of origin, while the occurrence of cancer among their descendants approximates that of the general population of the United States

Figure 1. Relative frequency of stomach cancer in males



SOURCE: Dunham and Dorn (3).

Figure 2. Relative frequency of lung cancer in males



SOURCE: Dunham and Dorn (3).

(4). It is as if the effect of some environment the migrants have left behind is diluted. We are, of course, very much interested in trying to define more closely what that environment may be. Dungal of Iceland, for example, emphasizes the role of smoked fish in his area (5). Yet in Japan, fish is not smoked but dried, and consumed with much salt. Thus, the carcinogens in smoke do not generally explain the occurrence of gastric cancer. One of a few leads we have toward the epidemiology of stomach cancer is its more frequent occurrence among members of lower socioeconomic groups.

Gastric cancer in the United States, to some extent because of the migration-dilution factor, is one of the few forms of neoplasia showing a true decrease in incidence during the past 30 years. There has been about a 30 percent decrease, when corrected for age and other factors and not attributable to changes in diagnosis. The reasons for this decrease are conjectural.

Pulmonary neoplasms. Cancer of the lung in males (fig. 2) is explainable to a great extent to exposure to environmental situations. On the basis of many sophisticated epidemiologic studies, I am one of those who believe that at least 60 percent of the tragic rise in lung cancer in the United States and Western Europe during the past 40 years can be attributed to the ever-accelerating consumption of tobacco products, particularly in the form of cigarettes. There remain some 40 percent of lung cancers which are not as easily ascribed to smoking. A proportion of these may result from environmental atmospheric pollutants from industry and other sources, but approximately 15 percent cannot be accounted for by either etiological explanation (6).

Lung cancer also demonstrates dilution with migration. Among English people who emigrate to New Zealand, the incidence of lung cancer is comparable with that in England, whereas their descendants have a definitely lower rate. This reduction is probably a result of withdrawal from a noxious environment in the homeland, but does not contradict the role of tobacco smoking.

Mammary cancer. Cancer of the female

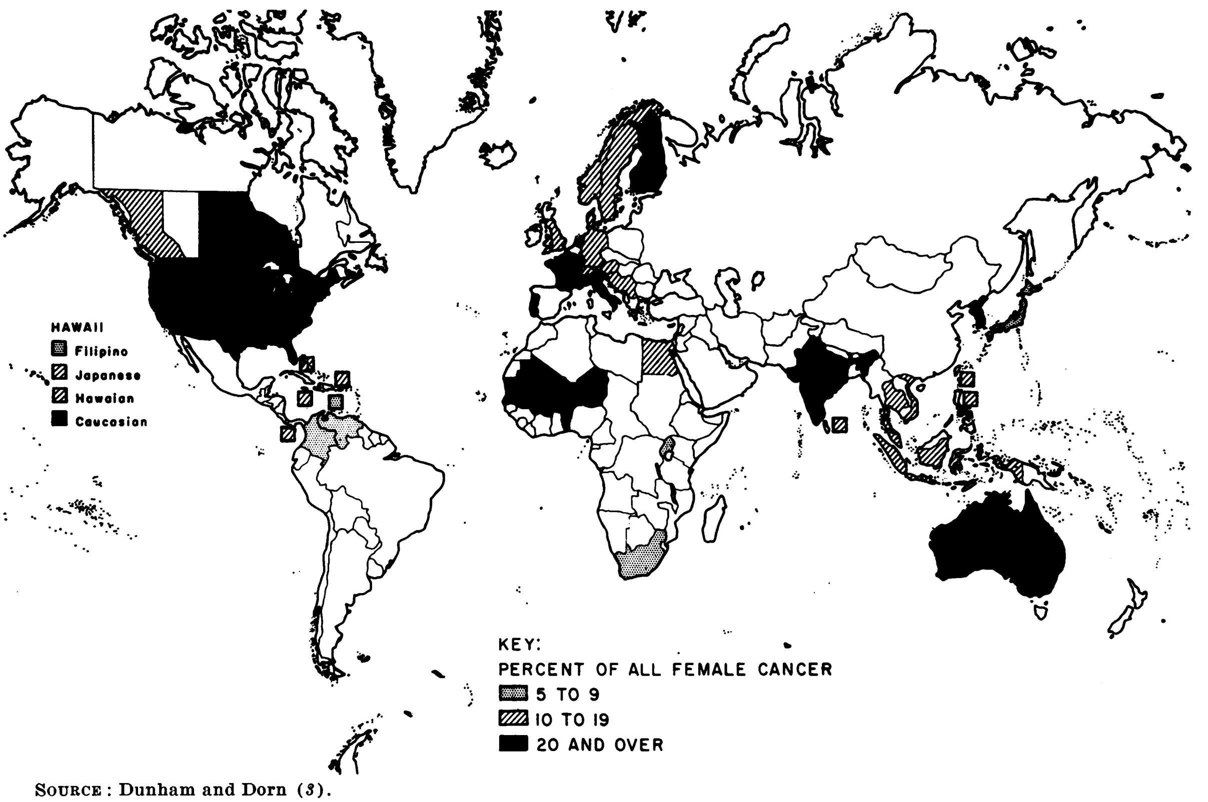
breast (fig. 3) is the most prevalent sex-specific neoplastic entity in the United States. It is one neoplasm which has remained steady in incidence and mortality in this country during the past 30 to 40 years, if proper age adjustment is made. The incidence and mortality rates from this disease have not been affected by the use of numerous steroid hormones introduced during the past 30 years. In many urban centers few women nurse their infants, and the breasts are rapidly dried up postpartum. This change in nursing habits and the sex steroids have not produced demonstrable effects on the pattern of occurrence of breast cancer in the United States. This negative information, of course, also casts doubt on claimed beneficial effects of certain therapeutic modalities.

Japan's low incidence of breast cancer is striking. Japanese statistics are reliable, and they show an incidence of breast cancer that is less than one-fourth that of the United States. No matter how those data may be corrected for pregnancies or other factors, such as social, economic, and nursing customs, this low rate remains prominent (*7*). Japanese women in the United States also show about a 25 percent occurrence of breast cancer as compared with the white population of the United States. Breast cancer, in contrast to cancer of the uterine cervix, is somewhat more frequent among women who have had no children, who have not married, and who are in the higher socioeconomic groups.

Cervical cancer. The incidence of cancer of the uterine cervix is extremely high in India and the Far East (fig. 4). In the United States, during the past 25 years, this type of neoplastic lesion has shown a true drop in incidence of about 20 percent. In addition, through earlier and better treatment of cervical cancer, the survival rate also has improved. Both factors, of decrease in incidence and of better therapeutic results, contribute toward a lower mortality figure.

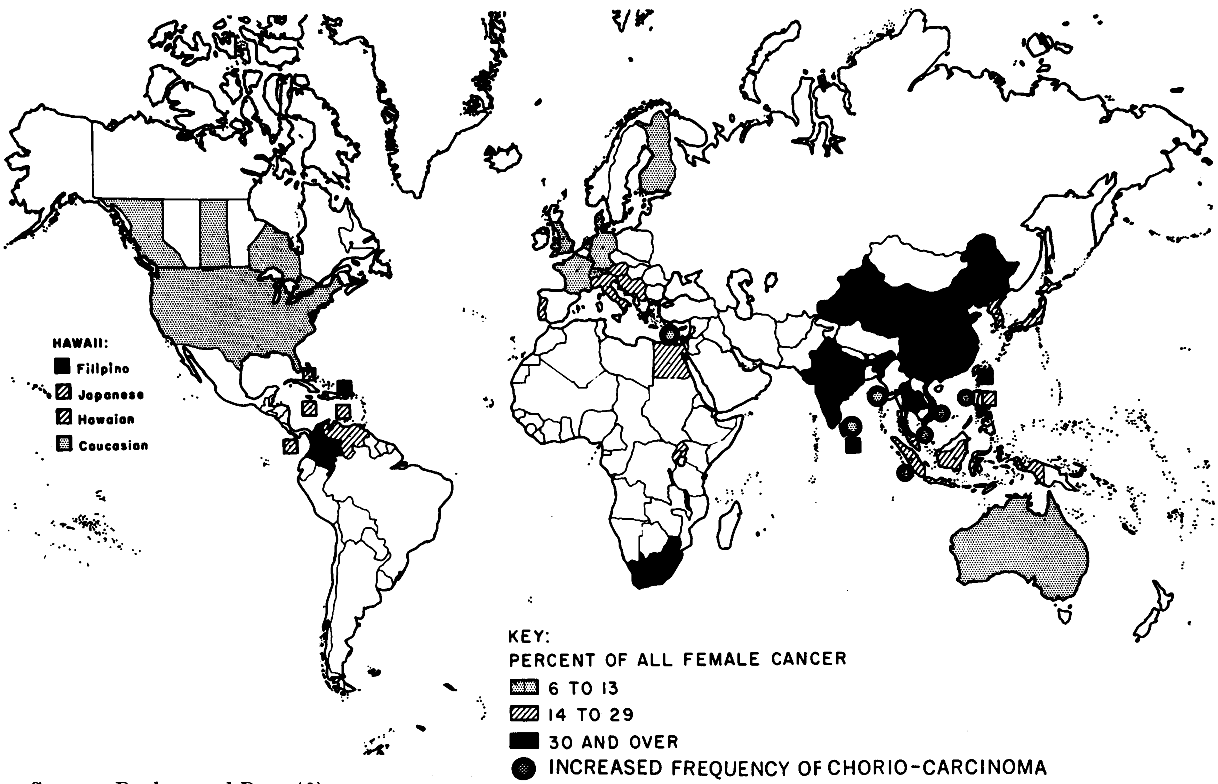
Cervical cancer is closely associated with environmental factors (*8*). It occurs most fre-

Figure 3. Relative frequency of breast cancer in females



SOURCE: Dunham and Dorn (*3*).

Figure 4. Relative frequency of uterine cervix cancer



SOURCE: Dunham and Dorn (3).

quently in women who start their sexual life early. If one were to grade women by their sexual experience, from virgin to prostitute, the incidence of cervical cancer would be related to the amount of sexual exposure. There is also a relationship with circumcision in the male, and smegma painted on the backs of mice has produced cancers. Good hygiene with soap and water may possibly be an adequate substitute for circumcision, and this may account for the epidemiologic lack of agreement on this point.

Liver cancer. Throughout the sub-Sahara belt in Africa and the Indonesian islands hepatic carcinoma is one of the most prominent neoplastic diseases (fig. 5). Hypothetically, there is a relationship to protein deficient diets in children, cirrhosis, and subsequent hepatic neoplasia. This neoplasm is relatively rare in Western Europe, the United States, and Australia.

Africa provides a rich source of opportunity for etiological study of cancer, because it has at least six semiepidemic neoplastic situations. In Egypt, the most common neoplastic disease is bladder cancer, secondary to massive infestation by a fluke, *Schistosoma haematobium*, acquired by the farming population along the Nile. This particular type of bladder cancer is seen much less frequently in Western Africa, where *S. haematobium* also exists, but where agricultural patterns are quite different from those of Egypt. While this massive neoplastic epidemic has lasted for centuries in Egypt, little laboratory work has been done, and our knowledge is limited to descriptions (*9*).

Another recent development from Africa has been the description of an interesting variant of lymphosarcoma in children (*10*). The neoplasm remains as a solid tumor rather than invading the bloodstream, and is first manifested by the early involvement of the mandible and the maxilla resulting in massive swelling of the face. It is so common in many villages throughout the tropical zone that village headmen have no difficulty in recognizing and identifying the disease. This is an area now avidly being studied by epidemiologic and laboratory methods.

In the South African region, there are two interesting local areas of cancer concentration. In a region of the eastern provinces the Bantus have a high incidence of esophageal carcinoma (*11*), and in a northwest province about 75 cases of mesothelioma of the pleura were recently described (*12*). The Bantus' esophageal carcinoma is attributed by local workers to kaffir beer. As for the cases of mesothelioma, most occurred in an area noted for its production of asbestos, and the primary suspicion is focused upon this possibility.

Lastly, there is a high occurrence of a queer semineoplastic lesion, Kaposi's sarcoma, which is particularly evident in the native populations of the sub-Sahara regions (*13*).

Africa is a gold mine of opportunity for epidemiologic research in cancer. Unfortunately, because of its political situations, exploitation of the opportunities cannot be rapid or systematic. However, as one step in this direction, the National Institutes of Health has established a research station in Ghana which could be used as a base for further studies of these intriguing conditions.

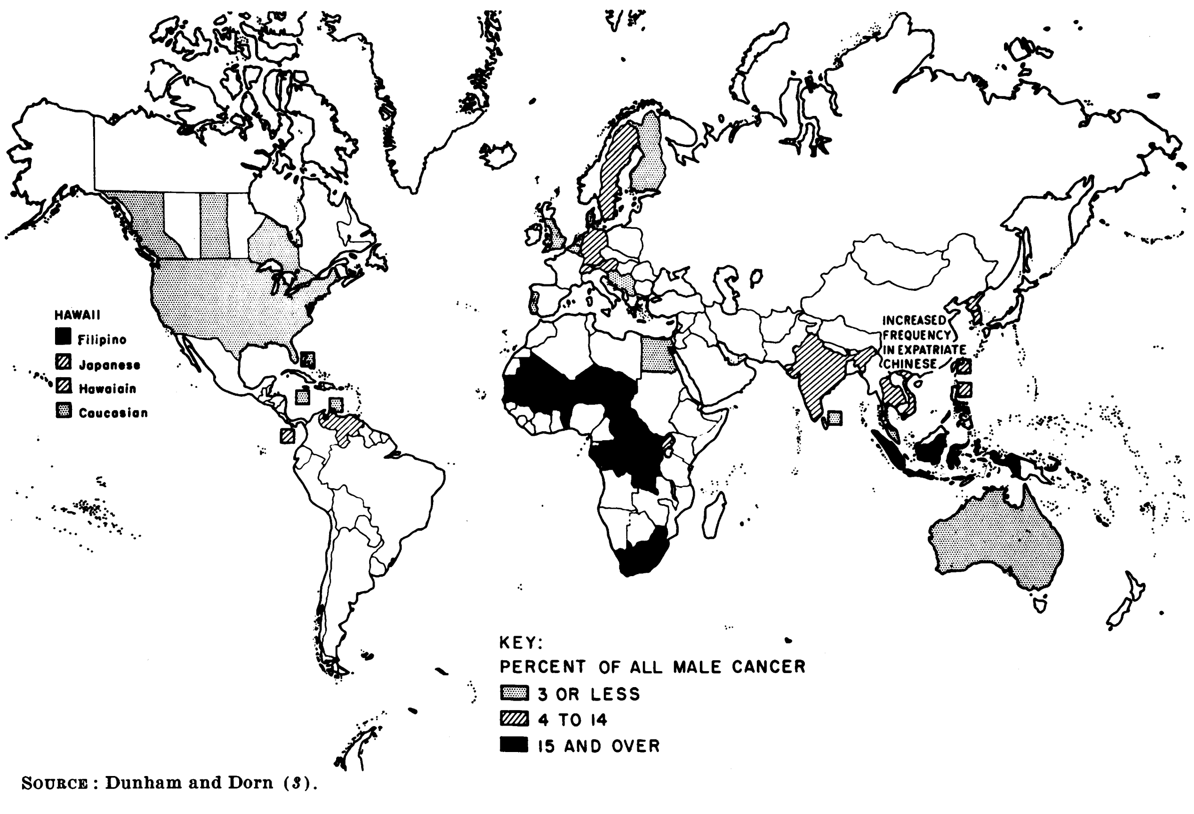
Distribution of Cancer in Animals

In the total ecology of neoplasia, the possible relationship of man's biological environment has been more or less forgotten until the resurgence of studies on the virus etiology of cancer. Tumors in animals are of interest today, not only because they may demonstrate environmental factors shared by man, but because some animal species may be vectors and transmitters of viruses that may cause neoplasms in man.

Figure 6, from a symposium on comparative medicine (*14*), demonstrates man's position relative to other animals in Iowa. Man stands approximately in the middle of several species with which he has close contact. A point to remember is that in terms of biological turnover, for every lifespan of the human being there are several generations of other animal species. For chickens, for example, there may be 50 to 100 generations during a human lifetime.

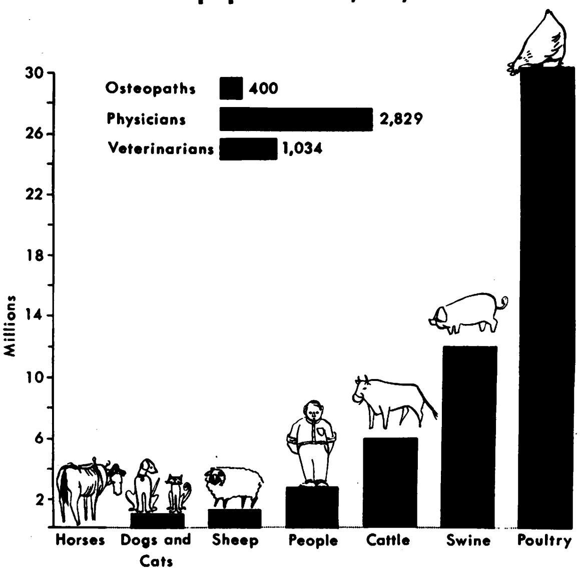
Another point to remember is that we are in close contact with many animal species, not only farm animals and household pets, but also

Figure 5. Relative frequency of liver cancer in males



SOURCE: Dunham and Dorn (*3*).

Figure 6. Man and his animal neighbors in Iowa (population 2,600,000)



Courtesy of Dr. Ian M. Smith (*14*).

through food products. Many cattle and other stock animals are condemned yearly for human consumption because of the discovery of gross neoplastic lesions in their carcasses (*15*). The proportion would be higher if the animals were kept for longer periods of their natural life-spans.

The neoplastic spectrum is not limited to the animal kingdom. Even plants develop a cellular abberation, crown gall, that meets the criteria of neoplasia. Figure 7 shows a tomato plant with such a lesion. Erwin Smith (*16*) in the early 1920's showed that this plant tumor was induced by a bacterium, *Bacterium tumefaciens*.

Neoplasms are found in fish, amphibia, and reptiles as well as warm-blooded animals. Last year, attention was sharply attracted by an outbreak of hepatoma in epidemic proportions in the most popular game fish in this country, the rainbow trout (*17*). Figure 8 shows a rainbow trout, with relatively small multiple nodules of hepatic carcinoma. In some fisheries, well over 50 percent of the trout develop such lesions, usually when they reach the brooder age of over 2 years.

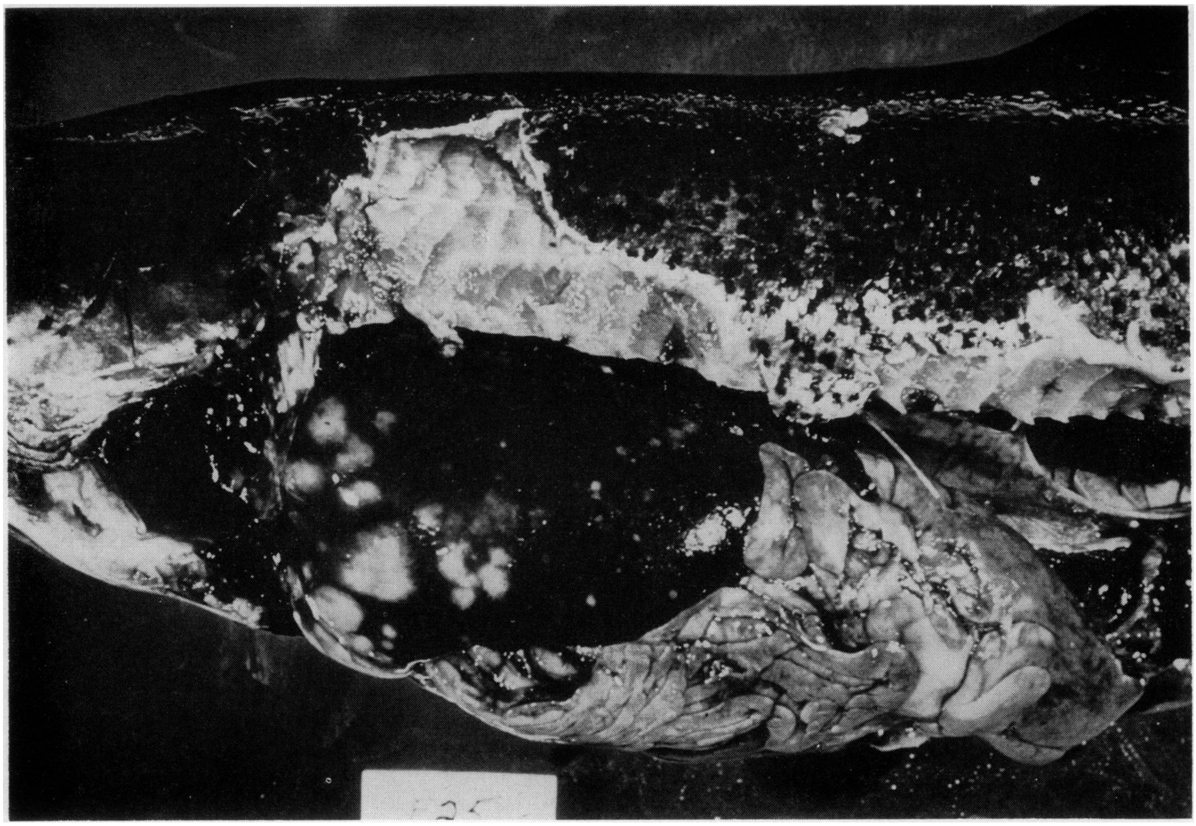
Most of the U.S. fish are raised artificially, and the feeding habits have been markedly altered during the last decade. Food in the form of pellets of dried fish meal and other ingredients has replaced the diet of high protein meat scraps. The carcinogenic factors appear to be in the fat fractions of the diet. It may well be that the hepatomas in fish present a situation not too dissimilar to the African hepatomas of man.

There has been a resurgence of interest in a neoplasm common in this country among amphibians, the kidney tumor in frogs. The occurrence of this neoplasm is particularly prominent in some streams in the New Hampshire area, a major source of frogs for physiological laboratories in U.S. high schools and colleges. We have not explored the frog populations of streams in other parts of the country to any great extent, but we do know that kidney carcinoma is also present in frogs from Michigan and North Carolina. Data indicate that this neoplasm can be transmitted by cell-free filtrates, and that it answers some of the requirements for a transmissible, perhaps virus-caused neoplasm (*18*).

An example of a common canine neoplasm in areas where dogs run without control, the venereal lymphosarcoma, is shown in figure 9. This

Courtesy of U.S. Department of Agriculture Research Service.

Figure 7. Crown gall on tomato plant



Courtesy of Dr. W. C. Hueper (*17*).

Figure 8. Hepatoma in rainbow trout

was the first neoplasm successfully transmitted from one animal to another. Novinsky in 1877 transplanted this tumor to puppies; his work was unrecognized for many years, partly because it appeared as an obscure Russian thesis (*19*). The tumor is transmissible both by sexual and oral contact among dogs. This may be a cell-implantation phenomenon, but the role of a virus in its occurrence requires further investigation.

Dogs develop a large number and variety of tumors, mammary carcinomas, testicular tumors, adrenocortical adenomas and carcinomas, lymphosarcomas, plasma cell tumors, and even lung tumors. About the only neoplasm I have not seen described in dogs is gastric carcinoma, but they do have cancer of the esophagus associated with a parasitic infestation (*20*).

Dogs are the animals with which many Americans have the closest contact, and in our culture they seem to be considered as 3-year-old children with fur. Until now, the possible neoplastic significance of contact with dogs has not been considered, but the possibility is one that deserves reappraisal with modern methods.

Perhaps these are sufficient examples of neoplasms in animals, other than to mention leukemia and cancer-eye in cattle, plasma cell tumors in cats, the lymphoma complex in fowl, and a wide variety of tumors that have been described to occur in wild animals kept in zoological parks.

Virus Research in Cancer

The most popular laboratory animal in cancer research is the mouse. Its mammary apparatus extends subcutaneously from the ear down to the perineum, and breast cancers thus can appear anywhere with the exception of the mid-dorsal line (fig. 10).

One of the true advances in our attack on cancer was the discovery by Bittner (*21*) in 1936 that these tumors need three factors for

Courtesy of Armed Forces Institute of Pathology.

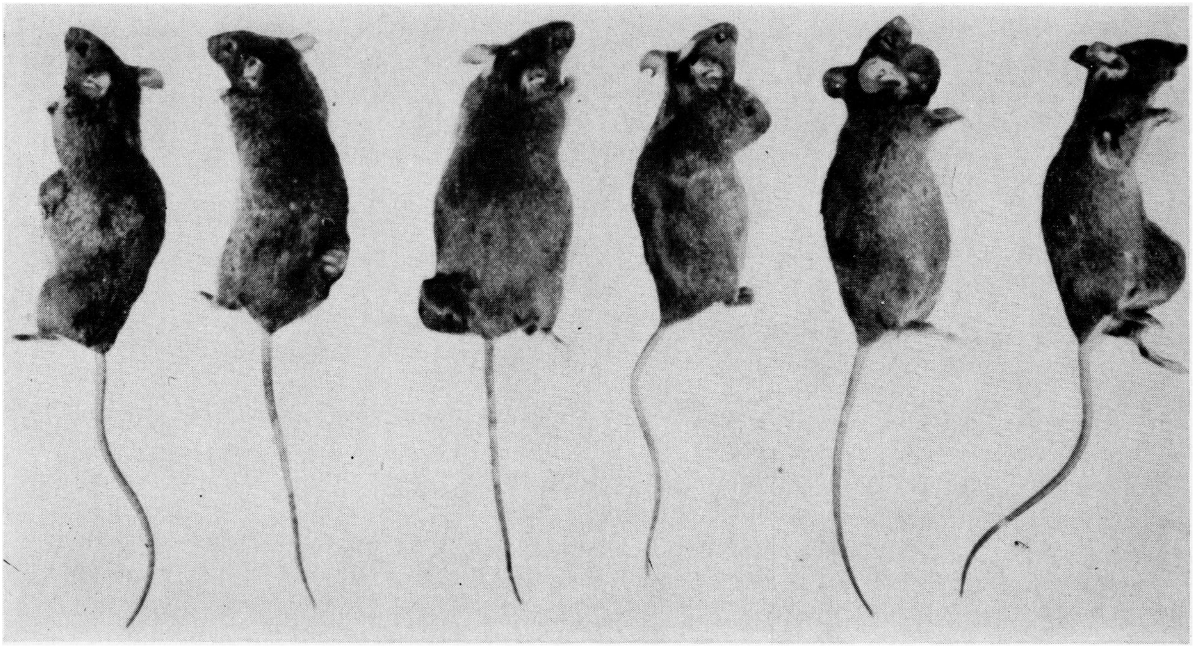
Figure 9. Venereal transmissible sarcoma of the scrotum in dog

their development in mice; the genetic capabilities of the mouse, the hormonal substrate found in females or induced in males with estrogens, and a factor transmitted from mouse to mouse through the mother's milk. The last factor has now been clearly defined as a viral entity, and is called the Bittner virus. It can be grown in tissue culture, and there are diagnostic tests for its presence in the animal population.

It was in mice also that Ludwik Gross of New York, about 10 years ago, observed that leukemia is also capable of cell-free vertical transmission from progeny to progeny (*22*). To date, in mice at least five types of defined leukemia have been observed in which viral particles can be identified, grown in tissue culture, and then used to produce leukemia in seriatim.

Even more interesting, a related virus was discovered in one of the leukemia variants which caused parotid tumors in mice. Eddy and Stewart (*23*), by growing this particular tumor virus on tissue culture, found that it was not species specific. The virus induced a wide variety of neoplasms, not only in mice but also in hamsters, rabbits, and rats. Currently, more than 20 different neoplasms can be induced in animals with this polyoma virus.

Polyoma virus (fig. 11) is a DNA type which exists not only in the tissues of infected animals, but also in the urine and feces. It is probably transmitted by the gastrointestinal route under natural conditions. Huebner (*24*)



Courtesy of Dr. W. E. Heston.

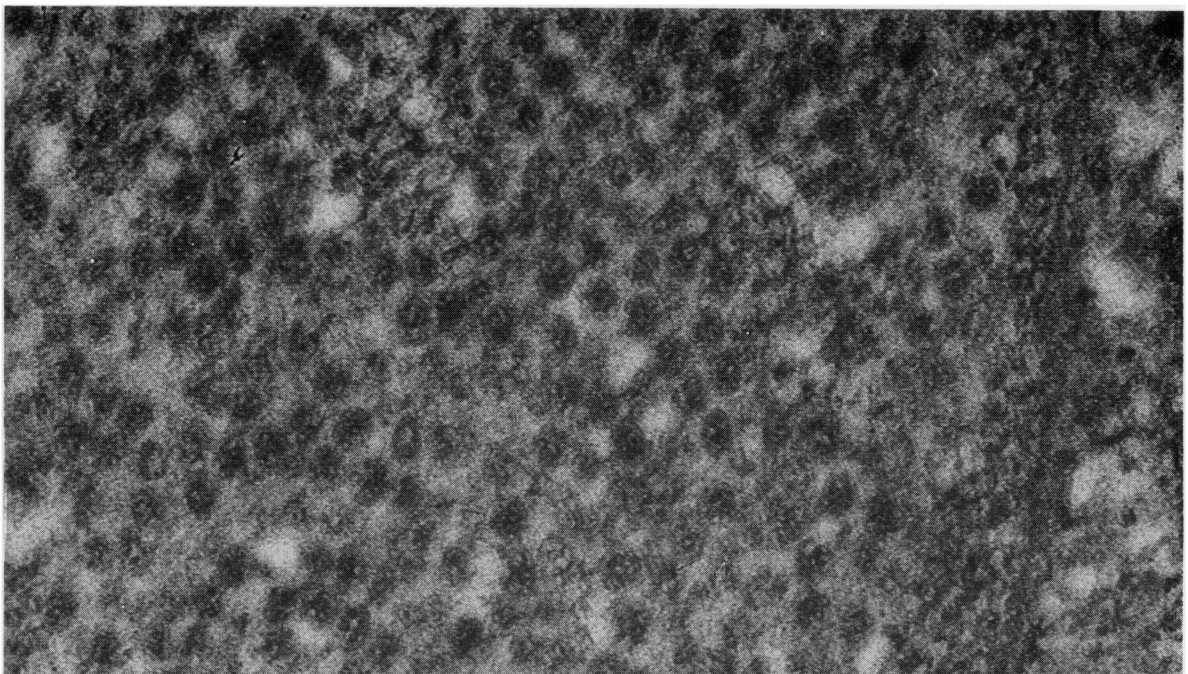
Figure 10. Mammary carcinoma in mice

has made a number of studies in both urban and rural environments regarding the distribution of the polyoma virus. It was recovered in some mouse nests in the field, in granaries, and in Harlem tenements.

The polyoma virus entity is a member of the "Papova" group of nuclear DNA viruses that includes the Shope papilloma and the vacuolating Simian virus 40. The Simian virus, after passage through tissue culture, has produced sarcomas in hamsters at the site of injection (*25*). Of more significance for man is that a similar carcinogenic activity in hamsters has been demonstrated (*26*) for the human adenovirus, type 12.

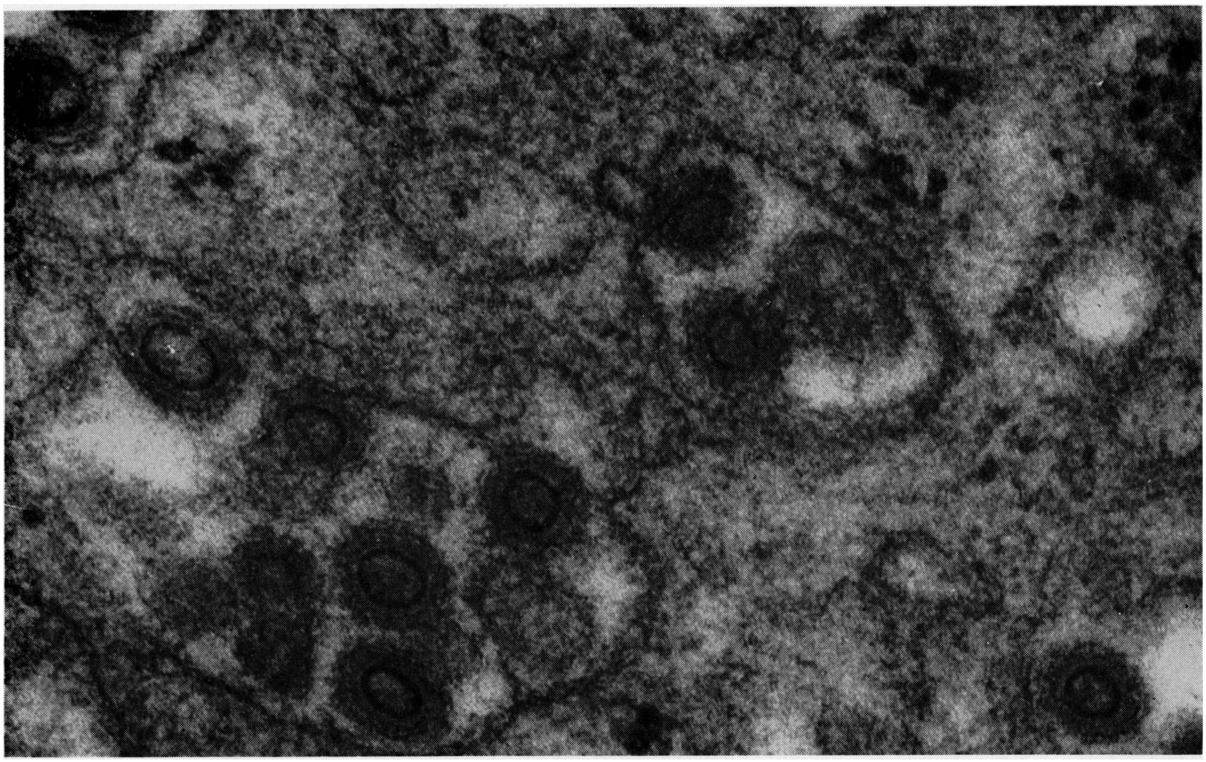
Another example of a well-defined, virus-induced neoplasm in mice is shown in figure 12, which is a 170,000 magnification of the Moloney leukemia virus in a cytoplasmic vacuole of a megakaryocyte (*27*). These particles appear to lack DNA, and are thus an RNA-type cytoplasmic virus. Similar yet distinct viruses have been demonstrated in at least six other leukemias of mice, and one of rats. The ubiquitous avian leukosis group of viruses is also of the cytoplasmic RNA type. Recently the concept of species specificity of tumor viruses has been further shattered by the induction of tumors in rats with the Rous sarcoma virus of chickens.

There are now thoroughly established virus-induced neoplasms in chickens, mice, rats, and rabbits; less firmly established situations are seen in frogs, squirrels, deer, and cattle. Intracellular particles compatible morphologically with viruses have been described in several types of human tumors and leukemia. However, the presence of such particles certainly does not prove that the tumors are related etiologically to virus. For this, it would be necessary to cultivate the virus in tissue culture, to reproduce the disease in a recipient, and again to recover and to identify the viral agent. This is difficult to do in man, for many obvious reasons.



Courtesy of Dr. A. J. Dalton.

Figure 11. Polyoma virus in tissue culture (X 150,000)



Courtesy of Dr. A. J. Dalton (*27*).

Figure 12. Moloney leukemia virus in megakaryocyte (X 170,000)

In cancer, virus research has provided a refreshed endeavor, so well expressed by Wendell Stanley in 1956 at the Third National Cancer Conference (*28*). He stated that for research purposes it should be assumed that most, if not all, kinds of cancer, including cancer in man, are due to viruses. Unless we are to believe that man and the animal species inhabit two separate and distinct universes, the assumption is now a fairly safe one. The question is no longer, "Is human cancer due to virus?" but rather, "What viruses and what specific tumors are etiologically related, and what are the mechanisms involved?"

I happen to be traditionalist enough to believe that viruses do not have to be invoked in every animal or human neoplastic situation, and that neoplastic alterations in DNA and RNA can occur under the influence of ionizing radiations or carcinogenic hydrocarbons as well as following infection by transmissible, reproducible virus particles. Nevertheless, the possibilities for understanding the neoplastic diseases and for controlling and preventing them have gained a new dimension through the intensified research attacks upon the virus aspects.

No other approach in cancer research at present is as active or has produced as many changes at the research level as the exploration of the virus aspects of neoplasia. We should remember, however, that this is not new. The discovery of a virus tumor was originally made only a few years after the turn of the century. One Nobel prize, long overdue, should go to Peyton Rous (*29*) for his 1911 discovery in chickens of cell-free transmission of a tumor which now bears his name, the Rous sarcoma. The observations of Rous lay in abeyance for many years until they were extended by Shope to a papilloma and carcinoma in rabbits (*30*), by Bittner to mammary tumors in mice (*21*), and by Ludwik Gross to leukemia in mice (*22*).

The reason for this seemingly wasteful delay is that cancer research can progress only as fast as the general knowledge of medicine moves forward. We can now attack the problem of neoplasia logically and systematically because of techniques developed primarily by the stimulus created by the entirely different problem of poliomyelitis. The concentrated attack on poliomyelitis has placed the United States in the forefront of techniques of tissue culture, electron microscopy, and immunochemistry. Perhaps the most important yield of research directed against and culminating in a triumph over poliomyelitis will yet be in making it possible to solve the neoplastic problem.

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