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THE CONTINUING PROGRESS OF CANCER RESEARCH[1]

By Professor WARD J. MacNEAL

NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL, COLUMBIA UNIVERSITY

DURING a period of serious difficulty in the adjustment of human relationships throughout the world we find ourselves engaged in the consideration of a campaign against a common enemy of mankind which still defies us and which we do not quite fully understand. The worker in the field of cancer research sometimes feels discouraged because progress has been less rapid than he had hoped. The general public also appears to have the impression that cancer research is not making very rapid progress. In fact, however, there are many reasons for optimism. A comparison of the present outlook in regard to malignant disease with that of thirty years ago will indicate that a very marked advance has been accomplished. It is, however, quite evident that continued effort in cancer research must be maintained. The lengthening of the average life of the human individual has served to increase the population in the older periods of life and it is in these age periods that malignant disease is most prevalent. For this very reason we have to expect a continuing increase in the incidence and death rate from malignant disease for some time to come. Modern civilization has also made the lives of persons beyond fifty years of age of greater value to the community, and it is becoming increasingly important to preserve these individuals in a state of efficiency for the service of humanity. Nowhere will one find any outcry against the expenditure of effort in the study of cancer except from those who feel that these efforts are being misdirected or are utterly futile.

The precise nature of malignant neoplastic disease can not be said to be fully elucidated as yet. In the study of a disease process a beginning is ordinarily

[1] Address of the president of the American Association for Cancer Research, Toronto, March 28, 1934.

made by the examination of symptoms and gross signs of the disease. This is followed by a study of the anatomical structure, both gross and microscopic, and finally there is an attempt to ascertain the relationships of cause and effect which we ordinarily class under the study of etiology. Some advance has been made in all these fields in recent years. In the clinical field of symptomatology we have learned that emaciation, severe pain and disability are not the ordinary signs of early malignant disease. We have learned that, as a rule, these evidences appear only late in the disease. This recognition is of great importance to the patient, for it places proper emphasis upon the recognition of cancer in the earlier stage before such signs and symptoms have appeared, at a time when the disease may still be regarded as amenable to treatment. This knowledge has been acquired not only by physicians but has been imparted to the public in such a way that now one often sees cancer in a very early stage, so early in fact that one might be justified in stating that the very early cancerous lesion is not particularly dangerous. This changed attitude in regard to symptoms and signs represents an advance in the attitude toward malignant disease of the very greatest practical importance.

Study of the structure of neoplasms has been carried on assiduously by a very large number of scientific investigators. From these studies we have learned the various peculiar structural forms of tumors which are observed in various parts of the body, and by using this knowledge in conjunction with a record of the subsequent history of the individual, there has gradually been accumulated by most painstaking work quite definite criteria to guide the physician in the care of patients presenting each of these various kinds of lesions. In this way a very detailed and elaborate classification of various types of neoplastic growths has been worked out on the basis of the histological elements and their arrangement in the tumor. This work is also of supreme practical importance. At the present day it furnishes the information upon which a diagnosis, prognosis and outline of treatment for the patient must be based.

The earnest student of medicine is not, however, completely satisfied with the knowledge of signs and symptoms and the knowledge of anatomical structure. In the study of neoplastic disease we find numerous investigators who have turned their attention to the question of etiology. There has existed, perhaps, some antagonism between those who have devoted their lives to the study of structure of tumors and those who would make an attempt to ascertain the causative factors by some other method of investigation. This antagonism has certainly been very much ameliorated in the last thirty years, and this amelioration in itself may be looked upon as a distinct advance in cancer research. A tremendous impetus to the study of etiology was given by the recognition of transplantable animal tumors. These tumors occurring in small animals with relatively short duration of life offer the opportunity to study many generations of tumor-bearing animals during the lifetime of one man. Perhaps the chief interest in this field hinges upon the questions of heredity, the influence of irritation and the possible relationship of bacterial agents or filterable agents in the causation of malignant neoplasms.

In regard to heredity, clinical observations on human families had already revealed some striking contrasts. Although the records of human families are far from satisfactory for the purpose, it has, nevertheless, been possible to recognize that there are families in which cancer occurs with unusual frequency and that there are other families in which neoplastic disease as a cause of death is practically unknown, even though the individuals in these latter families attain to old age before death. Apparently there is an actual inheritance of the tendency to suffer from malignant tumors and also an inheritance of resistance to this type of disorder.

From the purely scientific point of view the study of heredity in animals is much more satisfactory. Here the material is subject to more precise control and fairly complete evidence, including post-mortem examination of nearly all individual animals, can be made available. The genetic experts who have devoted attention to the study of cancer heredity in mice are not wholly in agreement in regard to interpretation of observations. However, it is now certain that there are families of mice in which malignant tumors are exceedingly common and that there are other mouse families in which neoplastic disease is practically unknown as a cause of death. It is possible to propagate, by pure line mating, races of mice which will continue to exhibit these phenomena of high cancer incidence or of practical freedom from cancer. The results of cross matings present difficulty in their interpretation. However, it now seems certain that there is something more than a simple genetic heredity involved in cancer of mice. The presence of cancer in the mother seems to be of greater significance in the production of cancer in the offspring than is the presence of malignant disease in the paternal ancestor. Perhaps it would be fair to say that the influence of heredity upon the incidence of cancer can now be clearly recognized as having a real existence, but that there is still lacking the proof that cancer is a genetic disease inherited in the same sense as polydactylism or hemophilia. One is reminded of the old controversy as to whether it is the soil or the disease which is being inherited. It seems

not improbable that the heredity actually has to do with the soil upon which the disease may develop. However, some students of genetics appear to be fully convinced that malignant disease in mice is actually dependent entirely upon genetic factors.

The study of malignant disease in animals has disclosed the fact that this type of disease is much more frequent in such animals as rats and mice, dogs and chickens than it is in cattle, horses, sheep, swine, ducks or geese. The evidence in regard to these latter animals appears to be fairly reliable, because animals used for food are subjected to a reasonably careful inspection in many instances.

The influence of irritation as a factor in production of malignant disease, first recognized by Percivall Pott in 1775, has in recent years commanded more and more attention. In addition to the cancer of chimney sweeps described by Pott it is now possible to recognize with certainty the influence of irritation in causing malignant disease of the mouth, for example, that due to burning the tongue with hot smoke, or that which follows the chewing of particular kinds of irritant vegetable materials, or that which is associated with the continuing irritation of jagged teeth. The influence of irritant chemical substances which are excreted in the urine as well as the influence of the bilharzia disease in the urinary bladder as factors in the incidence of malignant tumors in this region may be considered to be established beyond question. There is also suggestive evidence that irritation and disturbed function play a considerable part in cancer of the breast and uterus in the human being.

In experimental animals it has been possible to obtain a large amount of evidence indicating the positive influence of irritant substances in relation to the occurrence of neoplasms. The effect of aniline dyes and of crude tar itself is now distinctly recognized. Modern refinements of these studies have led to the recognition of quite definite pure chemical substances which exert an important influence in inducing cancer in experimental animals. However, the positive results obtained in this way are not sufficiently constant in any animal species to warrant the statement that such a substance may be looked upon as a specific carcinogenic agent. Especially when one attempts to produce malignant disease in a variety of different animals with such an agent, he finds that positive results are to be expected only in a relatively small number of animals employed for experimentation.

It is perhaps fair to state that prolonged irritation of any region of the human body may be looked upon as a factor favoring the development of malignant tumor in that particular region. It may also be fairly said that the application of irritant substances to various animals serves to bring about the appearance of malignant tumors in a number of such animals in which no tumors would be expected in the absence of such irritation. However, one has to recognize that not every tissue will respond to irritation by the production of a tumor and that there still remains some obscure factor of causation in the tissue which does respond by the production of a tumor. The possible interaction of hereditary influences and irritating factors in the production of neoplastic disease is strongly suggested by the observations made in this field.

The possible importance of microbic agents in causing neoplasm has intrigued the interest of various investigators for the last fifty years. In a disease of plants known as crown gall Dr. Erwin F. Smith was able to recognize a bacterial species as the etiologic agent, and he was inclined to regard the crown gall disease of plants as analogous to cancer of animals. However, it is a far cry from plants to animals and especially to a human being. The various bacteria which have from time to time been found in tumors of man and other mammals are now quite generally regarded as secondary invaders of no actual importance in the causation of the neoplasm as such.

More significance attaches to the observation of filterable agents, especially in the tumors in chickens. It has been possible to separate from such tumors a filterable agent which is either in solution or in such a finely divided state that it will pass through the pores of filters capable of retaining the smallest of the ordinary bacteria. When this filterable agent is introduced into healthy chickens in a suitable manner it is possible to bring about the development of a lesion similar in all respects to the natural neoplasm observed in the original bird. The exact nature of the lesion thus produced has become a subject of some controversy. However, it is only fair to say that these lesions would everywhere be regarded as typical neoplasms, were it not for the fact that a filterable agent has been shown to play a part in their causation. The numerous attempts to extend these observations to other tumors of vertebrate animals have not met with great success. It has been possible, however, to demonstrate a somewhat similar filterable agent in one type of malignant tumor of the mouse.

The nature of the filterable agent of the chicken sarcoma is not clearly established. Apparently the agent belongs to the so-called ultra-visible viruses and exists as particles in suspension, the size of the particles being somewhat less than 30 Ångstrom units in diameter, that is to say 30/1000 of a micron. In respect to size of particle this filterable agent seems to be in the same category as those agents which cause the destruction of bacterial cultures to which has been given the name of bacteriophage. Here also is a filterable agent, the exact nature of which is still

debatable. This agent appears to be able to stimulate a somewhat more active growth of bacterial culture, which is then followed by a disintegration of many of the bacterial cells or sometimes by a complete disintegration of all the cells in a culture. In some respects this phenomenon observed among the bacteria is analogous to malignant disease in the vertebrate, and it seems at least possible that an elucidation of the nature of the filterable agent of the bacteriophage may be helpful in elucidating the problem presented by the filterable agent of the chicken sarcoma.

A field of investigation which has presented many difficulties and which nevertheless seems to promise much for the future is that of artificial culture of neoplastic cells. The cultivation of animal cells in suitable glass containers has been successfully practised for about thirty years. The cultivation of neoplastic cells seems to present new difficulties in comparison with the culture of the cells of normal tissue. However, considerable success has already been attained and it now seems quite certain that the cultures of neoplastic cells tend to disintegrate and die more quickly than do the cultures of normal cells from a similar region of the animal body. Furthermore, in some of these cultures it is possible to recognize various examples of abnormal cell division similar to those which are seen in very actively growing neoplasms in the animal body. The successful culture of neoplastic cells presents many important new possibilities for the investigation of the problem of cancer. The possible existence of recognizable filterable agents in such tissue cultures is one that demands early inquiry.

The general public is chiefly interested in the practical control of cancer and the advocate of cancer research should be in a position to face frankly the challenge as to the practical value of all this abstruse study of malignant disease. Actually there is much reason to be optimistic about the matter. The scientist in his pursuit of truth can not at the moment pay too much attention to practical application. However, it is certain that the facts assembled by the research worker furnish the sound basis upon which one is able to formulate programs for a more effective control of human disease. The experimental study of heredity has already demonstrated conclusively that breeding plays an important part in the incidence of cancer. For a human being to escape malignant disease, therefore, it is important to select one or more ancestors from a line of human individuals who have shown resistance to this type of disease. Perhaps this suggestion may sound absurd, but it nevertheless does have some importance for the future generations. The individual of the cancer family is not necessarily condemned on account of the occurrence of this disease in his relatives, but he will do well in choosing his mate to select one from a family in which this disease has not been prevalent. Apparently for human affairs emphasis should be placed upon the inheritance of resistance to neoplastic disease rather than upon the inheritance of susceptibility. A second practical point of the greatest importance has to do with repeated and long-continued irritations of particular parts of the body. It is perhaps not too much to say that cancer of the mouth cavity is a wholly preventable disease. Irritation and maladjustments of function in other parts of the body should also receive early attention in order to diminish the danger of cancer in these regions.

The clinical and morphological studies of tumors as they present themselves to the surgeon and the pathologist have accumulated an enormous amount of information concerning the course of the various neoplastic diseases in different parts of the body and concerning the best method of their treatment. The general public is becoming cancer conscious so that tumors which show definite external signs are being seen very much earlier by the physician. This is a matter of greatest practical importance. Furthermore, the technical methods of dealing with cancer in various parts of the body have been very much elaborated and improved during the last quarter of a century. Cancer of the skin is by no means as serious a problem to-day as it used to be. In addition to surgical excision of cancer, which is highly effective in early stages of the disease, there are now available such physical agents as the Roentgen rays and the radiation from radium which are able to destroy the cells of cancer and permit healing in many instances without surgical excision. The organization of special institutions for the care of patients with malignant neoplastic disease has made possible the development of a very high degree of skill in the selection of the proper method of treatment and in the employment of these various agencies. These are practical results of cancer research.

The American Association for Cancer Research is the organization on this continent for the fostering of all investigations regarding neoplastic disease. I deem it a privilege to extend my personal congratulations to the investigators here assembled and especially to those who are bringing to us the fruits of their arduous labors which may add much or little to our understanding of tumors. Those, like myself, who have come with empty hands, are also fortunate in the opportunity to learn the new discoveries in this field, but especially in the privilege of intimate association with those earnest research workers who are even now creating the newer knowledge of cancer.