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Some Observations on Comparative Vertebrate and Invertebrate Pathology: A Summary Discussion of the Workshop

HAROLD L. STEWART

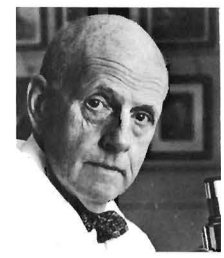
While there are some similarities among cancers of the same site in different species of domestic, laboratory, and captive wild animals and birds, there are also many differences. A point of view that many writers on comparative oncology have adopted is to emphasize, indeed, in my opinion, often to overemphasize, the resemblances between neoplasms of these animals and man. They have attempted to adapt the classifications and terminologies of human neoplasms to those of animals. This has misled investigators, in some instances, to believe that many animal tumors are suitable models for corresponding human diseases. Nothing could be further from the truth. There are no fixed and immutable criteria for the diagnosis of cancer in all species. Some cancers of lower animals may be similar and others dissimilar to those of man. Some cancers arise from cells and organs of lower animals that man does not possess. Moreover, there is still a hiatus in our knowledge about correlations of morphologic patterns and biologic behavior of certain neoplasms, some neoplastic-like conditions, and some lesions that may be confused with neoplasms. It required scores of years of observation and experience for clinical, veterinary, and experimental pathologists to develop the sophisticated knowledge about these subjects that now exists. But the troubles that beset the pathologist in his studies of cancerous and allied diseases in the vertebrates pale, by comparison, when investigators embark on studies of pathologic material of invertebrate species.

The anatomy, histology, and physiologic functions of these lower species confuse the oncologist as he attempts to apply the criteria for cancer that he has established for the higher forms of animal life. As Dawe[1] said at this workshop, the question "What is cancer?" constantly confronts the investigator as he examines abnormalities of form in these lower species. Mistakes have been made and perpetuated, as witness the misapplication of the term cancer to the melanotic lesions of *Drosophila* or to the lesions induced in cockroaches by nerve severance. In human beings, too, comparable mistakes have been made as, for example, the misdiagnosis of the non-neoplastic epidermoid hyperplasia surrounding insect bites of the skin or the dermal lesions of blastomycosis as carcinoma. There is a whole host of lesions of laboratory animals that at one time or another were misdiagnosed as cancer, lesions which do not progress beyond the stage of simple hyperplasia. Among these are the adenomatous hyperplasia of the gastric glandular mucosa of strain NHO and strain I mice, the papillary acanthomas of the forestomach of rats subsisting on an inadequate diet of bread and milk, the polypoid adenomatous lesion of the monkey stomach caused by a parasitic worm, squamous metaplasia of the lung of mice exposed to aerosols of gasoline, and adenofibrosis of the liver of rats, a self-limiting lesion that heals by scarring.

Despite the histologic resemblance of these lesions to cancer at some stage in their evolution, they do not infiltrate the surrounding tissues, and do not metastasize, and where feasible to test, do not transplant to syngeneic animals. The lesson that these experiences teach us is that appearances may be deceptive and mislead the observer. I would predict that with a newly emerging science like the pathologic study of cancer in mollusks, similar mistakes are bound to happen but to be forwarned will tend to minimize their number.

Clinical pathologists have learned not to rely too confidently on the histologic pattern of a given lesion without taking into consideration other factors. Thus a papilloma of the larynx in a teenager may look much the same as a papillomatous lesion of the urinary bladder of an adult. Yet the former disappears spontaneously, whereas the latter, if untreated, pursues a malignant course. Local excision will cure a benign looking, smooth muscle tumor lying in the subcutis of a patient, but a tumor looking exactly the same histologically may recur and metastisize if located deep in the thigh or in the retroperitoneum. Likewise the so-called extra-abdominal desmoid tumors of women are considerably more likely to infiltrate locally and to recur following resection, than are the histologically similar tumors of the abdominal wall.

These examples demonstrate the biological influence of location on lesions having a similar histologic appearance. Although most neoplasms exhibit pronounced departures from the histologic pattern of the normal organ, thyroid gland carcinoma may prove to be an exception: a metastatic deposit of thyroid gland carcinoma in bone may be indistinguishable histologically from a section of the normal gland in the neck.



Stewart

Harold L. Stewart is with the Registry of Experimental Cancers, Building 37 (ERF), Room 202, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014.

[1]Dawe, C. J. Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014.

Some cancers emerge from a milieu of inflammatory processes, as for example Kaposi's angiosarcoma; and other cancers from non-neoplastic cellular proliferations that persist for long periods of time, such as leukemia in patients suffering from Sjögren's syndrome. There are, in addition, debatable lesions that occupy a never-never land or have a shaky foot in two camps as exemplified by reticulosis, or Letterer-Siwe disease, which some regard as a metabolic process, others as a neoplasm.

The appearances of the early developing stages of many cancers are so innocent as to be disarming. This is true of alveologenic carcinoma of the lung of mice and rats, trabecular carcinoma of the liver of the same species, adenocarcinoma of the uterine corpus of the rabbit, and papillary carcinoma of the urinary bladder of man.

Using laboratory animals it has been possible to design carcinogenic experiments involving serial killings and serial sectioning of the affected site, to trace the origins of cancer to a single cell type, as for example the type II alveolar cell that comprises the alveologenic carcinoma of the mouse. One can, as Farley[2] told this workshop, take advantage of nature's experiment, where epizootics of cancer are arising in mollusks in a confined area, to trace the cancer back to its cell or cells of origin. As shown at the workshop, electron microscopic studies are an advantage in this exercise because many cells possess characteristic membranes and subcellular organelles that distinguish them from other cells which may look like them under the light microscope.

With man, even the skill possessed by the clinical pathologist has not prevented mistakes from time to time in the diagnosis of some common conditions. Thus the granulomatous pattern of Hodgkin's disease has been mistaken for tuberculosis and vice versa. I, myself, one time mistook the lesion of coccidioidomycosis for a clear cell carcinoma of the kidney, this after or perhaps because of too much reliance on the application of the periodic acid Schiff reaction for the demonstration of glycogen. My mistake is an example of where a fungal cell was mistaken for a cancer cell. Judging from some of the discussions at the workshop, this kind of mistake is a distinct possibility when trying to assign certain diseases of mollusks to a specific category—a parasitic infection or cancer.

Cellular immunity and other factors which control neoplasia, come into play with a variety of cancers of vertebrates. A common experience is with breast cancer in women, in whom the postoperative survival may vary from a few months to 25 or more years. Malignant melanoma may run a curious up-and-down clinical course. Patients with a kidney transplant, who are taking immunosuppressant drugs, may develop lymphoreticular type neoplasms of the brain, a nearly unheard of event in immunologically competent persons. Unexplained also is the vicious clinical course of the alveolar type rhabdomyosarcoma. It may appear suddenly in a localized part of a child's body and pursue a relentlessly fatal course in a brief period of 2 months. One must bear in mind that analogies may prove to exist between some of the debatable tumor-like lesions of man, the mouse, and mollusks. In children, in particular, considerable knowledge has accumulated on the morphology and behavior of pseudosarcoma, paradoxical fibrosarcoma and the like, lesions now considered not to be genuine neoplasms. With adults, too, certain proliferative fascial lesions present a histologic picture suggestive of a highly malignant tumor and yet these lesions do not pursue a malignant course.

With mice, the Moloney sarcoma virus induces a category of lesions classified as atypical granulomatous tumors with neoplastic-looking giant cells. These lesions tend to regress and disappear in immunologically competent mice but may evolve into genuine cancers in mice that are immunologically incompetent.

As the lantern slides, shown by the speakers at the workshop, were viewed by the other participants it became evident that some lesions diagnosed as cancer were considered by others to be non-neoplastic conditions. This is the same sort of evolutionary thinking that clinical and experimental pathologists experienced before they were able to separate neoplasms from certain non-neoplastic conditions in man and the mouse.

Development of further knowledge of the manifestations of neoplasia and neoplastic-like processes in the lower forms of animal life is also likely to throw light on some of the other mysteries connected with cancer that I have been talking about. While I cautioned earlier in my talk against too literal histologic comparisons among neoplasms of vertebrates this does not mean that important principles in oncology have not been established by comparative pathology studies. One need only recollect that the epochal discovery of the virus causation of cancer came from studies of leukemias and sarcomas of the domestic chicken. Temperature and altitude are critical factors in accounting for the geographic pathology of the Burkett tumor in the blacks of Africa. Moreover, there are striking differences in the frequencies of leukemia and glioma on the one hand and solid lymphoma and retinoblastoma on the other among black children living respectively in Washington, D.C. and Nigeria. With mollusks, the promotion and retardation of infections by viruses are known to be critically influenced by the temperature of the environment in which the animals are living. If viruses could be shown to induce cancer in mollusks then a model would be at hand to test one of the physical factors, namely, temperature, that influences certain cancers in human beings. Certain other neglected areas in the investigations of cancer in mollusks stand out. In the radiation experiments described at the workshop no mention was made about the effects of radiation on the induction of cancer in mollusks. This type of investigation should prove to be worthwhile as also would the exposure of mollusks to various known carcinogenic chemicals. The gills of fish exposed to aflatoxins have shown a curious affinity for the metastases of the hepatic cancers that arise from exposure to this carcinogen. Studies of phenomena like this strange pattern of metastasis might shed light on the spread of tumors in man.

[2]Farley, C. Austin. Oxford Laboratory, Middle Atlantic Coastal Fisheries Center, NMFS, NOAA, Oxford, MD 21654.

Comparative studies of cancer in primitive species have raised a critical problem centering about the evolutionary development of the thymic system of cellular immunity. To test the theory properly it is necessary to establish frequencies of tumors of invertebrate animals. This in turn depends upon the development of proper standards for the diagnosis of neoplasia in these lower forms. With its scope and dimensions and the prestige of the participants, the present workshop has gone a long way in these directions.

The accomplishments of the workshop will also have a bearing on a more practical problem. It is well known that the environment and habits of filter feeding mollusks place them in a position of exposure to carcinogenic agents. These undoubtedly account for some of the now known epizootics of neoplasms among mollusks. Scientists at the Oxford laboratory and other participants at this workshop are the pioneer leaders whose investigations of neoplasia in mollusks have placed an important tool in the hands of the environmental protectionists. Mollusks play an important role in the food chain. They are eaten by man and by bottom feeding fish. The fish are eaten by birds and they in turn by mammals. So mollusks, with their possible concentrated complement of carcinogens and poisons, make the full circle of the food chain. Moreover, the epizootics alert the environmentalists about the possible exposure of man to carcinogens in bays and estuaries and in the streams and rivers that flow into them. This can be an important clue leading to the identification of the source of the pollution which may be adversely affecting exposed people in the neighborhood of the source, as well as those living downstream who obtain their domestic water supply from the effluent.

From these remarks the value of this workshop is obvious.

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