Additional Comments on Differences between Cancers in Terms of Etiologic Factors*

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The diversity in tumors in terms of their etiological factors with emphasis on their genesis, i.e., carcinogenesis, has been ably presented by Dr. Berenblum. There can be general agreement with his viewpoints. Rather than to raise certain questions in emphasis, it seems desirable to mention another facet. This concerns the evidence for basic differences between cancers themselves correlated with their etiological factors.

The question posed by the program committee can be paraphrased to read: Judged by their carcinogenic factors, are neoplasms one basic disease or are they many different diseases? The problem whether the neoplastic state has an essential defect common to all tumors, formerly only of theoretical interest to a few, has become dominant to investigators in human etiological agents, cancer tests, and chemotherapy.

In behavior, all tumor cells, with few exceptions, have one characteristic which sets them apart from normal cells. This is their ability to reduplicate themselves persistently and continuously. Those tumors designated malignant have, in addition, the ability to disseminate. The cell proliferative chain reaction seems to be the essential defect; ability to metastasize appears to be secondary and proportional to the degree of the cell aberration. Morphologically, also, tumors have distinctive characteristics which permit their recognition with a high degree of accuracy. Since we have been here deliberating, a day and a half, about 1,500 new cancer cases have been diagnosed in the United States, chiefly by their morphological appearances, indicating that these changes are consistently a part of the basic abnormality. Every tumor cell is a composite of normal and abnormal (neoplastic) in varying proportions. They are morphologically recognized as tumor by their abnormalities, but the residual normal features indicate their origin.

What are the chemical equivalents to these functional and morphological features? Are they qualitative or only quantitative? We heard yesterday that no pathognomonic, chemically definable, qualitative features are yet known for tumors and that no consistent quantitative ones exist. This is no less distressing to the morphologist than to the chemist. Actually the changes appear morphologically to be rather large. They form the basis for tumor diagnosis from stained tissues, even though the chemical interpretations of the materials visualized are only partly known. The quantity and spatial distribution of the chemical constituents appear altered in tumor cells. No two tumors are ever alike in this regard, unlike normal tissues. Whether this visible abnormality and diversity represents quality as well as quantity of chemicals is not known. It nevertheless illustrates great diversity in tumors.

Several reasons suggest themselves for the failure to find greater and consistent chemical differences between cancers and between cancerous and normal tissue: In some types of analysis, an average of a heterogeneous cell population may be obtained—of microcytes and macrocytes, hyperchromatic and hypochromatic cells, etc., in which distinctive changes cancel each other. Transplanted tumors usually lose in heterogeneity, tending toward a morphologically and, perhaps, chemically less spectacular cell population. The topographical arrangements of the chemicals within the cells might be tremendously important, and this is lost in most analytical technics. Finally, most tumor cells partake also of the characteristics of their normal ancestors; on an analysis these normal features may dilute the differences contributed by the neoplastic state and thus mask the essential cancer defect.

Is cancer a disease entity like smallpox or even diabetes, or is it a group of diseases like the vitamin deficiencies or the infectious diseases? On purely clinical grounds it shows both great diversity and a unifying principle. With respect to signs and symptoms, tumors arising in the various parts of the body have little in common, and each may be simulated by non-neoplastic processes. Cutaneous, gastric, and uterine cancers appear to be separate diseases. They are diagnosed and treated by different methods and often by different specialists. However, constantly lurking in the physician's mind is an awareness of a unifying
basic biological characteristic shared by all tumors, namely, that of a relentless cell proliferation and its disastrous consequences.

Even those tumors having a common etiological agent may appear clinically quite dissimilar. Thus, a leukemia in a radiologist, a skin carcinoma on the hand of an X-ray technician, a bone sarcoma in a watch-dial painter, and a liver sarcoma following an injection of thorotrast clinically have little in common even though they were all induced by ionizing radiations, and they are treated by different methods. In contrast, gonococcal urethritis, endocarditis, arthritis, and salpingitis are clinically dissimilar, yet they have a common etiological agent and they respond chemotherapeutically to the same antibiotics. Judged by the criteria of a wide range in clinical manifestations, etiological agents, and therapeutic response, cancer appears, at this time, to be many diseases. Yet this deduction is unsatisfactory. Although they are not an etiological entity in the usual sense, cancers, like the infectious diseases, have in common a basic pathological abnormality. In the tumors this consists of regional, self-unrestrained cell proliferation.

Since it is impossible, biochemically or clinically, invariably to recognize cancer or to distinguish the types, it is necessary to resort to biological behavior and morphology to characterize the differences further and to judge whether cancer is one disease or many. It is also desirable for this purpose to distinguish between etiological agents and etiological factors. This permits a sharper analysis. In the example of gonorrhea already mentioned, the etiological agent was the gonococcus; the etiological factors that led to the infections may have been such things as age, sex, race, marital status, moral training, social and economic background, occupation with opportunity for travel, and others. The same separation into etiological agents and etiological factors is sometimes possible in cancer. Thus, not all persons having chronic radiation dermatitis develop skin cancer. They have been exposed to the agent but, presumably, other factors are lacking. The critical question now becomes: What evidence is there, based on behavior and morphological characteristics, for differences among cancers due to different etiological agents?

The etiological agents known for human cancer are chemical, physical, microbial, and a large miscellaneous group of cause-and-effect sequences in which the effective component cannot yet be characterized. To these may be added, in the experimental animal, an even larger group of chemicals and an additional microbial agent, the virus, for which no etiological role is yet recognized in man.

Let us briefly consider the evidence from behavior and morphology for a difference in tumors according to each class of agents.

1. Virus tumors. When a filtrate of Rous sarcoma agent is injected into a new host, a new growth quickly appears. Cell reduplication begins at once, and the cell doubling time is short, so that a new protoplasmic mass is soon apparent. A long preparatory period or induction time, such as is required for the tumors caused by the physical and chemical agents, is not needed. The agent gets into cells, and they begin dividing. Thus, in terms of these characteristics, the virus tumors are different; in terms of morphology they are not, the tumors appearing as rather ordinary sarcomas. One can conclude either that these growths are not true cancers, or that they are basically different from other cancers. They are also different in that the agent persists thru many cell divisions, if it does not actually cause them. Virus is regarded as both the initiating agent and as a part of the nuclear continuing mechanism.

These characteristics do not hold for the tumors caused by other experimental viruses. In the Bittner mouse mammary tumor, the induction time is long, and the agent persists. In the carcinomas ultimately derived by use of the Shope rabbit papilloma virus, the latent period is long, but the agent seems eventually to disappear. Thus, even in the virus tumors diversity is apparent.

2. Other living agents. In the human tumors associated with living agents, the induction period is long, and the resulting growths are morphologically no different from the other tumors in corresponding sites, except for the evidences of the infection. Thus, the carcinomas in relation to chronic osteomyelitis or mastoiditis, to lupus and luetic lesions, and others, show no distinctive features in behavior or morphology. The same holds for the bilharzial tumors of the bladder, the clonorchiasis cancers of the liver, and others. The cysticercus sarcoma of the rat liver falls into this group. The action of these agents seems to resemble that of the chemical and physical carcinogens to be mentioned, in that a prolonged stress is placed on cells. In these injured cells a reaction eventually occurs, and they proliferate without effective restraint and beyond the bounds of the damaged area.

3. Physical carcinogens. The tumors produced in man by ionizing radiation, by exposure to the elements including sunlight, or by heat burns are no different in behavior and morphology from their homologs induced by unknown factors. Only by their associated lesions or by the discovery of persistent agent are they sometimes set apart.
Thus, in a thorotrast cancer of the liver the agent may be demonstrated, and in a radium sarcoma of bone the irradiation changes which precede the emergence of tumor may be found also in other bones. In the mouse, an ultraviolet-induced skin cancer is no different from one caused by methylcolanthrene.

4. Chemical agents. The same comments pertain here as to the tumors caused by physical agents. The cancers elicited by specific chemical compounds are not distinguishable from those at corresponding sites due to factors as yet unrecognized. There is nothing specific in morphology or behavior about an aniline dye carcinoma of the bladder. Study of a lung tumor does not reveal whether it is caused by cigarettes, soot, automobile exhaust fumes, other agents, or inherited factors. Only when an excess of the agent is present as residue, as, for example, asbestos fibers, is the cause apparent. But the resulting tumor itself is not necessarily different from others.

GENERAL COMMENTS

It is clear that etiological agents of diverse types may cause similar tumors. Moreover, the character of etiological agents determines, in part, where a tumor will be produced by ordaining what cells will be exposed. Thus the principal action of ultraviolet is on the epidermis, of β-naphthylamine on the bladder epithelium, and of radium in bone. To this extent, agents determine the type of tumor which will occur. Other factors may, however, produce similar growths in these locations.

Much more important is the observation that a given etiological agent may produce tumors that differ widely in behavior and morphology. In fact, the differences between the tumors in a series produced by one agent may be as great as those between groups produced by various agents. Thus, in a series of 100 sarcomas induced subcutaneously by 3,4-benzyrene in mice, no two are exactly alike. Other series, each of a similar size but caused by other agents, would show the same wide range within the groups and between the groups. The causal agents could not be named by a study of the tumors. The differences between tumors are contributed by the heritage of the cell and by the neoplastic process itself rather than by the agents. Thus, one agent may cause carcinoma or sarcoma, or both, and various subtypes of each. In organs such as lung, in which, apparently, several agents may induce tumor, the relative proportions of morphological subtypes may be influenced by the carcinogen, but none is pathognomonic of any cause.

The same agent may also induce both benign and malignant tumors. These two groups share the phenomenon of self-unrestrained cell reduplication. They differ in that the capacity of dissemination is possessed only by malignant growths. Thus, by this criterion in behavior a wide range is elicited by the same agent. Until it is determined whether the chemical difference between normal and neoplastic and between benign and malignant behavior is basically quantitative or qualitative, it is impossible to say whether such tumors represent one or many diseases, despite their great diversity.

RECAPITULATION

To the critical question, whether cancer is one or many diseases with respect to etiological agents, two answers must be given depending on the conceptual level. In terms of clinical behavior and morphology, it is many diseases, each of which could be reduced if not eliminated by withdrawal or reduction of agent. On the other hand, in terms of the essential biological nature a definitive answer cannot be given at this time. Since the cellular self-replicating chain proliferation is not fully understood, it is impossible to say whether all tumors share a common biochemical abnormality.

The tumors produced by various agents, and even by one agent, differ in their behavior and in morphology to the degree that they are readily separable into groups. These groups are not sharp but arbitrary units in a continuous spectrum. They are based in part on the fact that the tumor cells morphologically partake of the distinctive characteristics of their ancestors and in part on the neoplastic properties of the cells. The cell deviates which are characteristic of the neoplastic state have a quantitative aspect regardless of whether there is also an essential qualitative difference. There appear on morphological grounds to be great quantitative chemical differences between tumors, and between tumorous and normal cells. Whether there are qualitative differences as well has not been morphologically determined, although histochemical studies have not yet been exhaustive.

In the final analysis, the problem of the ultimate nature of cancer cannot be answered in terms of etiological factors. These appear to be heterogeneous and, in a sense, nonspecific. The cell reaction to the agents is the distinctive thing. The property of neoplasia lies in the cells and not in the agents. This is, ultimately, a chemical problem, answerable only chemically. Until the essential nature of the neoplastic process is known, it is impossible to decide whether new growths are one or many diseases at this conceptual level.
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