It is readily apparent from the presentations at this Conference that several generalizations can be made concerning the nature of possible precursor populations during the development of cancer in several organs and tissues. Some of these can be summarized as follows.

1. A multiplicity of cellular and tissue structural changes can be seen in every organ system discussed, long before the appearance of cancer can be recognized by any criteria, including morphological. This overall pattern is seen in many human systems including skin, breast, gastrointestinal tract, urinary bladder, and tracheobronchial tree. It is certainly seen in most, if not all, animal models useful in the study of carcinoma, including cancer of the liver. This overriding generalization must be included in any valid hypothesis of cancer development that purports to be realistic and meaningful.

2. The patterns of cellular alterations seen in any organ or tissue during cancer development are remarkably similar, even with different chemical carcinogens. This is valid even with carcinogens that are widely diverse in their chemical structure. This seems to be true also in comparing the human with the animal models, although the data are very spotty concerning the response to specific carcinogens in humans.

3. The majority of such early lesions are proliferative. Doubts have been expressed periodically about whether the early lesions seen in the liver during carcinogenesis are proliferative. Alterations in preexisting hepatocytes without hyperplasia have been considered by some as playing the dominant role during cancer development. Clearly, from the presentations at this Conference, it is evident that the changes in surface epithelium during carcinogenesis are proliferative. This consideration, plus the data presented by Williams (11), would suggest that the liver is not exceptional with respect to the type of precursor lesion seen.

No evidence was presented to support an old suggestion that chemical carcinogens rapidly induce cancer and that the relatively long period of cancer development is concerned entirely with the control of the growth of these hypothetical so-called dormant cancer cells.

4. Several tissue or organ systems require only a relatively brief exposure (hours to days) to a chemical carcinogen to initiate cancer development. These observations would suggest that many if not all carcinogenic processes induced by chemical carcinogens have an initial short, more or less irreversible, phase ("initiation") followed by a period of cancer development (so-called promotion) of much longer duration. Thus the basic pattern of initiation and promotion (or better "development") studied most intensively in the skin seems to apply in principle to many other tissues.

5. The cellular proliferative response to chemical carcinogens is focal in nature. This seems to be obvious in many tissues, even though many biochemical effects or consequences of exposure to carcinogens seem to involve the majority if not all of the cells of any 1 type. The focal pattern of early cell proliferation suggests at least 2 possibilities: the varying state of receptivity of any population of cells at any time period in their life-span or the relatively uncommon nature of those induced biochemical events that have relevance to neoplastic development. There is a growing realization that similar cells in any organ may show gradients of many biochemical and physiological properties, e.g., hepatocytes in different zones of the liver. Conceivably, the carcinogen may have different quantitative or even qualitative effects on cells in different regions of the gradient. Thus, an element of selection may play a role in the early responses to carcinogens. The response of the surface epithelium of the urinary bladder (4) as a mosaic in the human conceivably could reflect in part such gradients. Major subjects for study would seem to be the essential nature of the molecular and metabolic alterations that characterize the focal responsive cells and the nature of the selection pressures or environment that favor their growth over the surrounding cells.

6. The focal proliferative cells are frequently organized or arranged in patterns differently than are the normal cells in the mature organ. This is seen to a striking degree in the urinary bladder (6) but is also observed in skin (9) and in liver (1, 2).

The patterns seem to indicate a new type of differentiation (urinary bladder) or a reversion to a more primitive or less mature type (skin, liver). Conceivably, such reversions or deviations may be essential to allow more biological options to the cancer cell that may ultimately evolve. For example, invasion or metastatic spread may involve properties that were needed during embryological and fetal development but not after maturation. The genetic availability of such options may be possible only if the cells are in a more undeveloped physiological state. Comparative studies of suitable precursor populations with the "appropriate" stage of development might be very profitable in this context.
E. Farber

Particularly provocative is the observation that a “promoting agent” in skin carcinogenesis induces a reversion to a more primitive pattern of differentiation. Conceivably, such an effect might be characteristic of many agents that can enhance neoplastic development in a system already initiated.

7. Interruption or disturbance in maturation or differentiation seems to be a common characteristic of many precursor cell populations. This is seen in the urinary bladder, skin, colon, stomach, liver, pancreas, and probably many other sites. In at least some sites (liver, bladder, skin), the early focal lesions manifesting such changes are ostensibly reversible, in that removal of exposure often leads to maturation of the cell population. Later in time, similar lesions appear that seem to have lost the ability to mature and these appear to be sites of further evolution or transformation to malignancy.

8. The time lag between the initial appearance of a cellular reaction to a carcinogen and the appearance of recognizable cancer by morphological or biological criteria is often relatively long—months or years in animals and many years in humans. Despite the rapidity with which carcinogens can induce many changes in the original target cell population, the subsequent history of most carcinogenic processes is very protracted. This period is often shortened by continued or repeated exposure to carcinogens or so-called promoting agents or cocarcinogens.

This slow development pattern was attributed commonly to host immunological control (surveillance). However, there is mounting evidence against the essential validity of this concept.

When viewed in perspective, the frequency of such long periods of development of malignancy, lasting probably 15 to 25 years in the human, coupled with the infrequent occurrence of effective long-term host control of frankly malignant cell populations, suggests the existence of as yet unknown host factors that have delayed the rate of cellular evolution to malignancy. Such a delay could have an important survival value for the host and the species. The peak of appearance of malignancy is past the reproductive period. Most cancers, therefore, have little or no influence on the survival of the species. On the other hand, prolongation of the period of evolution for cell malignancy during carcinogenesis beyond the reproductive period could have a significant effect in preserving the species. It is to be anticipated that host protective factors, operating to delay the appearance of cancer by prolonging the carcinogenic process, might well have developed during the long period of evolution. A search for such factors and the formulation of the possible specific nature of such factors could lead to new ways to analyze an important segment of the carcinogenic process.

General Considerations

The presentations during this Conference naturally have raised more questions than they have answered. This is 1 index of the profitable nature of the interchange of ideas. One of the key questions that dominates this whole area of cancer research is whether there is truly a preneoplastic or premalignant lesion. Given the chemical reactivity of ultimate carcinogens and the multiplicity of their interactions with target cell components, perhaps the lesions we see during the formative stages of malignant neoplasms are independent end-stage manifestations of such a “shot gun” effect of a carcinogen (Chart 1). What evidence do we have that any lesion appearing in the time-span between the initial interaction of a carcinogen with the target cells and the appearance of cancer has a precursor-product relationship to cancer (Chart 2)? The close correspondence between the occurrence of putative lesions and cancer could simply reflect the multiplicity of effects of carcinogens, as already mentioned.

Two groups of data offer support for the precursor-product hypothesis. The 1st is the well-known observations in humans and the less frequent findings in animal models (e.g., liver) that histological and cytological earmarks of malignancy are not infrequently seen in putative focal proliferative precursor lesions, such as polyps, hyperplastic or benign neoplastic nodules, areas of dysplasia, etc. This body of observation is impressive and highly suggestive. The 2nd relates to the occurrence of common markers in presumptive preneoplastic or premalignant and malignant lesions. There are many examples of negative “markers,” i.e., decrease or loss of some enzyme activity or other functional or structural component of cells. More convincing are positive markers, e.g., α-fetoprotein, preneoplastic antigen (2, 3), and enzyme activities (α-glutamyltranspeptidase) in liver carcinogenesis. Obviously, the need for many more markers, especially highly specific ones, is evident.

Another aspect to be greatly expanded is the need for additional functional handles for a more mechanistic analysis of cancer development. To date, the major emphasis has
been morphological. In my view, this must remain as a point of reference for studies in the future. Morphology is still one of the most useful approaches to cell biology, since it enables us to observe easily a host of modulations that often can be correlated with biological behavior. However, from this base must emanate a wide variety of functional and molecular approaches that almost certainly will help clarify many aspects of altered cell behavior.

In this context, we may draw again on the liver as a model. Recent research is pointing strongly to the development of resistance to the cytotoxic action of carcinogens and other hepatotoxins as an early manifestation of new hepatocyte populations in liver carcinogenesis (1-3). I would expect that each system would have its own functional base for the development of the appropriate selection pressure, dependent upon the normal physiology of that tissue. Naturally, liver plays a major role in drug metabolism and in so-called "detoxification." An environment based on this must emanate a wide variety of functional and molecular approaches that almost certainly will help clarify many aspects of altered cell behavior.

The identification and study of the selection environment would seem to be an especially profitable area for research that could lead to novel ways to interrupt the carcinogenic process.

Although the emphasis in carcinogenesis is shifting rapidly to in vitro studies, the knowledge to be gained must be related to intact organisms if it is to become knowledge and not simply the accumulation of trivial data. Models must be developed in which an easy flow of information from in vivo to in vitro and vice versa can take place. The in vitro must include organ as well as cell studies. The profitability of such an approach is already evident at this early stage of development, as demonstrated at this Conference (5, 10).

Another obvious lesson is the urgent need to study purer and purer cell populations during carcinogenesis. Methods of cell isolation and purification and manipulation of more complex systems in vitro and in vivo to obtain cleaner and cleaner cells would seem to be obvious requirements for the development of in-depth studies of carcinogenesis. The challenge is to develop simpler models in which we can pose more penetrating questions of mechanism, at both the biological and the biochemical levels. Cell culture of reproducible lesions induced in vivo would seem to have great potential in the immediate future (8).

In the liver, we are now able to ask a few more penetrating questions because of the increasing knowledge of carcinogenesis in this organ (e.g., Refs. 1 to 3). This is approaching the point where we can begin to develop testable hypotheses that relate to functional attributes of new cell populations on a quantitative basis.

The presentations at this Conference make one hopeful that we shall be able to do this to an increasing degree in several other systems. These results almost certainly foreshadow the development of a functionally meaningful merger of information at the molecular and the cellular levels, from which knowledge leading to new practical developments in diagnosis and therapy is virtually inevitable.

References

Putative Precursor Lesions: Summary and Some Analytical Considerations

Emmanuel Farber


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