Propagation of Cancer: Targets for Future Chemotherapy

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Summary

The growth of a tumor requires the coordinated participation of many components, the tumor cells, the surrounding interstitial tissue, and the terminal structures of the blood vascular system. The term proliferation usually has a more restricted meaning, referring to the increasing number of tumor cells that result from a sequence of successive cell cycles. I propose that the term propagation be used to encompass the diverse local intercellular reactions of both normal and tumor cells that are essential for continued proliferation of tumor cells in the intact host. Most efforts at chemotherapy involve the direct action of drugs on cell proliferation by modifying specific synthetic events in the cell cycle. Our understanding of tumor biology has reached the point where we can now broaden our approach to therapy. We should consider as appropriate targets for chemotherapy the various phenomena of propagation with the expectation that we may be able to inhibit tumor cell proliferation indirectly.

Introduction

The accepted dogma of cancer chemotherapy was expressed in a recent study of Beumer and Portón (6) as follows: ‘‘The ideal anti-cancer drug should be one that has a specific affinity for cancer cells without affecting normal cells.” In accord with this view, many cancer investigators consider the proliferation of tumor cells as the key problem in cancer control and have oriented their therapeutic efforts toward the goal of direct, selective inhibition of tumor cell multiplication. The histopathologist, however, sees cancer as an organized tissue, and in this context an additional approach to therapy presents itself. Inhibition of tumor cell replication may be attained indirectly since it appears that the propagation of cancer depends on a constellation of intercellular reactions. This paper sketches the case, as I see it, for considering tumor tissue in its totality as an end organ for cancer chemotherapy. Attention must be directed to the identification and the characterization of a wide variety of phenomena, all in the nature of cellular interactions, that in ensemble are responsible for the growth of tumors. Emphasis will be placed on model systems that seem to be applicable to chemotherapeutic study.

Tumor Tissue as a Growing Organ

For the histopathologist the organoid character of tumors serves several useful clinical purposes. In a primary tumor the degree of structural deviation from the normal tissue of origin provides cues for predicting the future biologic behavior of the tumor. When the first clinical manifestation is a distant metastasis, the tumor's microscopic architecture provides a means of recognizing the tissue, and often the organ, in which the primary tumor developed.

Gullino (22) has extensively studied the physiology of tumors as distinct organs. He has considered the tumor in terms of the neoplastic parenchyma in an environment consisting of two concentric compartments, the interstitial space and the vascular system. The exchange of metabolites between the parenchyma and the blood stream must take place through the interstitial space. Using some ingenious models, he observed that several biochemical parameters are constant for specific transplantable tumors. Of great interest to me among these indices is his observation that each tumor type produced a constant concentration of collagen per gram of tumor throughout many generations of transplantation. This constancy was observed for individual tumors whether they were growing as transplants in the ovary or in the kidney. The same characteristic collagen levels were found even for specific, actively growing tumors transplanted into cortisone, nonhistocompatible hosts. A more impressive expression of the organoid character of tumors was evident when the volumes of the vascular and the interstitial spaces were measured. Here, too, these compartments were of characteristic relative size for specific transplantable tumors.

The volume of blood flow was also distinctive for individual tumors. The characteristics of the normal host organ being replaced by the tumor tissue were evident only in the response of its blood flow to vasopressor or vasodilator substances. This physiologic observation was consistent with Gullino's anatomic observation that the major vascular trunks of each organ persisted even though the remainder of the organ was replaced by tumor tissue.

From the point of view of cancer chemotherapy, Gullino's model systems have enormous potential. They could provide us with more specific information as to the biologic differences between some common histotypic classes of tumors. In the subsequent sections we will dissect the components of tumor tissue, examining in turn the vascular component, the interstitial compartment, and the organization of the tumor parenchyma itself.

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**Blood Supply in Neoplastic Organs**

As a tumor grows in any organ, one regularly finds an altered vasculature in the adjacent supporting tissue and within the substance of the tumor. There is considerable confusion about the blood supply of tumors from the clinical point of view. Part of this uncertainty derives from futile efforts to generalize about all types of malignant tumors. But even a single specimen may provide two very different impressions about blood supply, depending on the conditions of examination. When a tumor is accidently cut through by the surgeon, he may encounter substantial bleeding and considerable difficulty in controlling the bleeding. This occurs because the vascular channels of the tumor are extremely thin walled and distended. The same tumor, examined by the pathologist after resection, may appear to be provided with a very meager blood supply since at this stage the vascular channels are collapsed, being compressed by tumor tissue.

There is an impressive body of evidence, based on both physiologic and anatomic observations, to support the view that large tumor masses actually have a poor blood supply. Gullino’s studies on the rate of blood flow through transplantable tumors demonstrate that when an isolated organ, such as the kidney, is progressively replaced by tumor, the rate of blood flow through it falls to very low levels. Clinical observations by Kolstad (25) and by Rubinstein (42) indicate that in invasive carcinoma of the uterine cervix, and even in carcinoma in situ, the intercapillary distance in the tumor area is greater than that seen in the normal cervix or in inflammation of the cervix. Metabolites must pass through greater distances than in normal tissue for exchange with slowly moving blood in the vascular system. Using autoradiography, Tannock (46) has studied the proliferation of tumor cells in association with capillaries. His model system consisted of a transplantable mouse mammary tumor in which viable tissue was arranged cylindrically around straight tumor blood vessels. Tumor cells in close proximity to the vascular channels had a relatively high thymidine-labeling index. The index fell progressively as cells in concentric peripheral zones were studied. Peripheral to the viable cuff of contiguous cells, the tumor was necrotic. However, the work of Rowe-Jones (41), in which Walker tumor was used, indicates that, even in areas of extensive tumor necrosis, scattered cells are viable as reflected by tritiated thymidine autoradiography.

The vascular status at the outer margin of a tumor differs from that of the bulk of the tumor mass. Goldacre and Sylvén (15) found that a few minutes after intravenous injection of a harmless dye, lissamine green, into mice bearing a variety of transplantable tumors, a thin margin of the tumor was stained, but the remainder was free of dye. This observation has been confirmed by other investigators (40, 41). In addition, Urbach (49) has pointed out that, in the periphery of tumors, there are many arteriovenous shunts denying oxygenated blood to the substance of the tumor.

A general picture emerges for large, solid, transplantable, epithelial tumors. These are composed of two zones with very different relationship to the blood vascular system. The peripheral margin of the tumor, the site of continuous rapid reconstruction and growth, appears to have a relatively rich blood supply. The bulk of the tumor has a poor blood supply, a slow rate of blood flow, and wide intercapillary spaces. From the point of view of chemotherapy, this situation restricts the effective penetration of chemical agents into the tumor mass.

Several model systems have been used to study the vascular alterations accompanying the formation of new tumors, either of spontaneous origin or following inoculation of transplanted fragments. In the case of spontaneous tumors, the studies of Kolstad (25) on carcinoma in situ of the uterine cervix are especially impressive. He has observed that the capillary bed of the cervix which involves two vascular arrangements, a “mosaic” pattern and a “punctuation” pattern, are each characterized by a widening of intercapillary spaces even in the presence of preinvasive carcinoma. His illustrations recall the earlier work of Lucké and Schlumberger (34) on epitheliomas of the mouth and lip of catfish. Here, even in the presence of very early tumors, marked abnormality of the underlying capillary bed is a consistent finding.

Various kinds of transparent chambers have been used to observe the early events following inoculation of transplantable tumors. The simplest of these is the naturally occurring anterior chamber of the eye. Using the guinea pig eye, Greene (19) noted that some highly malignant tumors required inoculation in combination with embryonic lung for vascularization and growth of the tumor to be attained. Schlumberger and Lucké (43) observed, in frog anterior chamber transplants of the frog renal carcinoma, that the vascularization, architecture, and growth of the transplants were influenced by the temperature at which the frogs were maintained. This point is important since it indicates that the vascularization of experimental tumors can be manipulated. Artificial transparent chambers have been employed with great effectiveness to study the vascularization of transplantable tumors (1, 2, 24). These have included as sites for chamber construction the rabbit ear, the mouse skin, and the hamster cheek pouch. A number of investigators have found that fragments of tumor evoke a more rapid, extensive, and persistent vascular proliferative response than do control normal adult tissues. The pattern of vascular arrangement in the new vessels is often relatively characteristic for the particular tumor. For example, Goodall et al. (17) found that characteristic vascular patterns were produced by hamster melanoma, hemangioepitelicytoma, and mammary adenocarcinoma studied in the hamster cheek pouch chamber.

Various investigators have suggested that tumors release chemical substances to stimulate vasoproliferative responses. The problem has been explored incompletely in the past few years. Greenblatt and Shubik (18) found that the Fortner melanoma in a hamster cheek pouch chamber induced a vasoproliferative response across a filter membrane. The specificity of the response cannot be evaluated since the control tissue was inadequate, consisting either of homologous connective tissue or of the filter membrane alone without tissue. Ehrmann and Knoth (8) used a similar filter membrane model to study the vasoproliferative response to chorio-carcinoma. This tumor evoked an intense proliferation of vessels while the control tissue, normal endometrium, had no such effect. Fragments of immature normal placenta might have been more appropriate as a control. Remaining unre-
solved by these two studies are at least two questions. Was direct cell contact completely prevented by the membrane? Or did cytoplasmic processes extend through the pores of the filter, providing for direct contact between tumor cells and normal cells? Gitterman and Luell (14) have described their transfilter induction of vascular proliferation on the choroi-
adaltic membranes of embryonated eggs. They found that chick embryonic tissues, as well as several transplantable tumors, were equally competent promoters of vascularization on the choroi
daltic.

From the point of view of chemotherapeutic studies aimed at the vascular characteristics of tumors, we should consider going in opposite directions at the same time. We should have as one goal the opening and extension of the vascular bed deep in a tumor so that cytotoxic drugs might be more effective by reaching more tumor cells in higher concentration. At the same time we must study the means by which the vasoproliferative response at the margin of a large tumor, or in association with a minute tumor, can be altered and inhibited. Here the oncologist may profit from the research of the ophthalmologist. The inhibition of vasoproliferation has been of concern to the ophthalmologist for a long time in his goal of preventing corneal vascularization following injury to the eye (10). The same agents that influence corneal vascularization when administered topically can probably be easily applied to a transfilter system in which tumor angiogenesis is seen.

The present level of knowledge concerning the vascular responses of the host tissue required for the propagation of tumors can best be considered as being at an early stage of development. Vascular responses are not chaotic, but express a high degree of organization within a tumor mass as well as at its growing periphery. Their manipulation with drugs in combination with cytotoxic chemicals may be expected to provide more effective therapy for some forms of cancer than are now available.

The Role of Connective Tissue: The Interstitium

The tumor parenchyma and its vascular bed are separated, yet connected, by the interstitial compartment. Although this intervening connective tissue must play a key role in the propagation of tumors, the relationship of stroma and cancer cells has been studied by only a very small minority of cancer investigators, and it has been almost totally ignored by students of cancer chemotherapy (50).

Connective tissue is composed of three elements: cells, extracellular fibers, and a complex extracellular matrix which in its totality is called ground substance. The cells are of several types, but fibroblasts and histiocytes predominate. The fibrous element consists primarily of coarse filaments of collagen, finer collagen fibers called reticulum, and, depending on the tissue, elastic fibers. The heterogeneous ground substance is made up of a colloid-rich phase in equilibrium with a water-rich phase (16). The colloid-rich phase is composed of macromolecules, including hyaluronic acid, other mucopolysaccharides, glycoproteins, soluble forms of collagen, and a variety of other proteins. The boundary between the interstitium and the vascular endothelium is defined by a thin perivascular basement membrane. A thin membrane frequently is seen also as the boundary between the interstitial tissue and the tumor parenchyma.

The interstitial compartment has all these cellular and extracellular elements in very different proportions and arrangements in different tumors, as illustrated in Figs. 1—4. Consideration of the microscopic anatomy of any of these tumors suggests some architectural requirements essential to the proliferation of tumor cells. As tumor cells replicate, as the mass of neoplastic protoplasm increases, the nutritional requirements of the cancerous parenchyma increase. We know from the work of Gullino cited earlier that the size of the interstitial compartment keeps pace with the size of the parenchymal component. The spatial arrangement of parenchyma and stroma, the orderly separation of tumor cells from one another, either in groups or singly, is also maintained.

The interstitium is an appropriate target for chemotherapy since it is the matrix through which metabolic exchange takes place and is in itself a proliferating supporting tissue for the tumor parenchyma. Thus, chemotherapy might be directed, on the one hand, toward affecting the permeability of the interstitium and, on the other hand, toward affecting its rate of growth. Preliminary trials should take diametrically opposite directions: an attempt to induce increased permeability so that cytotoxic chemicals would reach tumor cells in more effective concentrations and an attempt to induce decreased permeability leading to death of tumor cells through nutritional deprivation. Furthermore, since the ratio of the interstitium and parenchyma are constant, thus apparently interdependent, chemotherapeutic prevention of the growth of the interstitial compartment may stop or at least retard tumor cell replication. Such selective effects may not really be as farfetched as they appear at first glance. Terao and Miyaki (47) have found that, in tissue cultures of chick embryo livers, some cytotoxins acted on mesenchymal cells more effectively than on parenchymal cells. In an in vivo setting, since the matrix of the interstitium is proximal to the tumor parenchyma, higher concentrations of chemical agents would be obtained in the interstitial zones than in the parenchymal compartments.

We noted that the proliferation of tumor cells is accompanied not only by the continued growth of the interstitium but by a continuing rearrangement in the groupings of tumor cells. As tumor cells proliferate, the individual aggregates of parenchyma do not become progressively larger; instead they increase in number (aggregate replication). Not only single tumor cells but also small groups migrate from foci of dense tumor cell population to invade surrounding uninvolved tissue. The role of cells of the interstitium in either of these events, aggregate replication or invasive migration, is not really known. However, the microscopic anatomy of some carcinomas suggests that both fibers and cells in the connective tissue matrix may be important in the propagation of cancer and also responsive to chemotherapy.

The relationship of fibrous collagen to the movement of tumor cells may be important. The amount and arrangement of fibrous collagen may either provide surfaces and routes for tumor cell attachment and centrifugal migration or, on the
other hand, barriers to tumor cell movement and diffusion of essential metabolites. In 1959 we reported (31) that, in sponge matrix cultures, infiltration by tumor cells was found where the alignment of fibrillar connective tissue was at right angles to the margin of the growing tumor cells. Where fibrillar connective tissue was parallel to the surface of the growing mass of tumor, invasion was slight. Other investigators have reported similar findings (4). A number of questions need to be answered. In a tumor with an interstitium of abundant ground substance and few collagen fibers, is the relative absence of collagen surfaces a “barrier” to the invasive migration of a tumor? Do the cells of the interstitium play a direct role in the propagation of tumors? In aggregate replication, may fibroblasts penetrate potential planes of cleavage in large aggregates, thereby participating in the replication of the nests of tumor cells? While we would like to have these questions answered through in vivo studies, at the moment the simpler models using tissue culture are more practical. The author has recently reviewed data from the field of tissue culture that relates to these subjects (27). Eagle has also discussed recently the interaction of mixed populations of cells on two-dimensional surfaces (7).

The orientation of fibroblasts has been studied in two-dimensional tissue culture by Elsdale (9) and by Bast and Mills (5). Foley et al. (12) have observed that the colonial architecture of HeLa cells when mixed with fibroblasts varies, depending upon the source of the connective tissue. Fibroblasts obtained from adult malignancies produced an increased percentage of compact HeLa colonies whereas fibroblasts from embryonic tissues favored diffuse HeLa colonies. These differences could not be correlated with either collagen or mucopolysaccharide production by the fibroblasts. Redier and Lustig (39), using an organ culture system, observed that the peritumoral stroma of carcinomas of the human skin, when combined with the epidermis of the chick, exhibited a growth-promoting effect on the epidermis. Normal and inflammatory dermis of human origin did not have this effect. In my view the most relevant tissue culture models for studying the interaction of the cells of the interstitium and the parenchyma are those that most closely approximate the in vivo situation, those that take into account the fact that the margin of a tumor is in reality the surface of an expanding sphere and not the edge where two sheets of cells make linear contact. Furthermore, adequate tissue culture models should provide three components analogous to the vascular, interstitial, and parenchymal compartments found in the intact animal. There are at least four distinct model systems that meet these requirements. The first is organ culture combinations of mesoderm and epithelium used by McLoughlin (36). The second is the transfitter organ culture system of Grobstein (20) using explants of epithelial rudiments and of mesenchyme. Third is the reaggregation system of Moscona (37) using a gyratory shaker to bring together dissociated cells. The last is the method that I have introduced using a sponge matrix to support three-dimensional growth of interacting connective tissue and carcinoma (32).

Unfortunately from the point of view of oncology, the first three models have been used extensively only in the study of the epithelial-mesenchymal interactions of normal morphogenesis. The filter membrane model is most intriguing. If carcinoma were substituted for an epithelial anlage, the plane of the membrane would define precisely the surface of the expanding sphere of carcinoma in near contact with the stroma. Punctate defects produced in the membrane could bring the two components into direct contact at selected sites. In his studies on embryonic tissue, Grobstein has developed the concept of a reciprocal interaction between stroma and parenchyma in the evolving histologic architecture of various epithelial rudiments. In his view, collagen, perhaps in one of its smaller molecular species, plays an organizing role for epithelium, determining the configuration of epithelial conglomerates. This may be accomplished by means of the mesenchymal contribution to the formation of the basement membranes that ultimately separate mesenchyme from parenchyma. We may cite studies attesting to the importance of the stroma in normal organogenesis of thyroid (23), nervous system (48), pancreas (11), and tooth buds (45). The same questions are of equal interest in tumor-stromal interactions.

The sponge matrix system has been employed in the study of clinical tumors in vitro and for the study of interactions between stroma and parenchyma using embryonic tissues and established cell lines (28). In the latter connection we have recently observed that cultures of a fibroblastic line, 3T6, do not form histotypic collagen fibers when fed on routine tissue culture media. They do form a dense meshwork of fibrous collagen (reticulum) when the medium is supplemented with ascorbic acid for 8 or more days (Figs. 5, 6). This observation suggests that much of the tissue culture data on the interaction of fibroblasts with one another or with tumor cells apply to the scorbutic state. We are now combining in matrix culture carcinoma cells and 3T6 fibroblasts, feeding some cultures on control (i.e., deficient) medium and others on medium containing a supplement of vitamin C.

The influence of scorbutic stroma on the propagation of tumors can be studied in vivo using transplantable tumors in the normal and the scorbutic guinea pig. Since there are profound changes in both ground substance and collagen homeostasis in scorbutus (16), this situation could very well advance our understanding of the interaction between stroma and parenchyma. So far as I can determine, tumor-host interaction has not been studied in this experimental setting.

The Packaging of Neoplastic Protoplasm

The tumor cells in carcinomas commonly appear in distinct packages, generally referred to as nests or aggregates, which sometimes are relatively uniform in size and architecture throughout all the tumor masses of any one patient. A basement membrane may be seen as a tight wrapping around each nest. The origin of this membrane is not completely settled. Its function in the propagation of tumors is even more obscure.

Some studies of Pierce (38) demonstrate convincingly that the basement membranes of several types of tumors may be derived exclusively from the clusters of tumor epithelial cells themselves. On the other hand, Grobstein (20) and Slavkin and Bavetta (45) support the view that basement membranes in their systems are an expression of the interaction of both
epithelium and mesenchyme. These conflicting views may really not be contradictory since the conclusions have been reached through different tissue systems under different conditions of experimentation.

The function of basement membranes in the growth of tumors appears to warrant intensive investigation for two kinds of reasons. The permeability of the basement membrane is one of the determinants of the metabolic exchange of the tumor with the stroma. Secondly, basement membranes appear to be important in the configuration attained by groups of tumor cells.

Embryonic glandular tissue also occurs as regularly structured, functional groups of epithelial cells enveloped by a basement membrane. Collagen, either in the substance or in the region of the basement membrane, is a significant factor in the morphogenesis of embryonic salivary epithelium in vitro. Using the transfiler system, Grobstein and Cohen (21) found that collagenase prevents the normal segmentation of the salivary epithelial rudiments into many adenomeres. Basement membranes are found consistently around groups of tumor cells in some carcinomas and are absent in others (Figs. 1—4). When basement membranes occur around organoid groups of cancer cells, the assumption is sometimes made, by analogy with embryonic tissue, that the membrane is an essential feature of the constructed configuration. The interrelationship of basement membranes, polarization of carcinoma cells in individual nests, and replication of tumor cells remains to be determined.

Many carcinomas are composed of cell aggregates of relatively uniform size and architecture. Also, growth in cell population is accompanied by an increasing number of aggregates. These two observations lend support to the idea of an internal regulation of aggregate replication (27). Another quality of tumor cell aggregates reflecting internal regulation is the orientation of the cells seen within individual aggregates. In the matter of regulation within communities of cells, there are a number of exciting approaches now under exploration. The possible exchange of RNA between cells (35), the ionic communication bridges joining cells (33), the direct contact interaction essential for contact inhibition of fibroblasts (44), and the evidence for metabolic cooperation between genetically different cells (13) may all be relevant to the social interaction among epithelial cells and the regulation of aggregate replication.

Aggregate replication and the configuration of cells within aggregates are both of potential chemotherapeutic interest. If aggregate replication could be inhibited with chemical agents, obviously the replication of tumor cells would also be decreased. Manipulating the spatial relationships of the cells making up the aggregate may also result in decreased proliferation. Progress in our studies of aggregates has been frustrated largely because we have not had an adequate model system for manipulating either replication or the configuration of cells within aggregates.

This impasse may be over. We have recently been working with an established line of dog kidney cells (MDCK) that lends itself readily to studies on epithelial cell polarization and aggregation. The cell line derived from normal dog kidney more than 10 years ago is aneuploid, and in matrix culture it now has the appearance of an organoid papillary adenocarcinoma (29, 30). Cultured on glass, in suspension, or in matrix, groups of cells engage in secretory activity, forming many cysts lined by a polarized epithelium. On glass, or in suspension, the polarization of the cells is expressed as a covering of microvilli on the outer surface of the cyst wall with nuclei oriented toward the cyst contents. No basement membranes are seen. On the other hand, in a matrix of collagen-coated cellulose sponge, or in a matrix of embryonic connective tissue, the polarization is reversed, i.e., microvilli line the lumen of the cysts, and nuclei are arranged toward the outer surface of the cysts. Furthermore, in the presence of a living stroma, the cysts are enveloped by a periodic acid-Schiff positive basement membrane (Figs. 7, 8).

Since MDCK can be cultured easily as organized aggregates of cells in a simple suspension system, we are attempting to follow concurrently two parameters of this growing population, the proliferation of cells and the replication of aggregates. We plan to vary the composition of the medium in an effort to identify the essential requirements for reversal of the polarization of the epithelial walls of the cysts. If such reversal can be obtained, we will determine whether either configuration of the cysts is accompanied by a reduced rate of cell replication.

We are also studying in matrix culture the interaction of MDCK with 3T6, the mouse fibroblastic line producing fibrous collagen (mentioned earlier), in order to simulate in three dimensions the interstitial and parenchymal compartments of cancer as seen in the intact host.

Discussion

Since mitosis is the most obvious event in the growth of tumors, the earliest efforts at cancer chemotherapy concentrated on the idea of mitotic poisons. The subsequent development of knowledge about the sequence of synthetic events that take place between consecutive mitoses has broadened our approach to the inhibition of the cell cycle. Cancer chemotherapy is clearly more effective today than several decades ago. It is time for us to recognize fully that although mitosis and replication of tumor cells are the essential events in the growth of tumors, the propagation of tumors requires the programmed interaction of cells at many levels.

A chemotherapy based upon indirect intervention in tumor cell replication through the enormously complex events of tumor propagation may at first glance seem unapproachable. Actually the many phenomena involved, including alterations in vascular architecture, endothelium, connective tissue, and basement membranes, as well as the packaging of tumor cells, offer a wide range of possibilities for developing new modalities of therapy. A variety of chemicals are available to serve as preliminary tools with which to expand our knowledge. In the case of the role of stroma in tumor growth, beta-aminopropionitrile, penicillamine, the antagonistic effects of cortisone and vitamin A, and the use of ascorbic acid deficiency might each serve as means of changing the interactions between the tumor and the interstitial compartments.
I know of one example of a compound developed for chemotherapeutic evaluation, tenuazonic acid (3, 26), that affects the parenchymal organization of a transplantable human adenocarcinoma of the colon. I suspect that during the past years of massive chemotherapy screening we have at times had in our hands compounds that alter the architecture of tumors and, therefore, potentially influence the propagation of tumors. The old programs for observing drug effects were based largely on increased survival time or reduced rate of tumor growth. Unless accompanied by histologic examination of the tumors receiving the chemical agents, such protocols would inevitably miss interesting compounds. Perhaps this consideration of the propagation of tumors will contribute to the design of more significant protocols in future drug evaluation.

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