The Clonal Evolution of Tumor Cell Populations

Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression.

Peter C. Nowell

Whether a tumor develops from one cell or many, and how changes in the biological characteristics of a neoplastic population occur over time, are related questions of theoretical and practical interest. That neoplasms frequently develop as a clone from a single cell of origin is a concept gaining increased acceptance, and various investigators, beginning with chromosome studies on transplanted tumors in the 1950's, have developed hypotheses of tumor "stemlines" that describe neoplastic progression in terms of sequential selection of mutant subpopulations (*1*) derived from a common progenitor (*2*).

This thesis is still being elaborated, but, in general, it has been supported for most neoplasms by evidence obtained over the last two decades through the following three approaches. (i) Cytogenetic studies have demonstrated that in many primary tumors all cells show the same abnormal karyotype, suggesting a unicellular origin; and even when several chromosome patterns are present within a single tumor, marker chromosomes in each cell often indicate that the different subpopulations derive from a common stemline (*3*). (ii) Studies of the isoenzymes of glucose-6-phosphate dehydrogenase in a variety of neoplasms in heterozygous women have indicated that typically the same member of the X chromosome pair is functional in all cells of a given tumor, indicating descent from a single precursor (*4*). (iii) The immunoglobulin produced by plasma cell tumors (and perhaps other lymphoproliferative neoplasms as well) has in almost every case the homogeneity characteristic of a single clone (*4, 5*).

The author is professor of pathology, School of Medicine, University of Pennsylvania, Philadelphia 19174.

Despite this wide recognition that most neoplasms have a unicellular origin and clonal growth pattern, relatively little emphasis has been placed on the developmental evolution of tumor cell populations, and the apparent genetic instability underlying the sequential acquisition of biological characteristics that we associate with tumor progression. This article suggests a model for the evolution of tumor cell populations in terms of stepwise genetic variation, and considers some of the evidence that this model is a valid one for most mammalian neoplasms. Some of the theoretical and practical implications of this concept of tumor development are briefly considered. It is recognized that in many respects this model derives from formulations previously proposed by others (*2, 6*), and also that characteristics of certain tumors can be cited which do not appear to fit the model. Given the heterogeneous nature of what we call "neoplasia" and our limited present understanding of this general process, some exceptions to any unitary approach must be expected.

An Hypothesis of Tumor Evolution

The proposed model is summarized in Fig. 1. Tumor initiation occurs at the left of the figure, by an induced change in a single previously normal cell (N) which makes it "neoplastic" and provides it with a selective growth advantage over adjacent normal cells. Neoplastic proliferation then proceeds, either immediately or after a latent period. From time to time, as a result of genetic instability in the expanding tumor population, mutant cells are produced [in Fig. 1, genetic variants (T_1 to T_6) are indicated by differences in chromosome number]. Nearly all of these variants are eliminated, because of metabolic disadvantage or immunologic destruction (for example, T_3), but occasionally one has an additional selective advantage with respect to the original tumor cells as well as normal cells, and this mutant becomes the precursor of a new predominant subpopulation.

Over time, there is sequential selection by an evolutionary process of sublines which are increasingly abnormal, both genetically and biologically. Because this sequence is not completely random, certain similarities are acquired by different tumors as they progress; but divergence also occurs as local conditions in each neoplasm differently effect the emergence of variant sublines. Ultimately, the fully developed malignancy as it appears clinically has a unique, aneuploid karyotype associated with aberrant metabolic behavior and specific antigenic properties, and it also has the capability of continued variation as long as the tumor persists. The relative positions in this model of human solid tumors, benign and malignant, as well as certain leukemias, are indicated in Fig. 1, along with several biological characteristics associated with various stages of neoplastic development.

In the following sections, particular aspects of the model are considered in more detail, with major emphasis on evidence derived from cytogenetic studies of tumor cell populations.

Initiation of Neoplasia

The implication in Fig. 1 that tumors originate from a single cell is not intended to deny that carcinogens can simultaneously affect many cells in a tissue. It does suggest, however, that even though a large number of cells may be affected by a carcinogen, the macroscopic tumor that ultimately develops usually represents the progeny of a single cell, or at most, a very few cells. Presumably, other neoplastic or preneoplastic cells in the exposed tissue never successfully proliferate or they are destroyed before progressing to a fully developed tumor (*7*).

For the vast majority of neoplasms, both the cytogenetic evidence and the biochemical evidence cited above (*3–5*) supports the validity of this unicellular concept. The few exceptions are primarily tumors of viral etiology (for example, condylomata acuminata) where there has possibly been infection of adjacent cells, or they are neoplasms with a strong he-

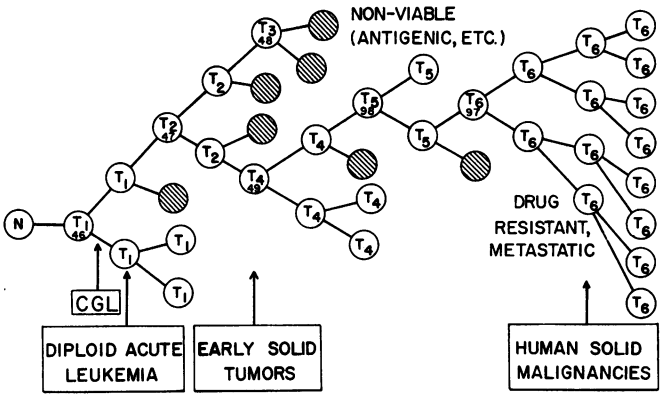

Fig. 1. Model of clonal evolution in neoplasia. Carcinogen-induced change in progenitor normal cell (N) produces a diploid tumor cell (T_1, 46 chromosomes) with growth advantage permitting clonal expansion to begin. Genetic instability of T_1 cells leads to production of variants (illustrated by changes in chromosome number, T_2 to T_6). Most variants die, due to metabolic or immunologic disadvantage (hatched circles); occasionally one has an additional selective advantage (for example, T_2, 47 chromosomes), and its progeny become the predominant subpopulation until an even more favorable variant appears (for example, T_4). The stepwise sequence in each tumor differs (being partially determined by environmental pressures on selection), and results in a different, aneuploid karyotype in each fully developed malignancy (T_6). Biological characteristics of tumor progression (for example, morphological and metabolic loss of differentiation, invasion and metastasis, resistance to therapy) parallel the stages of genetic evolution. Human tumors with minimal chromosome change (diploid acute leukemia, chronic granulocytic leukemia) are considered to be early in clonal evolution; human solid cancers, typically highly aneuploid, are viewed as late in the developmental process.

reditary component (such as neurofibromatosis) where a familial gene defect presumably involves every cell and greatly increases its susceptibility to neoplastic change (*4*, *8*).

The nature of the alteration from a normal cell to the first neoplastic cell, as indicated in Fig. 1, must still be defined arbitrarily. For the purposes of this model, "neoplasia" is considered as some degree of escape from normal growth control (whether these controls are intracellular, local "chalones," or hormonal) that provides the cell with a selective growth advantage over the normal cell from which it was derived. In some instances, the process may include a latent period, until the altered cell is triggered from a resting state (G_0) into active proliferation (G_1); in other circumstances, the initial event may involve a stem cell that is already dividing, and simply increases the proportion of progeny remaining in the mitotic cycle instead of proceeding to terminal differentiation. The fundamental nature of this initial step, and degree to which it is specific for each neoplasm, remains a basic problem in cancer research.

The biological consequences of the primary alteration may be illustrated with various examples—transformed cells in tissue culture, benign and "precancerous" solid tumors, certain leukemias—no one of which is completely satisfactory from a theoretical standpoint since additional alterations may also have occurred. By definition, the primary event results in proliferation which is unrestrained to some degree, and this may be accompanied, particularly in tissue culture systems, by reasonably consistent morphological and biochemical alterations in the early neoplastic cells. Many studies in vitro point to changes in the external cell membrane as being of critical importance, causing deficiencies in normal growth control mechanisms mediated through cell-to-cell contact (*9*).

The specific gene products that produce these biological consequences remain uncertain. Equally obscure is the specific genetic event which produces them. Absence of new gene products in tumor cells and the reversibility of transformation in certain culture systems has led some investigators to suggest that initiation usually involves altered gene expression rather than structural mutation (*10*). It is certainly clear that visible alterations in chromosome structure are not essential to the initial change. Transformation can take place in tissue culture and certain tumors can develop in vivo without detectable cytogenetic abnormalities (*3*), and this has been indicated in Fig. 1 by showing the initial neoplastic population (T_1) with a normal complement of 46 chromosomes.

There may, however, be occasional instances in which the first neoplastic event is visible at the chromosome level, and the best candidates would appear to be those few tumor varieties in which the same cytogenetic abnormality is present in the neoplastic cells in nearly every case. These include the Philadelphia chromosome in chronic granulocytic leukemia (CGL), monosomy for chromosome 22 in meningeal tumors, an aberrant chromosome 14 in certain lymphoproliferative disorders, and other possibilities currently being revealed by the new chromosome banding techniques (*3*, *11*). When a cytogenetic abnormality is as consistent as the Ph chromosome in CGL (85 to 90 percent of typical cases are Ph positive), it is not unreasonable to speculate that this specific translocation alters the genetic control of proliferation in the affected cell and thus initiates the conversion of a normal marrow stem cell to the progenitor cell of a leukemic clone. For most tumors, however, it is generally agreed that this first neoplastic step cannot be visualized by available methods, and that structural changes in chromosomes need not be involved.

The specific agents that initiate neoplasia also remain under study. It appears increasingly likely that ionizing radiation, carcinogenic chemicals, and oncogenic viruses can interact with the host cell genome in a variety of ways to bring about the required alterations in gene function (*12*). Chromosomal breakage and rearrangement, point mutations, and insertion of viral components into the host genome have all been demonstrated. In a few instances, viral and chemical carcinogenesis is associated with specific chromosomes of the host. Incorporation of the simian virus SV40, for instance, into human cells characteristically involves chromosome 7 (*13*), and apparent cytogenetic specificity has also been demonstrated for certain chemically induced rat sarcomas (*14*). In a number of other experimental systems, however, no such correlation has been demonstrable between karyotypic changes and particular inducing agents (*15*).

For some tumors, inherited gene defects may potentiate the action of exogenous carcinogens, including viruses, and increase the probability of neoplastic alteration in the primary cell. A few such genetic errors have been elucidated, such as defective DNA repair in the rare disorder xeroderma pigmentosum, leading to multiple skin cancers (*16*); in most instances, however, the molecular mechanism by which inherited gene defects increase the probability of neoplasia has not been defined (*17*).

Major questions remain concerning the nature and mediation of the initial neoplastic event. The significance of both exogenous carcinogens and inherited gene defects in tumor initiation are indicated in Table 1, where I have listed a number of the factors discussed in the text, which influence one or more stages

in the evolution of tumor cell populations. Those factors which act *after* tumor initiation, by inducing genetic instability in the neoplastic cells or by influencing the emergence of variant subpopulations once they are produced, are considered below.

Table 1. Different influences on tumor cell evolution.

Factors influencing different stages	Stages of tumor development		
	Initiation of neoplasia	Genetic instability	Emergence of variant subpopulations
	Carcinogens (12)		
Radiation	+	+	
Chemicals	+		
Viruses	+	+	
	Gene defects		
Inherited (*17, 35*)			
Increased mutability (chromosome breakage, and other)	+	+	
Immunodeficiency			+
Undefined	+		
Acquired (*36*)			
Increased mutability (nondisjunction, and other)		+	
	Tumor environment (31, 40)		
Nutrition		+	+
Infection			+
Immune status of patient (*41*)			+
Therapy		+	+

*A plus sign denotes those stages of tumor evolution influenced by the factor indicated. See the text for details.

Clonal Evolution of Tumor Cell Populations

The biological characteristics of tumor progression have been extensively described. Of greatest significance is the acquisition by the neoplastic cells of the capacity to invade locally and to metastasize, still the fundamental definition of malignancy. In addition, over time, there is a tendency for neoplastic populations to increase their proliferative capacity and to show further evidence of escape from normal growth control mechanisms. One obvious example is the progression of endocrine tumors from dependence on specific hormones to independence from such regulatory influences (*18*).

Concurrently, it is common for tumors as they become more malignant to show morphological and metabolic alterations generally interpreted as loss of differentiation. Organelles and metabolic functions necessary for specialized activities of the cell tend to decrease or disappear, and the neoplastic population increasingly is directed toward maximum efficiency in proliferation and invasive growth. Certain products may be elaborated which appear to aid this process, such as tumor angiogenesis factor (*19*); others, such as fetal antigens and inappropriate hormones (*20*), are less obviously of selective advantage.

The major contention of this article is that the biological events recognized in tumor progression represent (i) the effects of acquired genetic instability in the neoplastic cells, and (ii) the sequential selection of variant subpopulations produced as a result of that genetic instability. A number of studies, both in vivo and in vitro, have indicated that, in contrast to normal cells, neoplastic populations have a higher frequency of mitotic errors and other genetic changes (*21*). The data further suggest that the increased mitotic activity in tumors only partially accounts for this difference, and that, in addition, each cell division carries an increased risk of genetic variation. It also appears, particularly from chromosome studies of human solid tumors, that this genetic instability may become more pronounced as the neoplasm evolves. In advanced malignancies, a wide range of mitotic variants are commonly observed with each cell generation (*3, 22*), as compared to relatively few in early, benign lesions.

The specific types of genetic alterations occurring in evolving tumors may range from point mutations to major chromosomal aberrations, and changes in chromosome number are used in Fig. 1 only for illustrative purposes. As noted above, however, it has generally been difficult to demonstrate new gene products in tumor cells, and neoplastic traits appear usually to reflect alterations in the expression of preexisting genes rather than structural gene mutations (*10*). These changes in genetic expression could result from mutations in regulatory genes, from dosage and position effects following chromosomal rearrangements, or from position effects produced by integration into host chromosomes of viral genome. There is little evidence to indicate the relative importance of these different mechanisms, but certainly chromosomal nondisjunction and translocation play a significant role. This has been well demonstrated in CGL, where progression of the disease to its terminal accelerated phase is frequently associated with emergence of a new predominant subpopulation having one or more cytogenetic changes in addition to the Ph chromosome (*11, 23*). Similar relationships between more malignant characteristics and additional karyotype alterations have also been observed in several other neoplasms, both human and experimental, where it has been possible to obtain sequential biopsies. Perhaps most striking is the work of Mitelman (*24*) with rat sarcomas produced by the Rous virus, in which a stepwise increase in chromosome number was typically associated with progressive loss of differentiation in the sarcoma cells, as determined both histologically and by decreased collagen production.

In most studies of tumor chromosomes, only a single examination has been done on each neoplasm. Even these limited "snapshots" of tumor evolution, however, have generally revealed good correlation between increasing aneuploidy and greater "malignancy," as judged either morphologically (*25*), or by other characteristics such as loss of hormonal dependence (*26*), increased growth rate (*15*), and capacity to invade and metastasize (*3, 27*).

This correlation between observable genetic change and tumor progression does not, of course, prove causality, and some workers believe that at least some aspects of the evolutionary process, such as the appearance of "new" surface antigens and of drug-resistant subpopulations, may represent epigenetic, rather than genetic, phenomena (*10, 28*). One argument advanced in support of this view is that the frequency of appearance of such variants exceeds known rates of somatic mutation in normal cells, apparently ignoring the increased genetic liability recognized in neoplastic populations.

Specific Cytogenetic Changes and Tumor Evolution

The genetic-versus-epigenetic debate (*29*) will not be resolved until we know more about both processes in mamma-

lian cells, and the two approaches to understanding neoplasia are not necessarily mutually exclusive. It would be helpful if we could associate specific chromosomal alterations with particular aspects of tumor progression, but this is possible only to a limited degree. The few very consistent cytogenetic changes thought to be involved in tumor initiation have already been mentioned (*3, 11*). With banding techniques, additional nonrandom aberrations are being recognized in various neoplasms, although their relationship to specific stages of tumor development is not always clear. In CGL, for instance, the additional cytogenetic changes associated with clinical progression include one or more of the following in nearly every case: a second Ph chromosome, trisomy for number 8, or trisomy for the long arm of number 17 (*11*). Interestingly, however, trisomy 8 is also common in other human blood dyscrasias ranging from acute leukemia to relatively benign myeloproliferative disorders (*11*), and so the precise role which an extra chromosome 8 plays in abnormal hemic proliferation is difficult to evaluate.

In a number of the Rous sarcomas showing biological progression, Mitelman (*24*) has demonstrated an associated consistent pattern of karyotypic evolution, first involving addition of a chromosome 7, then a number 13, and then a number 12. In time, more examples may emerge of specific chromosome patterns in evolving tumors, but it is important to recognize that, even with the banding methods, cytogenetics remains a relatively crude means of exploring genetic phenomena. Mapping of the human genome, as well as our understanding of the biochemical basis of many tumor characteristics, is still too incomplete to expect that we shall soon be able to make many precise correlations at the level of the chromosome.

Furthermore, although certain genetic alterations may be consistently beneficial to the evolution of tumor cell populations, the fact that similar malignancies frequently have major differences in their predominant karyotypes suggests that at least in the later stages of tumor development, different genetic changes may be selectively advantageous for different individual tumors in their own particular environment.

For these various reasons, it is understandable that correlations between specific karyotypic aberrations and tumor progression remain few, but there are data which indicate the general types of change in chromosome number which are more likely to prove beneficial to a developing neoplasm. As is indicated in Fig. 1, an alteration frequently observed in tumor cell populations followed sequentially is the gain of a single chromosome, and this has been described in the Rous sarcomas and in a number of other neoplasms (*11, 15, 24*). Subsequently, through doubling of the chromosome number, a variant in the tetraploid range may emerge, and these are common in fully developed human solid malignancies (*3, 30*). Ohno (*31*) has discussed the theoretical advantage to the cell of gene duplication produced by the trisomic or tetraploid state. In some experimental systems, however, karyotypic progression may first involve a decrease in chromosome number followed by polyploidy, and this has also been observed occasionally in human neoplasms (*3, 23*).

Several workers (*32*) have attempted to resolve these apparent contradictions by suggesting that it is not simply the gain or loss of specific chromosomes or gene loci which are critical to the establishment and progression of the neoplastic state, but rather, a matter of imbalance among several genes, located on different chromosomes, that control either expression or suppression of malignancy. This concept, which has chiefly been explored through in vitro cell hybridization techniques, remains unproved. In several instances, particular chromosomes or chromosome segments have apparently been implicated as critical either to the maintenance or to the suppression of malignancy in such experimental systems; but other investigators (*33*), using similar methods, have had negative results. This approach may provide important information in the near future, but results to date are not sufficiently consistent to permit firm conclusions.

For the purposes of this discussion, the key point is not the specificity or lack of specificity of the chromosomal rearrangements, but the fact that major genetic errors do occur in tumor cell populations with sufficient frequency to permit sequential selection of mutant subpopulations over time.

Mechanisms for Increased Mutability in Neoplastic Cells

The basis for this acquired genetic instability in most instances is not known, but various hypotheses have been proposed. It is possible that one of the earliest changes in tumor cells involves activation of a gene locus which increases the likelihood of subsequent nondisjunction or other mitotic error (*34*). Such genes are known in *Drosophila* and also have been suggested in certain human families who appear to show increased frequency of Klinefelter's syndrome, Turner's syndrome, and other entities resulting from nondisjunction during meiosis. There are also families with the so-called "chromosome breakage syndromes" (such as Bloom's syndrome, Fanconi's anemia, ataxia telangiectasia, and xeroderma pigmentosum) in which breaks and rearrangements are increased as a result of inherited defects in DNA repair or other abnormalities of chromosomal integrity as yet undefined. Clones of cytogenetically aberrant cells and increased tumor incidence are observed in these individuals, with the inherited gene defect presumably contributing both to the initiation and to the subsequent development of the neoplasm (*35*). The production or activation of a similar genetic locus in an early neoplastic cell of a normal individual could provide the basis for increased mutability in the tumor cell population and subsequent clonal evolution (see Table 1).

It is also possible that the genetic lability of neoplastic cells in some circumstances reflects the continued presence of carcinogen. A long-lived radioisotope, such as radium deposited in bone, could have a continued mutational effect within the tumor, and thus be involved not only in the initial neoplastic event, but also in subsequent progression over many years (*36*). A similar, but less well documented possibility, is that oncogenic virus or viral components, incorporated into neoplastic cells, can produce not only the initial transformation but also subsequent genetic rearrangements within the evolving tumor (*37*).

Finally, it has even been suggested that nutritional changes within a neoplasm might play a role in its genetic instability. Deficiencies of single essential amino acids have been shown to increase the frequency of nondisjunction in cell culture, and with the recognized areas of reduced circulation in certain portions of rapidly growing tumors, such a mechanism might help explain the high levels of mitotic abnormalities observed in the late stages of aggressive malignancies in man and animals (*22, 38*). In general, however, despite these various hypotheses, which are included in Table 1 as possible factors contributing to genetic instability in tumor cells, the acquisition of this important characteristic has not been satisfactorily explained for most neoplasms, and investigation of the underlying mechanisms seems worthy of more vigorous study.

Tumor Environment and the Emergence of Variant Sublines

Such research might also uncover clues to the marked differences in the time course of these events in different tumors. In some instances, the sequence illustrated in Fig. 1 appears to occur in a very compressed time span, so that marked genetic rearrangements and associated biological characteristics of highly malignant cells are present by the time the neoplasm reaches macroscopic size. In most cases, the evolutionary process appears to be slower, perhaps contributing to long periods of latency or limited growth observed with some human tumors. In CGL, for instance, a benign clinical course of several years normally precedes the terminal accelerated phase associated with additional chromosome changes (*23*). Some transplantable experimental tumors and neoplastic cell lines in culture may also show very stable biological and karyological characteristics over a number of years (*3, 39*).

Presumably the observed rate of progression in a neoplastic population depends on the frequency of mutants being produced and on the environmental pressures for positive selection of variant cells. It may be that the controlled conditions of tissue culture or of transplantation in an inbred strain of rodents are insufficient to encourage the frequent emergence of a new predominant subpopulation. With human solid malignancies, however, although evolution may be slow in the early stages, once they reach clinical significance, the environmental influences being generated by the general health and nutrition of the patient, his exposure to infectious agents, reactions of his immune system, and therapeutic perturbations introduced by the physician, may all serve to accelerate the appearance of new sublines within the tumor (*31, 40*). Chemotherapy and radiation therapy may be particularly important in this respect, both through their direct mutagenic action on neoplastic cells and through their immunosuppressive effects. We need additional knowledge of the factors influencing emergence of mutant cell populations once they are produced, as well as of the types and causes of the genetic variants themselves (see Table 1).

Theoretical and Practical Implications

The considerable evidence supporting a unicellular origin for most tumors suggests that the cells of a given neoplasm, derived from a single progenitor, should share certain common characteristics. Perhaps most likely would be a common membrane-related metabolic alteration or antigen, acquired at the time of the initial neoplastic change, and through its exploitation one could hope to eradicate the clone and effect a cure. Only in the relatively few tumors that appear multicentric, reflecting either an inherited gene defect in all of the patient's cells or perhaps infection of adjacent cells by oncogenic virus, might recurrence be likely after elimination of the original clone.

The search for such presumed common alterations in the cells of a single neoplasm, or more importantly, among several similar neoplasms, is made extremely difficult, however, by the many evolutionary steps, indicated in Fig. 1, between the initial change and the fully developed malignancy as one sees it clinically. These alterations are not only multiple, but also, to some degree, random, reflecting the particular environmental pressures that influence the development of each individual tumor. The expression of inappropriate gene products, such as hormones and fetal antigens, as well as possible new gene products, such as "private" antigens and aberrant peptides (*10, 20*), all indicate how disordered genetic function, and perhaps genetic structure, may become in the later stages of human cancer.

It is not surprising, therefore, that consistent alterations from case to case, either antigenic or metabolic, have been difficult to identify in the common human solid malignancies. Perhaps in searching for early specific changes associated with neoplasia, in addition to experimental systems, more attention should be directed toward those human neoplasms which, based on chromosome studies, show the least evidence of genetic alteration. These include approximately half of the human acute leukemias, which have no demonstrable cytogenetic abnormality, as well as the few other tumors, already noted, which have minimal and consistent cytogenetic rearrangements (*3*) (see Fig. 1).

The fact that most human malignancies are aneuploid and individual in their cytogenetic alterations is somewhat discouraging with respect to therapeutic considerations. It helps to explain the failure to discover a metabolic alteration in cancer sufficiently consistent to permit specific chemotherapy and also the variation in response to nonspecific agents. One may ultimately have to consider each advanced malignancy as an individual therapeutic problem after as many cells as possible have been eliminated through the nonspecific modalities of surgery, radiation, and chemotherapy. Then, perhaps, immunotherapy becomes a leading candidate for the easiest means of destroying the remainder of the neoplastic clone. Without discounting the present very important limitations to our knowledge of tumor immunology and the problems of rejection versus enhancement (*41*), one can at least consider theoretically that it is more feasible to produce specific cytotoxic antiserums or lymphocytes against a particular tumor than to design a specific chemotherapeutic agent for each neoplasm.

Even if this approach ultimately proves useful, however, one must still recognize the definite handicap to the therapist which the genetic lability of tumor cell populations continues to impose. With variants being continually produced, and even increasing in frequency with tumor progression, the neoplasm possesses a marked capacity for generating mutant sublines, resistant to whatever therapeutic modality the physician introduces (*31, 40*). The same capacity for variation and selection which permitted the evolution of a malignant population from the original aberrant cell also provides the opportunity for the tumor to adapt successfully to the inimical environment of therapy, to the detriment of the patient.

Finally, one can consider what the model illustrated in Fig. 1 suggests about the potential reversibility of the neoplastic process. If the genetically unstable, highly individual malignancy is difficult to eradicate therapeutically, what is the likelihood of producing a "cure" by providing an environment which forces the tumor cell population to cease unlimited proliferation and move into a state of controlled differentiation? Recently, such circumstances have been demonstrated, both in vivo and in vitro, for a few tumors (for example, neuroblastoma, teratoma) (*42*). In general, this result seems most probable when the karyotype of the tumor is normal or near-normal, and the approach is worthy of further study, particularly for neoplasms such as the diploid acute leukemias illustrated on the left side of Fig. 1. For the highly aneuploid malignancies indicated on the right in Fig. 1, the possibility of generating in vivo the conditions necessary to force differentiation in a neoplastic population selected through many steps for proliferative capacity and lack of response to growth controls seems much less likely. However, even in these tumors with major chromosomal abnormalities, it is probable that the components of the normal genome are still

present, although rearranged, and their potential reversibility to normal growth patterns cannot be categorically excluded.

Continued investigation of this possibility is certainly warranted, as well as the efforts to find therapeutically exploitable consistent alterations in neoplastic cells, both early and late in tumor development. The purpose of this discussion is not to discount these important lines of study, but to suggest that, in addition, greater research effort should be made to understand and control the mechanisms which permit the early benign diploid tumor to evolve into the highly aneuploid malignancy, which is the typical clinical presentation of human cancer.

Summary

It is proposed that most neoplasms arise from a single cell of origin, and tumor progression results from acquired genetic variability within the original clone allowing sequential selection of more aggressive sublines. Tumor cell populations are apparently more genetically unstable than normal cells, perhaps from activation of specific gene loci in the neoplasm, continued presence of carcinogen, or even nutritional deficiencies within the tumor.

The acquired genetic instability and associated selection process, most readily recognized cytogenetically, results in advanced human malignancies being highly individual karyotypically and biologically. Hence, each patient's cancer may require individual specific therapy, and even this may be thwarted by emergence of a genetically variant subline resistant to the treatment. More research should be directed toward understanding and controlling the evolutionary process in tumors before it reaches the late stage usually seen in clinical cancer.

References and Notes

1. "Clone," as used throughout the text, simply implies a population of cells descendant from a single cell of origin. "Mutant" is used quite loosely, and interchangeably with "genetic variant," to describe tumor cell populations displaying heritable altered characteristics, whether resulting from demonstrable gene mutations, chromosomal rearrangements, or apparent alterations in gene regulation.
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