Perspectives in Cancer Research

Many Growth Factors May Not Be Growth Factors

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Abstract

Both organ growth and tumor growth are dependent upon a biased ratio of cell births to cell deaths; this ratio is independent of the frequency of mitosis. Thus, so-called growth factors that affect only the frequency of mitosis are not really growth factors. I shall advance two hypotheses: that the normal adult growth rate of cell births to cell deaths is maintained by the activity of a factor or factors produced by the stem cells; and that the differentiating cells, as well as the stem cells, produce a different factor that limits the frequency of mitosis.

I have the impression that some investigators, who are working on problems concerning the control of the cell cycle and the rate of cell division, believe that they are engaged in cancer research. Although an increased rate of cell division can produce faster tumor growth and provide a greater opportunity for the development of variant cells (1), it seems obvious that the rate of cell division per se does not distinguish neoplastic from normal tissue (2). It is the burden of this article to make the obvious point that both organ and tumor growth are dependent upon an imbalanced ratio of cell births to cell deaths but, further, that this ratio of births to deaths, which I will call the "growth ratio," is essentially independent of the frequency of mitosis. I shall also advance two hypotheses: that the normal adult growth ratio of 1/1 is maintained by the activity of a differentiation-inducing factor or factors, produced by the stem cells, that I will call, for reasons that will become apparent, the "symmetry preventer"; and that the differentiating cells, as well as the stem cells, produce a quite different factor or factors, the "mitosis preventer," that limits the frequency of mitosis.

Mitosis and Tissue Growth

In most tissues of higher animals, there is cell turnover; cells are constantly dying, usually by sloughing or apoptosis (3). In a tissue of constant size such as the epithelium of the skin or the mucosa of the bowel, mitotic activity is almost entirely confined to a layer of stem cells. When these divide, one half must remain as stem cells in the stem cell layer; the other half must begin a process of differentiation and be gradually displaced toward the surface to be eventually sloughed (2). (A stem cell is, for present purposes, defined as any cell which, at division, gives rise to at least one daughter with an undiminished capability of regenerating the tissue.) In other tissues, in which surface attrition does not occur, the situation is not as clear, but the principle must be the same; in those nongrowing tissues in which there is cell turnover, stem cell divisions must result, at least statistically, in one half of the daughter cells becoming new stem cells and the other half beginning, perhaps via secondary mitoses, a program of differentiation, called "terminal differentiation," that ultimately leads to cell death. The tissue will grow like compound interest if this ratio, the growth ratio, is even slightly biased in favor of new stem cells. It seems to follow that the essence of the cancer problem is the disturbance of this growth ratio, not the rate or frequency of cell division. Of course, once the 1/1 ratio is disturbed in favor of stem cells, a high mitotic rate (mitotic events/unit of tissue volume/unit of time) will result in faster tissue growth than will a low mitotic rate. However, there does not seem to be any direct coupling of mitotic rate with the growth ratio; some growing tumors have an essentially normal or even a subnormal mitotic rate as compared with the tissue of origin (4, 5) and some nongrowing tissues, such as the lining of the small bowel, have higher mitotic rates than do most tumors.

Given the above, it follows that many so-called "growth factors," that are identified only by an effect upon the rate of cell division in tissue culture, cannot be essential variables distinguishing between normal and malignant cells; they are not growth factors, but cell division factors. The only factors that could be involved in the essence of tumor physiology are those that can elevate the growth ratio of cell births to cell deaths.

"Constitutive" Natures of Mitosis and of the Lack of Differentiation

Evolutionary considerations can provide some clues concerning the interactions of various factors in the control of growth. For convenience, the discussion is couched in teleological terms. Free-living cells tend to multiply as rapidly as the supply of nutrients will permit, i.e., mitosis is "constitutive." When, during the course of evolution, there was aggregation into a morula or primitive multicellular organism, a need arose to develop a mechanism to prevent this constitutive mitotic activity and thus regulate the size of the aggregate. The mechanism had to be sensitive to the overall size of the cellular population so that mitosis would be permitted when the numbers fell too low, but mitosis would be prevented when the size exceeded the genetically determined norm. This suggests the production of an extracellular preventer of mitosis, the "mitosis preventer," the concentration, and thus effectiveness, of which is proportional to the number of cells in the organism.

With the development of cellular specialization, a need probably arose to develop more refined methods to control population size within each specialized subpopulation, especially those on surfaces that might be subject to extensive attrition. This led to the development of "programmed" cell death; in this scheme, within each specialized lineage, a further differentiation occurred which earmarked, in a nongrowing tissue, one-half of the cellular offspring for death, either by apoptosis or by sloughing. It is not clear whether this earmarking results from asymmetrical mitosis per se, i.e., only one of the daughter cells of each mitotic event differentiating, as was proposed by Rolshoven (6), or by a mechanism, perhaps more common, in which one half of the mitotic events result in both daughter cells differentiating and the other half result in both daughter cells remaining as stem cells. This issue has been extensively
discussed by Leblond (7). In either case, it is clear that there is a mechanism in nongrowing, but renewing tissues, which ensures at least statistical asymmetry among the cellular offspring. Inasmuch as free-living cells tend not to differentiate, a lack of differentiation, i.e., a state of symmetry, should probably be considered the constitutive state which must be overcome in higher organisms.

In tissues, such as the skin, it has been proposed that the signal to undergo terminal differentiation may be a result of crowding in the germinative basement layer which results in some cells being pushed mechanically into a more superficial environment that induces differentiation (7). However, Leblond (7) found that, usually, either both offspring of a dividing cell were pushed superficially to differentiate or both remained in the germinial layer; this suggests to me that the decision to differentiate or not to differentiate is apparently made in the germinial layer.

On the basis of the above considerations, it seems reasonable to postulate that stem cells in higher organisms generate an inducer of differentiation, a preventer of tissue symmetry, that I will call the “symmetry preventer.” This preventer would ensure that, in the presence of a normal adult number of stem cells, any mitoses that occurred would, at least statistically, be asymmetrical in the sense that one-half of the cellular offspring would eventually undergo terminal differentiation and the growth ratio would be at unity. Differentiating cells, on the other hand, would generate only the mitosis preventer. The interplay of these two preventers would determine the speed of growth, if any, of the tissue.

Soto and Sonnenschein have argued persuasively that, inasmuch as the propensity to divide is a constitutive property, a property that must be prevented in multicellular organisms, factors that appear to stimulate cell division in such organisms must, in actuality, work indirectly by counteracting the naturally occurring mitosis preventer. They have presented some evidence that the trophic steroids do, indeed, promote cell division indirectly by blocking the activity of such a preventer. The presence of a preventer was inferred from the fact that trophic steroids failed to stimulate mitosis of sensitive target cells if the latter were growing in charcoal-dextran stripped serum. This argument was expanded in a number of publications (8–10). Although these workers did not distinguish between the mitosis preventer and the symmetry preventer, it is probable, for reasons I will develop shortly, that, in the case of the steroids, only the mitosis preventer is inhibited.

Noble (11) also made an observation that is most easily explained by postulating that estrogen stimulates indirectly by blocking a mitosis preventer. He noted that estrogen-dependent rat tumors would continue to grow in estrogen-deprived animals if the tumors were in the liver; estrogen was superfluous in that location. One could suggest that the liver was supplying the missing estrogenic activity, but this seems unlikely since estrogens are inactivated in the liver. It seems more probable that the postulated preventer was, itself, relatively inactivated in the liver and, therefore, its blockage by estrogen was unnecessary for continued tumor growth.

If either the putative mitosis preventer and/or the symmetry preventer were, indeed, less active in the liver, as Noble’s work suggests, the observation that most human tumors grow faster in the liver might be understood. Some tumors have been shown to grow as much as 5 times faster in the liver than in the lung (12). It also might be relevant that the liver itself has such remarkable powers of regeneration (13). Of course, many other explanations of the good growth of tumors in the liver are possible.

Although the putative symmetry preventer may remain to be isolated (14), its postulation is almost necessitated by considerations of the nature and character of organ and tumor growth, a subject I have recently reviewed (15), but which I will summarize here. Laird (16) showed that the growth of a variety of long-transplanted tumors, if sufficiently extrapolated, followed a Gompertzian curve that approached an asymptotic plateau; essentially similar findings, at least showing a slowing of tumor growth as tumor size increased, have been reported by others (2, 17, 18). This same curve characterizes liver regeneration and the growth of normal organs during ontogeny (16). It is apparent, from these observations and others (15), that the growth of both tumor and normal organ is sensitive to tumor or organ size; presumably, there is an increasing concentration of symmetry preventer that eminates from the organ or tumor itself as the organ or tumor becomes larger.

**Tumor and Organ Dependency**

It is instructive to note the observation of Bruchovsky (19) that testosterone is incapable of stimulating growth in a so-called dependent organ, the prostate, unless that organ is less than normal size (as a result of immaturity, surgery, or previous hormonal deprivation). This observation again confirms the overriding importance of organ size but suggests, additionally, that there is a concentration of symmetry preventer, when full size is attained, that cannot be overcome by excess hormone. I can rationalize this observation by suggesting, in accord with the Soto and Sonnenschein hypothesis, that the physiological function of the steroid may be to permit mitosis, by interfering with the multicellular organism’s mitotic preventers, and that regulation of the growth ratio is dependent not on the hormone but, via the symmetry preventer, only upon organ or tumor size. In the full-sized organ, the ratio remains persistently at unity and no increase in mitotic rate, induced by the hormone, could produce persistent growth. The regression, which is induced in the normal organ or in the hormone-dependent tumor by hormone deprivation, might then represent mere lack of interference by the hormone with the normal preventers of mitosis; the shrinkage of tumor or normal organ would occur as the cells, which had already been started on the path of terminal differentiation, completed that journey and were not replaced. This supposition is compatible with the observation that, during tumor regression, the number of apoptotic cells per unit cell number increases drastically (3). This formulation also explains the failure of the regression that is induced by hormonal deprivation, in either tumor or normal prostate, to go to completion (19). It also implies that the bulk of the normal prostate gland and of most prostate tumors is composed of cells programmed to proceed, rather slowly, through terminal differentiation and that the number of stem cells which will remain in the absence of androgen-dependent mitotic activity is relatively small. This postulated sparsity of stem cells might help to explain the relative difficulty encountered, even in the presence of Matrigel (20), in trying to grow human prostate carcinomas either in nude mice or in tissue culture (21).

**Mitotic Rate and Differentiation**

I have tried to make a careful distinction between factors that merely alter the mitotic rate and those that alter the growth...
ratio of daughter cells that remain in the replicative stem cell pool. While this distinction is, I think, intellectually useful, it may at times be a difficult distinction in practice. In growing tumors, altering the mitotic rate, without further changing the growth ratio, will of course alter the growth rate of the tissue. The situation is analogous to compound interest on a bank account; the speed of growth of the account (tumor growth) is altered by the frequency of compounding (the rate of mitosis) without any need to change the interest rate (the growth ratio of daughter cells remaining in the stem cell pool). This analysis leads to the perhaps unexpected conclusion that, in a tumor, factors that alter only the rate of mitosis may alter the apparent degree of differentiation that will be seen histologically. An increase in mitotic rate would accelerate the increase in the size of the replicating pool; the proportional size of of the differentiating population would fall behind and never catch up to the proportional level it had had before the increase in mitotic rate. Thus, in a growing tumor, where the growth ratio is biased in favor of stem cell births, an increase in the mitotic rate, with no further increase in the growth ratio of daughter cells remaining in the stem cell pool, would, if this analysis is correct, produce a decrease in the apparent level of differentiation.

The conclusion, that any factor that can increase the mitotic rate in a tumor can cause apparent dedifferentiation, may influence the interpretation of the work of Hammond.2 This investigator found that tumors, produced by a chemical carcinogen and either transplanted syngeneically or left to grow in the animal of origin, showed histologically, by blind examination, a degree of differentiation that was inversely related to the level of the immune capacity of the host animal. Tumors growing in, or transplanted through, the animals of least immune capacity showed the greatest degrees of differentiation. In other words, the greater the immune capacity of the host, the less differentiated the tumors appeared to be. Note that the result is opposite that which conventional wisdom might have predicted. Hammond did not speculate upon the mechanisms that might underlie his important observations but was content to point out that an “epigenetic” mechanism, the immune response, could apparently alter the degree of differentiation, or lack thereof, in a tumor.

In view of the previous analysis, the Hammond observations might be interpreted in at least three different ways: the immune response may have increased the mitotic rate and thus reduced the apparent level of differentiation; the immune response may have killed the more differentiated cells preferentially; or the immune response may have actually altered the growth ratio of daughter cells remaining as stem cells to those embarking on a program of differentiation. Since it has been shown that immunity may, under some circumstances, promote tumor growth (22, 23), the first alternative cannot be dismissed a priori. However, more data will be necessary before the mechanisms of Hammond’s interesting findings can be understood.

Mechanisms of the Inhibition of Growth

The discussion, thus far, has not distinguished among the various mechanisms by which a tumor may differ from the tissue of origin with regard to the symmetry preventer. There are several logical possibilities: the tumor might be relatively insensitive to the preventer; the preventer produced by the tumor cells might be defective; the tumor cells might produce the preventer in less than normal quantity; or the tumor may produce a product that inactivates the symmetry preventer. All of these possibilities seem compatible with the known facts, they are not mutually exclusive, and it seems quite likely that not all tumors make use of the same one. I think it probable, furthermore, that many tumors may, during the course of progression, acquire multiple mechanisms for evading the postulated symmetry preventer. It is tempting and not unreasonable to suggest that the ideal tumor suppressor gene, perhaps p53, would be a gene vital to the production or function of the putative symmetry preventer (24, 25).

Although it is not possible to rule out any one of the several mechanisms by which a tumor might evade the symmetry preventer, there are data that may bear upon this problem. Osgood (26), who anticipated much of this discussion, put forth the case for the tumor’s being deficient in its production of a preventer of mitosis by virtue of the fact that the differentiating cells of a tumor may often (always?) have a shorter than normal life span. Thus, if there are, because of a shorter cellular life span, fewer differentiating cells and these are the source of the preventer, the tumor must necessarily produce the preventer in less than normal quantity. Osgood’s heuristically appealing general thesis was that any abnormality (mutation?) that would shorten the cellular life span of the differentiating cellular population would produce neoplasia via the consequent reduction in the level of a preventer of mitosis. The notion that a preventer is released by the differentiating cells, which then prevents mitosis among the stem cells, is the essence of the “chalone” hypothesis proposed by Bullough (27); the existence of chalones is heuristically appealing, but their actual existence has been strongly challenged (28).

The ideas of Osgood were predicated upon the postulated central role of a preventer of mitosis that would be diminished if the differentiating cells had a shorter than normal life span (26). However, as I have tried to make clear, an increase in mitotic rate cannot, of itself, be the essence of neoplasia; for a tissue to grow, other than temporarily, there must be a decrease in the activity of the postulated stem cell factor that prevents one-half of the daughters of stem cell divisions from remaining as stem cells and forces them, instead, to leave the stem cell pool and differentiate. It is also apparent that the symmetry preventer cannot be, as is the mitosis preventer, a product of the differentiating cells. If it were, loss of differentiating cells alone, as might occur in a superficial skin abrasion, would reduce the concentration of symmetry preventer, thus increasing the rate of symmetrical mitosis and the size of the stem cell population; it seems necessary, therefore, to postulate that in a normal adult tissue there must be a loss of stem cells before stem cell production and replacement can occur. This argument also reinforces the idea that the symmetry preventer is a blocker of a primative cellular function rather than a positive, direct acting inducer of differentiation; its activity must be increased rather than decreased by cell loss.

It was observed by Nair and DeOme (29) and by Argyris and Argyris (30, 31) that at least some implanted tumors could cause hyperplasia in adjacent normal epithelial tissues. This phenomenon seems to suggest the production of a diffusible factor by the tumor. The diffusible factor, generated by the tumor, might have been a defective mitosis preventer and/or a defective symmetry preventer that competed with the native factors in the normal tissue, or it might have been an active blocker of the native factors. Judging by the work of Argyris

and Argyris (31), the phenomenon was not entirely tissue specific. It is apparent that these observations may contribute to an explanation of the contention, by Willis (32), that tumors often can be seen to arise in a field of altered cells rather than at at single focal point.

Preneoplastic Lesions

Observations of preneoplastic lesions may also offer some insights into the mechanisms of growth prevention.

Similar principles appear to apply to most and perhaps all preneoplastic lesions. The application of an appropriate carcinogenic stimulus results in focal hyperplastic lesions that will, in some cases, progress to carcinoma but which, in most cases, stop growing or regress; it is my general contention, with minor variations in different systems, that those with limited growth potential have a defect that diminishes the amount or effectiveness of the mitosis preventer while those that produce carcinomas have, sometimes additionally, a defect in the production or utilization of the symmetry preventer. In this section, I will discuss briefly three systems that have been extensively examined.

Breast. The mouse breast is one of the best studied systems. In a strain of mouse that is highly susceptible to the milk-transmitted MTV,3 viral activity results in HAN scattered throughout the ductal system of the breast. However, the MTV is probably a predisposing factor rather than the immediate cause of the HAN inasmuch as many of the cells of the mouse are infected but relatively few give rise to HAN (33). The virus does have systemic effects on mitosis; the toe nails of infected mice have been shown to grow much faster than do those of uninfected animals (34). HAN have been shown to be the precursors of carcinomas (35). There is suggestive evidence that the HAN begin to appear during the growth phase of the mammary ductal system, which begins at the time of puberty; the data also suggest that the HAN cease appearing once mammary duct development is complete. This can be inferred from a study, at successive weeks of age, of the incidence of overt tumors (36) and from the observation of Slemmer (37) that HAN can be very long lived. The incidence of carcinoma rises in the most susceptible mouse strain, after puberty, to a plateau and then remains constant throughout most of the remainder of life (36). Therefore, the number of HAN, at least of the type capable of giving rise to carcinoma, is probably also a constant throughout most of adult life. The size attained by each HAN is limited by an influence from the surrounding normal breast; in the absence of the normal tissue, the HAN will grow to fill the entire mammary fat pad (36). Thus, it seems clear that the HAN have a defect affecting the growth ratio; whether they also have a defect altering the production or effectiveness of the mitosis preventer is not clear. Experiment has shown that the normal ducts are the source of a preventer that limits the growth of both normal ducts and HAN but which the HAN cannot produce, at least in effective quantity (37). Carcinomas neither produce nor respond to the preventer and consequently they can overgrow the normal ducts. Whether or not there is, in this system, a population of hyperplastic lesions, the aberration of which is confined to the mitosis preventer alone, is not known.

These data are consistent with the hypothesis that a symmetry preventer, present in normal adult tissues, is produced to a lesser extent during growth. The effect of such a deficit would be potentiated by the accelerated mitotic rate presumably produced by the MTV. Under these circumstances, rare cellular variants, less able themselves to produce the symmetry preventer, are able to escape the meager supply of preventer provided by adjacent proliferating ductal cells. Such a variant cell produces a clone of tissue, the HAN, which continues to grow until the growing size of the lesion brings it into close proximity with surrounding, now mature, ducts; the associated increase in concentration of the symmetry preventer causes growth of the HAN to cease. Further progression occurs when rare variant cells, arising among the cells of a HAN, not only share with the cells of the HAN their lack of production of the symmetry preventer but, in addition, are less susceptible to its action. These variants are the source of carcinomas (38).

Although there is, I believe, no evidence to support the idea that the MTV may be cytotoxic to a proportion of the stem cell population, such a hypothesis would suggest that the HAN, and the carcinoma that arises within it, may be part of a compensatory mechanism to provide replacement stem cells. Such a hypothesis would bring the MTV system into closer alignment with chemical carcinogenesis in the liver and in the skin.

Liver. Some preneoplastic lesions, which have been studied in detail, appear to differ from the MTV system in important ways, but in ways that do not violate the general principles I have been developing. For example, in the liver, most focal hyperplasias that result from a modest treatment with a chemical carcinogen regress by a process of differentiation (39). Farber (40) suggests that the chemical carcinogen produces, throughout the liver, a generalized defect which reduces the ability of the liver cells to respond by compensatory mitosis to injuries induced either by the carcinogen itself or by partial hepatectomy. This type of toxicity was first noted in the skin (41); presumably, any type of injury might in compensation reduce the levels of the normal mitotic preventers. Cell clones that are less susceptible to injury by the carcinogen, i.e., that can still respond to mitotic stimuli, would have a selective advantage, undergo compensatory hyperplasia, and proliferate to form hepatic nodules. It is noteworthy that cancer cells, in general, are resistant to the toxic effects of carcinogens (42, 43). Those focal hyperplasias, which cease to grow or which differentiate and regress when the acute effects of the carcinogen have dissipated, may be those in which heritable compensatory mechanisms reduce the response to, or the production of, the normal preventers of mitosis without affecting the growth ratio; such lesions would return to normal size when the general level of preventers returned to a sufficiently high point. These lesions would thus be locally exuberant markers of a compensatory, organ-wide reaction to injury (40). In a small fraction of the lesions, alterations affecting both the growth ratio and the propensity to mitosis might occur; these lesions would be more persistent and would be truly preneoplastic. It seems probable that, in the liver, such a double lesion might be necessary for a truly preneoplastic change to be visualized. Even a profound change in the growth ratio might, by itself, produce only a very slowly growing tumor in the liver owing to the virtual absence of mitotic activity in the normal organ (44). By contrast, in organs in which there is an appreciable rate of mitosis, such as the epithelium of the skin or the mucosa of the bowel, a lesion affecting only the growth ratio would be sufficient to produce neoplasia and, as has been discussed previously, no increase in

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3 The abbreviations used are: MTV, mammary tumor virus; HAN, hyperplastic alveolar nodules.
the normal mitotic rate, in that circumstance, would be necessary.

Skin. Regressing papillomas occur in the epithelium of the skin in response to the topical application of polycyclic hydrocarbon carcinogens. It is in this system that the concept of a "two-stage mechanism," initiation and promotion, had its genesis, to a large extent in the work of Berenblum (45), but foreshadowed in the studies of Deelman (46), Mottram (47), Rous and Kidd (48), and others. In this system, clear evidence of "immunosurveillance" has been found (49); under proper experimental conditions, immunity can and does accelerate papilloma regression. However, most papillomas that do regress would do so even in the complete absence of any host immune capacity (50) and "spontaneous" papillomas, that appear to be nonantigenic, also regress (50). In the work of Andrews (50), the promotional stimulus, applied after the carcinogen, was the injury of skin grafting, which produces profound mitotic activity in the surviving cells of the graft; papillomas appear on the carcinogen-treated, grafted skin, but particularly around the margins of the graft where wound healing is most active. The percentage of papillomas that regressed most slowly or that progressed to carcinoma was directly related to the concentration of carcinogen used for initiation (50).

I believe that this work is consistent with the hypothesis that the transient, rapidly regressing papillomas were lesions in which the cellular defect was a relative deficiency in the cellular production of, or responsiveness to, the mitosis preventer that normally prevents mitosis in the epithelium, i.e., the epidermal chalone (51). Wound healing, as produced by the healing of a skin graft, would promote their growth; regression would result when this stimulus subsided. Those lesions which went on to carcinoma would be those that, additionally or alternatively, possessed a defect in the production or utilization of the putative symmetry preventer and thus had an alteration of the growth ratio in favor of the stem cells.

In sum, the work on preneoplastic systems seems consistent with, but certainly does not prove, the hypothesis that small regression-prone lesions (hyperplasias) are usually the result of a cellular abnormality in the expression of, and/or responsiveness to, the normal preventer of mitosis that is produced by the differentiating cells. Lesions that can grow progressively have, alternatively or additionally, a lesion that interferes with the factor, produced normally by the stem cells, that regulates the growth ratio. In organs with very low natural rates of mitosis, such as the liver, both types of lesion may be obligatory if carcinoma is to appear. The tumor can, with little difficulty, be regarded as a pathological manifestation of a compensatory reaction to injury, i.e., an aberrant form of wound healing or of regeneration after amputation of tissue (52). These ideas are somewhat similar, with some translation of terminology, to proposals advanced by Zajicek (53).

Carcinogenesis is, of course, a complex process and the effects of the alteration of the growth ratio, by whatever means, will be modified by other influences such as the immune response, which was shown to be operative in the carcinogen-induced papilloma system of mouse skin; these other influences are beyond the scope of this paper.

Clinical Implications

Whatever the mechanism by which a tumor evades the symmetry preventer, the probable existence of such a preventer, the effectiveness of which is dependent upon organ size, suggests that the debulking of tumors should be counterproductive. In the adult, incomplete surgical removal does, indeed, tend to increase the growth rate of the remaining tumor, sometimes explosively (54–56). On the other hand, chemotherapies or radiation can result in cures of some tumors, especially in infants, and there is little evidence, in these cases, of compensatory growth of the treated tumors. The implication of these facts may be that if sufficient damage to stem cells can be produced, by whatever therapy, this effect may overshadow the growth-promoting effects of debulking.

The hypothesis that the growth ratio is maintained by a factor, the concentration of which increases as organ size increases, may help explain one of the important mysteries of tumor biology. The newborn and the infant seem to have a remarkable facility to produce spontaneous regression of even large neoplasms; giant hemangiomas commonly regress in infancy and, especially in the very young, Wilm's tumors and neuroblastomas may differentiate or, at least, be surprisingly amenable to treatment (57). It may be a reflection of this same phenomenon that many childhood leukemias now carry a good prognosis. This unusual capacity of the very young to control neoplasia could be explained as the result of the postulated increase in the concentration of symmetry preventers as the organs increase in size.

Although the very young seem better able than adults to overcome their cancers, they also have an increased susceptibility to tumor formation. Newborn animals are apparently more susceptible to chemical carcinogenesis (58) and the cancer incidence in human infants is higher than that in young adults. These statistics, the latter in particular, are unlikely to result from any vagaries of a hypothetical immunological surveillance; most "spontaneous" tumors are not detectably immunogenic and the number of types of cancer that are increased by immunodepression in the human is small indeed (59); any immune reaction that does occur may be more likely to aid and abet the carcinogenic process rather than to inhibit it (22, 23). However, the increased susceptibility of the very young could be anticipated because of the relative ineffectiveness, in the growing organism, of the putative preventer that maintains the growth ratio, the symmetry preventer. It would seem that the infant, because of its rapid growth, is more susceptible than the adult but, at the same time, is more likely to cope with its cancer successfully because of the increasing concentration of symmetry preventer as organ size and maturation increases.

The rising incidence of cancer with aging is often attributed to the necessity for a clone of variant cells to accumulate multiple alterations before it can grow as an overt cancer (60–63). Assuming that deleterious alterations do accumulate with age, the story of aging would be one of chronic progressive injury. When the injury causes loss of stem cells, compensatory repair mechanisms would reduce both the inhibition to mitosis and the maintenance of the growth ratio. Thus, progressive nonspecific injury during aging may contribute to the selection of clones better adapted to the environment that results from injury, an environment in which increased capacity for compensatory growth would be advantageous, both to the repair of injury and to the carcinogenic process. Carcinogenesis in aging would thus be somewhat as I described, in the skin or liver, except that the injury of aging would substitute for the injury produced by a carcinogen.
Conclusions

I believe the data I have discussed, as well as the philosophical arguments expounded by Sato and Sonnenschein and by Ogood, make a reasonably good case for the existence of symmetry preventers produced by stem cells and mitosis preventers produced by most cells of multicellular animals; these data suggest that normal adult tissues may be the best place to search for these factors. This analysis also suggests that the prevention of mitosis and the prevention of symmetry are separable functions, but functions that may, in practice, be difficult to distinguish. Despite this difficulty, I believe that people who investigate problems in cancer research would be well advised to keep these distinctions in mind and to recognize the fact that abnormalities in the rate of mitosis, while of probable importance in organs with very low mitotic rates, such as the liver, are not fundamental to the regulation of of the growth of either normal organs or of neoplasia. Thus, many of the currently popular factors that stimulate (block prevention of?) mitosis, such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, etc., probably have little direct role in the regulation of tissue growth, either normal or malignant. It seems more likely that factors that apparently alter the growth ratio, such as those related to the retinoids, are factors more relevant to the regulation of cancer and normal tissue growth.

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References

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