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Immunostimulation of the Lymphodependent Phase of Neoplastic Growth

Most oncologists are probably of the opinion that the immune system constitutes an important defense against the occurrence of cancer, a concept embodied in the term "immunologic surveillance" (*1*). However, increasing numbers of cognoscenti are now persuaded that the role of immunity has, in most tumor systems, been vastly overrated (*2–5*). I have begun to entertain the diametrically opposite hypothesis that an immune reaction, rather than killing incipient neoplasms, may actually stimulate them to grow (*5–7*). My purpose in this editorial is not to persuade you that the immune reaction is a significant cause of tumor growth, but rather to persuade you that this hypothesis merits serious consideration.

Before one questions whether the action of an immune response is predominantly stimulatory or inhibitory to target tumors, it would be well to ask whether or not the neoplasm stimulates an immune response of any kind. The answer may be affirmative in some systems, but it is by no means clear that this is always so, or indeed that this is frequently so.

There appears to be no question about the fact that most tumors induced in the laboratory, either by viral, chemical, or physical agents are, at least potentially, immunogenic (*8*). The growths of transplants of these tumors can often be modified by specific immunization; in vitro tests of various kinds are often positive, and immunodepression of the host animals often leads to faster growth of transplants. Furthermore, in some viral systems it is clear that immunodepression potentiates the appearance and growth of the primary, untransplanted neoplasm, and conversely, that vaccination is successful (*8*).

In chemical tumor induction, potentiation of oncogenesis by immunodepression is difficult to demonstrate, perhaps partly because of the immunodepression produced by the oncogen itself (*9*). Positive, statistically significant reports exist, but they are nonetheless usually of marginal degree (*10, 11*). Failures have also been revealed, and one suspects that many negative results have not been reported (*2*). Under these circumstances, the real significance of the positive reports remains questionable.

Most important is the fact that so-called spontaneous tumors in rodents, i.e., tumors that arise in low frequency, often in older animals and for no overt cause, are seldom immunogenic (*12, 13*). (By immunogenic, I refer only to the capacity of a tumor to induce an immunity in vivo that will restrict to some degree the subsequent growth of implants.) In chemically induced tumors, immunogenicity tends to be directly related to the concentration of the inducing oncogen; low concentrations that presumably mimic the spontaneous condition produce tumors of little or no immunogenicity (*14*). The reason for the low or nonexistent immunogenicity of spontaneous tumors or those induced by low doses of carcinogen is not yet known, and indeed it may vary from case to case. An absolute paucity of tumor-associated antigens is to be suspected, but alternatives such as induction of "blocking" factors, shedding of antigen, elicitation of suppressor cells, or induction of a competing tumor-stimulatory reaction have, in most instances, not been ruled out.

The possibility of course exists that "spontaneous" tumors might be more immunogenic at their inception and that this property is lost via immunoselection during tumor "progression" (*8*). That some selective effects do occur in relation to tumor immunogenicity has been directly demonstrated by Bartlett (*15*) and Bubeník et al. (*16*). However, tumors that arise in the immunologically free confines of tissue culture or in diffusion chambers are, unless a chemical or virus has been deliberately added, seldom immunogenic. This suggests that immunoselection is not the fundamental reason for the lack of immunogenicity in spontaneous tumors (*15, 17–20*). Immunogenicity seems to be a property initially conferred by the oncogen, if one is overtly present; immunoselection can certainly then occur but need not be invoked to account for the lack of immunogenicity of spontaneous tumors or tumors induced by low doses of carcinogens.

That the immune system does interact with spontaneous human tumors has been forcibly argued by Ioachim (*21*) in defense of the concept of immunologic surveillance. He has rightly pointed out that many human tumors, especially in the early stages of their evolution, are associated with an intense infiltration of lymphocytes and/or related cells. It seems reasonable to suppose that this infiltrate is indicative of immunologic recognition of the neoplasm. Furthermore, the presence of this infiltrate suggests that many human tumors may result from the action of chemical carcinogens and others from the action of oncogenic viruses. How many human neoplasms are really spontaneous in the sense of the spontaneous rodent tumors? In the rodent, the term spontaneous is perhaps best equated with tumors that arise infrequently and sporadically. However, this infrequency is usually in an inbred population in which all the members are at equal genetic risk. In man, where genetically susceptible individuals cannot yet be identified, it is possible that some tumors, thought of as spontaneous, may actually occur in nearly 100% of the genetically susceptible population! Are these then to be considered spontaneous, or are they more akin to those rodent tumors induced in high frequency

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Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.

by a virus or an appreciable dosage of carcinogenic chemical? In the rodent, the chemically induced tumor is the type most typically associated with a lymphoid infiltrate. Thus it is clear that we should be cautious in assuming that spontaneous rodent tumors are a better model of human disease than are those induced by viruses or chemicals.

Apart from the evidence of lymphocytic infiltration, evidence for the immunogenicity of human tumors is, unfortunately, suspect. The numerous in vitro tests designed to demonstrate tumor antigens are, in my estimation, difficult to interpret and their meaning is not yet clear. Human tumor regression, which in some tumor types is frequent, is not necessarily a manifestation of immunity. However, for the sake of argument and the purposes of this editorial, I will take the evidence of lymphoid cell infiltration at face value and assume that many human tumors are indeed recognized as "foreign" by the immune mechanism. We can now consider the possible biologic effects of this recognition.

It is perhaps important to consider at what point in tumor evolution such recognition may occur. As has already been mentioned, the infiltrate of lymphocytic and associated cells sometimes found in human neoplasms is most characteristic of early lesions. The infiltrate is perhaps most dramatic in premalignant skin lesions or in lesions just beginning dermal invasion. In early melanoma of the skin, for example, the pathologist is commonly aided in distinguishing "malignant" from innocuous lesions by the intense lymphocytic dermal infiltration commonly associated with malignant lesions (*22*). At later stages of the disease, the lymphocytic infiltration is usually less intense or may even disappear (*22*).

Although the lymphocytic infiltrate supports the argument that immune recognition may occur early, other data suggest that the lesion must nonetheless reach a size containing hundreds and perhaps thousands of antigenic cells before an immune response can occur. For example, in chemically induced mouse breast cancer, strong evidence exists to indicate that the hyperplastic nodule (the precancerous lesion) usually fails to immunize the host despite the fact that the nodule contains the necessary antigens. Immunization does not occur until the lesion grows and extends outside the breast fat pad (*23*). Likewise, evidence suggests that chemically induced, antigenic, mouse skin tumors may fail to immunize the host when they are left undisturbed in the skin (*24*). These data suggest a lack of antigen recognition in early lesions.

A further argument against the hypothesis that immune recognition occurs when the neoplasm is very small is the phenomenon called "sneaking through." It has been repeatedly observed that an antigenic tumor implant may fail to produce effective immunity against its own growth if the inoculum is sufficiently small (*25-29*). That this curious effect could be the result of any type of immunologic tolerance seems doubtful [although some evidence supports the tolerance hypothesis (*28*)], since the same effect can sometimes be even more pronounced in previously immunized hosts (*29*). The explanation of sneaking through may be that, by the time the lesion is discovered by the immune response, the lesion is too large to be greatly affected by it.

These varied data argue that any effect of immunity on a neoplasm, be it surveillance or stimulation, probably occurs *after* the tumor has reached a respectable size. Even in viral systems, in which immunization may occur prior to, or simultaneously with, neoplastic transformation, the existence of the sneaking through phenomenon in previously immunized animals suggests that the tumor per se would not stimulate a second-set reaction, i.e., attract immunologic attention, while still very small. (However, sneaking through has not, to my knowledge, been sought in a viral tumor system). Thus the original idea of immunologic surveillance, namely, that there is an immune elimination of neoplastically transformed cells or clones virtually as soon as they occur, does not seem tenable. Possibly, mechanisms exist that inhibit or eliminate neoplastically transformed cells or clones virtually at their inception but, if so, these mechanisms do not appear to be immunologic. The fact that the immune mechanism does not interact with the tumor directly until the lesion is of considerable size is important to my overall thesis, as will soon be apparent.

It would be hard to argue that a lymphoid infiltrate, when present, is irrelevant to tumor growth. Therefore, it must be either aiding or inhibiting tumor growth—or both. I will present arguments on both sides of this question.

The argument that the lymphoid infiltrate is inhibitory to the tumor depends, as far as I can see, on two sets of essential facts. The first fact is that lymphoid cells can, under the proper circumstances, be cytotoxic to their specific targets in vitro and can also specifically inhibit the growth of tumor transplants. Furthermore, in some virus systems immunity definitely inhibits oncogenesis (*8*). These facts need no elaboration.

The second set of facts is the series of observations that a lymphoid infiltrate is usually associated with a better prognosis. This association is apparent in cases of human breast cancer in which a heavy infiltrate is present (*30*). Furthermore, many of the premalignant skin lesions associated with a lymphocytic infiltrate never become overtly malignant. The apparent association of a lymphocytic infiltrate with a good prognosis would certainly seem, at first glance, to be a strong argument in favor of a defensive antitumor role for the infiltrate. Furthermore, it is generally believed that the defense of the body against antigenically distinctive invaders is the lymphocyte's raison d'etre.

The argument in favor of a tumor-stimulatory role for the lymphocytic infiltrate, although in my opinion strong, is less familiar and requires more elaboration. It depends on three points: 1) Under proper circumstances, either specifically immune or normal lymphoid cells, mixed with tumor cells, *can* stimulate growth rather than kill, and the proper circumstances probably often exist in the early in situ neoplasm (*7*). 2) Lymphoid cell depletion can sometimes inhibit, rather than enhance, tumor occurrence and/or growth (*6, 31*). 3) The good prognosis associated with lymphocytic infiltration is compatible with a tumor-stimulatory, rather than a defensive, role for the lymphocytes, a point I shall explain shortly.

The fact that under certain conditions the immune reaction can stimulate target cells appears to be well established, but the mechanisms remain obscure (*32-43*). Much of the work suggestive of direct immunostimulation of tumor cells is not absolutely conclusive, since the observations could sometimes be interpreted by alternative explanations. For example, I was able to show that immune spleen cells, when

mixed at low ratios with target tumor cells, specifically stimulated tumor cell growth in Winn-type assays in immunodepressed mice (*32*). Although direct immunostimulation was the simplest explanation, it could be argued that spleen cells, when present in small numbers, expressed a disproportionately effective suppressor cell activity and so interfered with a small residual host immunity. In in vitro settings it is also possible to argue, though I think with some difficulty, that suppressor cells might be disproportionately activated when lymphoid cell:tumor cell ratios are low (*41*). That actual stimulation, rigorously distinguishable from any kind of suppressor cell activity or blocking effect, does indeed exist is best shown in the work of Shearer (*40*). This investigator has shown, in completely in vitro allogeneic systems, that antibody in low titer can specifically stimulate target cells, whereas in higher concentration the same serum is specifically cytotoxic. This observation makes it probable that the Winn-type data and the in vitro studies with lymphoid cells were also demonstrating actual tumor cell stimulation rather than, or in addition to, suppressor cell or blocking activity. The possibility is also raised that many or all of the effects described as "enhancement" by antiserum and studied in great detail by Kaliss and his associates in allogeneic systems were due to direct stimulation of the target tumor cells (*44*). It seems unlikely that all instances of immunostimulation are mediated by antibody, but I think this remains a possibility. It is also evident that many competing mechanisms, including suppressor cells, are probably at work confounding simplistic interpretations.

In work apparently demonstrating immunostimulation of tumor by immune cells or antiserum, several observations seem to have been common to many of the varied experimental designs. Seemingly most important was the effect of the relative concentrations of immune cells or antibody and the target cells. Characteristically, a biphasic result was seen in which low relative concentrations of immune cells and/or effectors produced stimulation, whereas higher concentrations were inhibitory or cytotoxic. In many experiments a strong nonspecific stimulation of the target cells was also seen, over and above the specific component of the response (*32, 45*). However, variations were great from tumor to tumor, the reasons for which remain unknown. Some data suggested that blood leukocytes harvested early after the implantation of an immunogenic tumor may have been specifically stimulatory, the same relative number becoming indifferent or inhibitory when harvested during a later period of tumor growth (*35*); perhaps this phenomenon is explicable in terms of the probably greater proportion of specifically immune cells harvested at the later periods.

Although purely quantitative variables seem to be of great importance in determining whether the effect of an immune reaction is stimulatory or inhibitory to target tumor cells, it is almost certain that important qualitative determinants also exist. The cellular composition of the leukocytic infiltrate is known to vary morphologically depending on the particular tumor. Gorer (*46*), who divided the types of infiltrate into three basic categories, believed that these types were associated with functional differences. Furthermore, the mast cell and eosinophil content of the infiltrate can vary widely. It is reasonable to suppose that the functional attributes of various forms of leukocytes, not recognizable morphologically, may vary greatly from infiltrate to infiltrate, and analysis of these variations is only just beginning (*47*). Although these qualitative variations in the infiltrate are undoubtedly very important, so little is understood about them that they cannot be considered in the development of the argument of this editorial.

A number of observations suggest a possible role of immunostimulation of tumor growth in actual oncogenesis as well as in a variety of transplantation phenomena. I have pointed out that clear evidence exists that depression of the immune mechanism by experimental means can often potentiate viral and, more debatably, chemical oncogenesis, but in view of the biphasic character of the lymphoid cell effect (discussed above), is this observation due to a decrease in tumor inhibition or to an increased level of stimulation? Furthermore, precisely the opposite is also true. For example, in the mammary tumor system of mice (a "weak" immunogenic system), immunocrippling inhibits rather than potentiates tumor formation (*6*). There is also some evidence, which needs further substantiation, that transplants of weakly immunogenic tumors may be inhibited in immunodepressed hosts (*9*). Others have observed that allogeneic and xenogeneic tumor transplants tend to grow more slowly, to be less invasive, and to metastasize less frequently in nude mice than in the syngeneic strain of origin (*48*). This is so despite the fact that athymic nude mice have no detectable resistance to the growth of allografts of normal tissues. Since the immunogenicities of chemically induced tumors are inversely correlated with the latencies of their formation and since the growth rates of these same primary tumors are also inversely correlated with their latencies, it can be deduced that the growth rates of primary tumors are directly correlated with their immunogenicities, although direct evidence of this latter correlation did not reach statistical significance (*15*). Thus the more immunogenic the primary tumor, the faster it tends to grow! A further argument in favor of a role for stimulation in tumor biology derives from the observation that tumors are constantly throwing variants of lesser immunogenicity (*49*). How is it then that most, but not all, tumors are immunogenic and remain so to varying degrees through numerous transplant generations (*49*)? Is immunogenicity sometimes maintained by immunoselection? All of these observations can be interpreted to mean that some degree of immunologic responsiveness may sometimes favor tumor growth, but in each instance alternative explanations of the observed phenomena are possible.

From what has been determined concerning the conditions under which immunostimulation of tumor growth is likely to occur, what can be said about conditions in the de novo tumor that has just reached a sufficient size to effectively signal its presence to the immune mechanism? As has already been discussed, this size is probably on the order of many thousands of cells, even in virus systems in which immunization may have occurred prior to the particular neoplastic transformation being considered. Initially the immune response must necessarily be small, even in such immunized hosts. Put another way, lymphoid cells will be attracted to the tumor at some finite rate—initially the number accumulated must be small. Thus early in the process, and for a certain indeterminate period of time, the

number of lymphoid cells relative to the number of tumor cells must be low; these are the conditions in which stimulation rather than inhibition is likely. Furthermore, on examining the early neoplasm that has already achieved a heavy lymphoid infiltrate, I am struck by the fact that the infiltrate often tends to be concentrated outside the tumor, e.g., in the dermis in an incipient epithelial tumor of the skin. Few, if any, lymphoid cells may be discernible within the tumor per se or even in close contact. Thus the concentration of effector substances, antibody, or other lymphoid cell products is probably low within the tumor proper and, therefore, probably stimulatory rather than inhibitory. It is perhaps reasonable to suggest that the immobilization of lymphoid cells in the dermis may occur because of the release of diffusible antigen from the neoplasm (*50, 51*); the lymphoid accumulation might be analogous to the precipitin line in an Ouchterlony plate.

If one can judge by the analogy with the tuberculin reaction or the reaction to a skin allograft, most of the lymphoid cells attracted to the area of the tumor do not specifically recognize tumor antigens (*52*). In tests done with normal (i.e., not specifically immune) lymphoid cells, only target cell stimulation was usually seen, at least until the ratio of lymphoid cells to tumor cells became exceedingly large (*32, 45*). Thus even if the number of lymphoid cells around the tumor eventually becomes high, the infiltrate attracted to the tumor may be largely nonspecific and, therefore, may tend to remain stimulatory.

If the lymphoid infiltrate usually stimulates the tumor, why the good prognosis often associated with such an infiltrate? At least three, not mutually exclusive, explanations can be offered.

First, the lymphoid infiltrate may be a marker for a tumor of lesser malignancy rather than a cause of that behavior. There are many reasons to believe that the capacity to be stimulated to hyperplasia by a lymphoid infiltrate is a property that a tumor shares with its normal tissue of origin (*7*). Apart from the controversial literature concerning the possible stimulation of fetal growth by immunity (*7*), many examples exist in pathology of situations in which an immune reaction and/or a lymphoid infiltrate of one kind or another is associated with hyperplasia. In rheumatoid arthritis, the characteristic lesion often exhibits a tumorlike hyperplastic quality (*53*); the arterial smooth muscle proliferation in chronic allograft rejection has been often noted (*54*); and the association of lymphoid infiltration with epithelial hyperplasia in an insect bite is astounding (*55*). Numerous other such associations have been documented, including a role for lymphoid cells in compensatory hyperplasia in the liver and kidney (*56*). In fact the idea that the lymphocyte may be a growth promoter has a long and honorable history dating back to Carrel (*57*); it is not a new or novel idea. If the tumor shares with normal tissues the capacity to be stimulated by lymphocytes, it is reasonable to think of the early tumor that attracts lymphoid cells as "lymphodependent." Presumably this is a property that might, with time, be lost during the course of tumor progression, just as an estrogen-dependent mammary tumor may gradually lose its dependency on estrogen. Dependency of any kind is a characteristic property of the early tumor, although in some instances it may be retained indefinitely (*58*). In this context, it should be noted that in human lung carcinoma, the leukocytic infiltrate is more marked in the better differentiated tumors (*59*). Lymphoid dependence is thus a marker of a tumor still young in its biologic evolution—a tumor that will generally carry a better prognosis than will one that is biologically more advanced, i.e., less differentiated.

The second reason why lymphodependency is compatible with a good prognosis requires a further consideration of the neoplastic process as seen in skin. The preneoplastic skin lesions associated with a marked lymphocytic infiltrate, such as senile or actinic keratosis, probably represent clones of epithelial cells in which an antigenic change has occurred, and repeated episodes of compensatory hyperplasia have produced a lesion large enough to signal the immune reaction. If my thesis is correct, this reaction then serves to amplify and maintain the hyperplasia, not eliminate it, thus increasing the chance that the further changes necessary to full-blown neoplasia may eventually occur. Although a dermal lymphoid infiltrate may often be necessary to maintain a hyperplastic lesion in the epithelium, possibly the same infiltrate may simultaneously prevent the antigenic epithelial cells from metastasizing. Perhaps any epithelial cells that penetrate the dermis might find the concentration of effector substances and/or antibody too high and therefore be inhibited. There might thus be selection for neoplastic cells of less susceptibility to lymphoid effectors and with fewer antigens. Such cells might be the only type that could safely traverse the lymphoid area. In order to then leave the area of lymphoid concentration, such cells, now low in antigenicity, would also have to acquire the capacity to proliferate in the absence of the lymphoid cells, which they could not themselves attract. Thus a metastasis from a primary skin neoplasm would usually be expected, because of selection, to exhibit less immunogenicity than the primary in situ lesion and to be less lymphodependent. This expectation conforms to the observation that the lymphoid cell infiltrate is most marked in the lesions that are still largely in situ or still in the early stages of dermal invasion (*22*).

Of course, if my thesis has merit, there is a third and obvious reason why lymphodependency may be associated with a good prognosis. Lymphoid cells tend to be unusually sensitive to radiation and chemotherapeutic chemicals (*60*); perhaps these therapies are effective largely because of, not in spite of, their effects on the lymphoid infiltrate!

If the early lymphocytic infiltrate is really important in early tumor development, one important and seemingly contrary observation must be rationalized; the athymic nude mouse appears to be essentially not more susceptible or resistant to the occurrence of either carcinogen-induced or nonlymphoid spontaneous tumors than are heterozygous controls (*3, 61, 62*). This fact is a strong argument against either a stimulatory or an inhibitory role for the lymphocytic infiltrate. On the other hand, it seems, a priori, most unlikely that the heavy lymphocytic infiltrate seen in early carcinogen-induced tumors in normal rodents could be completely inconsequential.

The explanation of this seeming paradox could perhaps be contained in the previously discussed biphasic nature of the effect of immune lymphoid cells on their target. Let us consider a nearly total lack of lymphoid infiltrate as the baseline (i.e., the condition in the nude or newborn mouse).

Under these conditions tumor growth will be poor (*48, 63*); however, a small increase in the number of lymphocytes would produce accelerated tumor growth. This acceleration has actually been observed by Giovarelli et al. (*64*) and may explain the potentiation of chemical oncogenesis sometimes seen in partially immunocrippled or young animals (*65*). With increasing numbers of lymphocytes, i.e., the normal situation, the stimulation should give way to increasing inhibition and the incidence curve should again decline to the baseline and, perhaps, beyond (*64*). Therefore, the difference in oncogenic susceptibility might be difficult to detect between a nude mouse with little lymphocytic infiltrate and a normally reactive animal in which stimulation and inhibition of a primary untransplanted lesion might be nearly at the balance point. Thus the net effect of the infiltrate on the incidence of cancer might be small. However, the explanation is undoubtedly more complicated, since the nude mouse has recently been shown to possess a radiosensitive mechanism of tumor resistance (*66*).

Speculations along the lines I have been pursuing may explain a curious phenomenon often observed in animal experimentation, so-called "concomitant immunity" (*67*). The phenomenon consists of the observation that a primary tumor inoculum may persist and grow in an animal in which subsequent inoculations of the same tumor are inhibited. In fact, the growth of the primary inoculum may even be "enhanced" by the subsequent challenge (*68*). The survival of the primary inoculum is not a result of selection of resistant tumor cells, since it can be observed in successive transplant generations of the same tumor with no indication that the tumor has changed, as would be the case had selection occurred. The phenomenon can be seen in normal tissue allografts and in certain infections, especially those giving rise to granulomas. In both syphilis and tuberculosis, the organism is commonly found alive as a result of the primary infection at a time when there is immunity to superinfection (*69*). The same phenomenon occurs in some parasitic diseases (*70*). The trite explanation that a target tissue is more vulnerable to any resistance mechanism prior to establishment of a blood supply (the added insult to injury theory) might be applicable to tumor or tissue grafts, but hardly seems tenable for a parasite, nor would it account for the previously discussed, sometimes enhanced growth of a primary tumor graft.

Why is the larger primary colony of target cells relatively unaffected by a level of immunity capable, simultaneously in the same animal, of suppressing a smaller challenge inoculum? The cells of both colonies would supposedly be exposed to the same concentration of immune effectors. The answer may lie in the geometry of the situation. I propose, as previously discussed, that the target cells are releasing antigen into their immediate surroundings and that a concentration of antigen exists that immobilizes immune effector cells—lymphocytes and macrophages. A large colony will release more antigen than will a small one. Thus at some distance from the border of the large colony, leukocytes will be immobilized and/or antibody precipitated. Immune effector substances, lymphokines and/or antibody, will therefore be localized at some distance and be at low concentration in the large primary colony per se; they may, in the lesion proper, even be in the stimulatory rather than the inhibitory range of concentration. The small, secondary, challenge colony releases less antigen and is overwhelmed by the same concentration of immune effectors that is stimulatory to the primary colony; the leukocytes and/or antibody, rather than being immobilized at a distance, invade the colony to form an inhibitory concentration. In the larger colony, the volume of antigen-producing cells is larger relative to the surface area of the colony, where the interaction with lymphoid cells occurs, because of the surface-to-volume relationship of a sphere ($S = 4\pi R^2$, $V = 4/3\pi R^3$).

Why did the immune response evolve in a way that stimulates as well as inhibits? It seems to be of no obvious benefit to the host to stimulate the primary neoplasm. However, if stimulation is a necessary price to pay for the inhibition of tumor spread and metastasis, then the situation is understandable. If the immune response evolved from a more primitive growth-regulatory mechanism, the linkage of stimulation to inhibition might be basic and unbreakable. Alternatively, in the strategy of defense against bacteria and parasites, there might actually be an advantage in stimulating the first invaders. For common environmental pathogens, the odds are great that the first chance encounter would involve fewer invaders than some subsequent meeting. It would be to the host's advantage to become maximally immunized as a result of the first exposure. This might require that the first invasion be amplified to some extent to provide optimal and perhaps prolonged antigenic stimulation and to prevent "low-zone" tolerance. This strategy entails the risk that the first encounter might sometimes prove overwhelming as, in fact, it sometimes is. It is interesting in this context that tumors induced in athymic nude mice by the Moloney sarcoma virus do not regress as they do in normal hosts; however, the tumors grow initially more slowly in nude mice; this suggests that in normal animals the Moloney sarcoma virus tumors are perhaps stimulated by the early immune reaction (which is missing in nude mice) but inhibited by the later immune response (*71*).

In summary, I believe that the available evidence is compatible with the hypothesis that many tumors in humans and other animals pass through a stage, most notable early in their progression, when they are, to varying extents, lymphodependent. Furthermore, there are important quantitative effects such that the same lymphoid cell population that is stimulatory to tumor cells at low concentrations may be inhibitory at higher concentrations, a phenomenon that might sometimes limit the spread of a lymphodependent tumor. The commonly biphasic nature of the effect of an immune reaction on target tumor cells may contribute to the difficulty in demonstrating an effect of immunodepression on tumor induction in some tumor systems. The biphasic response also makes a rational attempt at immunotherapy difficult; in some cases the best result might be achieved by a reduction rather than an increase in immune reactivity. I would intuit, however, that the already successful tumor has, by selection, usually achieved an optimal (for the tumor) level of immune interaction with the host (*49*) so that an alteration toward either increased or decreased immunity might prove beneficial to the patient. At least it seems reasonable to hope that, under these circumstances, there may be little possibility that the patient will be harmed by attempts to alter the immune response

and there may, on the other hand, be some chance of a beneficial result. The hypothesis that many human tumors are to some extent lymphodependent offers some hope of developing truly effective immunologic approaches to prevention and therapy—at least the prospect is much better than might be were most human tumors analogous to spontaneous rodent tumors and perhaps truly immunologically inert.

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