Stimulatory Effects of Immune Reactions upon the Growths of Untransplanted Tumors

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Abstract

The accumulated literature suggests that altering the immune capacities of animals or humans seldom has detectable effects on tumor incidence nor, it seems, does the growth of an untransplanted tumor, either spontaneous or induced, immunize the host against the growth of a subsequent implant of that tumor. These observations suggest that even clearly immunogenic transplanted tumors may not have had their growths modulated by an immune reaction when they were as yet untransplanted in their primary hosts. Also, there are many data that have been interpreted to show that spontaneous tumors of rodents are, even when transplanted, nonimmunogenic.

A reconsideration of the available studies, especially those in which either host immune capacity or tumor immunogenicity was titrated, has led me to different conclusions. I believe that the data suggest that probably all tumors, including spontaneous ones, are immunogenic but that the weak immune response in the primary host to the antigens of even the more immunogenic induced tumors usually produces stimulation of tumor growth rather than growth inhibition.

The prevalence of immunogenicity suggests that vaccination or other forms of immunotherapy will eventually succeed; however, the analysis also suggests that, in the case of weakly immunogenic tumors, increasing the immune reaction, unless the increase is massive, may have little effect or may actually stimulate rather than inhibit the growths of these tumors in their primary hosts. Immunosuppression might actually be therapeutic in these cases; this may be an unrecognized benefit of the chemotherapy of many human tumors.

Introduction

For reasons of technical practicality, most of what is known concerning the immunogenecities of tumors is derived from studies of transplanted tumors. This is unfortunate because it is the role of immunogenicity in the growth of the untransplanted tumor that is of primary concern if results are to be successfully extrapolated to the problems of immunotherapy in humans. Available evidence suggests that the role of immunogenicity in the behavior of untransplanted tumors is very different from its role after transplantation and inferences drawn from the one can be transferred to the other only with the greatest caution. In fact, there are reasons to question whether tumor immunogenicity has any significant effect on the behavior of most untransplanted tumors. I argue in this paper that immunogenicity does play an important role in the behavior of many untransplanted tumors; despite uncertainties, enough facts are at hand to make a discussion of the issue both timely and useful.

I need not review the rodent data that show unambiguously that many rodent tumors, especially those known to have been induced overtly by a chemical, by irradiation, or by a virus, are, as judged by transplantation tests in syngeneic animals, immunogenic (1). Suffice it to say that immunization of syngeneic animals with material from such tumors usually induces a resistance to the growth of subsequent implants of tumor. In the cases of tumors induced by chemicals or by radiation, the resistance is usually highly tumor specific; a tumor designated “A” will immunize against subsequent implants of that same tumor “A” but usually fail to immunize against implants of a different tumor “B” even if “A” and “B” had been induced in the same original animal, in the same type of tissue, and by the same kind and quantity of chemical carcinogen (2).

The recognition of the fact that many rodent tumors contain tumspecific transplantation antigens led inevitably to the concept of immunosurveillance (3). The fact that so called “spontaneous tumors” apparently failed to exhibit such antigens was attributed to the effects of immunoselection and was taken as evidence supporting the surveillance hypothesis; supposedly only nonimmunogenic tumors could pass the immunosurveillance screen unless the immune mechanism of the animal had been suppressed by an overt oncogen. It had been shown earlier that most and perhaps all types of oncogens were immunosuppressive (4). The concept of immunosurveillance had so much heuristic appeal that it soon became dogma, and even to this day it remains central, at least in a modified form, to the thinking of many (3, 5, 6).

If the immune mechanism actually suppressed the growth of most or even of many incipient tumors, as the surveillance hypothesis states is the case, it follows that immunodeficiency, as occurs in the nude mouse or in kidney transplant patients, should produce a marked increase in the tumor incidence. It does not. Stutman (7), in a masterful and exhaustive review of the literature up to 1975, and little has changed since, concluded that, with a few possible exceptions, perhaps most notably some virally induced tumors, the immune capacities of the hosts had no consistent effect upon the incidences of either spontaneous or induced tumors. Some studies seemed to show some increment in tumor incidence in immunocompromised animals, but others showed no effect or even a decrease; the overall effect was judged to be nil.

In the human, immunodepression is associated with an increase in the incidences of a few tumors such as lymphoma, cervical carcinoma, some skin tumors and, possibly, Kaposi’s sarcoma, but the incidences of most tumors appear unaffected (8). It therefore seems probable to me and to many others that the incidences of most of those few tumor types that are increased may be, in fact, affected by some mechanism in the immunodepressed patient other than a lack of a putative immunological surveillance. The only obvious, and not mutually exclusive, alternative to this conclusion is to postulate that most tumors are inherently nonimmunogenic and that immunosurveillance, rather than being a general phenomenon, is confined to a very few exceptionally immunogenic tumor types (5, 6).

The essentially negative results in the nude and other immunodeficient animals have prompted some to suggest that, although the thymus-dependent immune mechanism may lack a surveillance function, such a function may be the raison d’être of the NK cell (9). Studies in the beige mouse, which is deficient in NK cells, have given, in some cases, suggestive results. It seems reasonable to postulate that...
Thus, an NK surveillance may not be relevant to the question of the growth of incipient tumors and this mechanism might well involve the NK cell (10). Such a mechanism, if it exists, is probably not directly related to the presence of the transplantation antigens that engendered the surveillance concept; the NK cell appears to be relatively nonspecific, albeit that T-cell-induced activation of NK cells may occur (9). Thus, an NK surveillance may not be relevant to the question of the role of an immunogenicity that is dependent upon tumor specific antigens of the transplantation type.

The role of macrophages in both tumor stimulation and tumor inhibition is also indubitably important (11). However, in this paper, I am primarily concerned with the role of those tumor antigens that give rise to a tumor-specific transplantation immunity; this immunity is primarily dependent upon T cells and a functioning thymus (1). Thus, the dramatic effects of the local administration of adjuvants, such as Bacillus Calmette-Guérin, on the prognosis of some tumors (12, 13) will be completely ignored because of the evidence that such effects may be due in large part to the activation of macrophages, that the effects can be seen even in immunodepressed animals (12), and that, despite T-cell involvement, the antitumor activity is localized and does not induce systemic immunity (14). I recognize that probably no form of tumor resistance, including that induced by the local administration of adjuvants, is independent of other forms, but I am narrowing the discussion for the sake of simplicity despite being cognizant of the dangers involved.

The Case against a Role for Immunogenicity in Modulating the Growth of Untransplanted Tumors

There is evidence, which I will later challenge, to suggest that a whole class of tumors, namely so-called spontaneous tumors, are nonimmunogenic. Spontaneous rodent tumors, in contrast to those induced overtly by a known oncogen, characteristically show no immunogenicity even after transplantation (15, 16); they presumably lacked immunizing potential when they were in the untransplanted state. It is not known what percentage of human tumors are analogous to the spontaneous rodent tumors and thus presumably nonimmunogenic, but the percentage may be high. In any event, it seems certain that even the human tumors that are known to be induced by environmental exposure to carcinogens are usually induced by relatively low exposures and, by analogy with mouse tumors, would probably prove to be of low immunogenicity if transplantation tests could be performed. In the mouse there appears to be a rough correlation between the immunogenicity of the resulting tumor and the magnitude of exposure to the carcinogen (17-19), although not all observers have seen this correlation (7). Tumors induced by exposure to high concentrations of more potent carcinogens tend to be highly immunogenic whereas at the other end of the spectrum spontaneous tumors appear to be nonimmunogenic. This relationship is apparently independent of the immunosuppressive effects of the carcinogen; it is seen during oncogenesis in immunologically depressed animals and during oncogenesis in vitro or within the protecting confines of diffusion chambers and also occurs when the concentrations of carcinogen are lower than those required for detectable immunosuppression (7, 20-23).

The lack of a general and consistent effect of immunodepression on tumor incidence (7) and the observation that the untransplanted, carcinogen-induced tumor apparently fails to immunize the primary host against subsequent challenge implants of that same tumor (24, 25) suggest that even when tumor antigens exist, they may play no role in regulating the growth of the untransplanted tumor.

This could conceivably be caused by a lack of antigens on the nascent tumor (perhaps they develop later during progression); by the production, for reasons unknown, of tolerance rather than immunity; by the fact that untransplanted tumors arise in the orthotopic organ and the orthotopic organ may be a relatively poor site for immunization (26); or perhaps the untransplanted tumor fails to immunize because the initial presentation of antigen is nontraumatic and/or is in very small quantity (a very few cells). Support for the latter idea comes from the fact that some highly immunogenic tumors that may have difficulty growing when transplanted to immunized or even to normal syngeneic hosts may grow better when the challenge inoculum is exceedingly small (27). An apparently analogous effect has been seen in the naive C57BL/6 mouse that is challenged with Taenia taeniaeformis; a large inoculum may be rejected; while a tiny inoculum may cause infection (28). This effect, in relation to tumor, is known as the "sneaking-through" phenomenon (29). It should be noted that although the untransplanted tumor produces no detectable immunity in the primary host (24, 25), the primary host can be immunized, by repeated implants of that same primary tumor, against subsequent implants (30); to what extent the growth of the untransplanted tumor would have been affected by such immunity is not known.

The sneaking-through phenomenon may be related to some observations that were made in the mouse with the aid of a transparent chamber technique. Merwin and Hill (31) were able to observe the fate of tiny allografts of Harderian or thyroid gland that were placed in such a relation to the s.c. blood vessels of the host mouse that they usually failed to vascularize or vascularization was much delayed. Lack of vascularization resulted in indefinite survival of the allograft. If blood, and presumably lymphatic, vascularization were delayed for 3-5 weeks, and only then, the now vascularized graft would also survive indefinitely. Such a vascularized graft was promptly destroyed if the animal were immunized at a distant site by tissues of the same donor strain as the graft; thus, the graft remained susceptible to immunity if immunity were present. Apparently immunization by the original graft could occur only while the graft was undergoing vascularization during an initial adjustment to the trauma of transplantation. After an adjustment period of 3-5 weeks, vascularization no longer resulted in immunization; it seems most likely that immunizing antigens were no longer shed from the graft into the lymphatics of the host and thus immunization failed to occur. A more detailed discussion of some of the possible implications of the work of Merwin and Hill is contained in Ref. 32.

It seems to me that the possible failure of a potentially immunogenic nascent tumor or a tiny inoculum thereof to effectively immunize the host may be analogous in some degree to the behavior of the Harderian and thyroid allografts described by Merwin and Hill (31), especially in view of the fact that untransplanted tumors originate as tiny avascular nodules (33) and it is possible that the vascularization of tiny, as opposed to large, tumor implants may be relatively delayed. In a later section of this paper I will suggest that the nascent tumor does trigger the immune system but is often stimulated rather than inhibited by the reaction thus induced. Whether or not the Harderian and thyroid allografts that survived in the experiments of Merwin and Hill were also stimulated by a weak immune reaction was not determined.

Although it is possible to suggest analogies between the sneaking-through phenomenon and the work of Merwin and Hill, a major difference must be noted. Sneaking through can be observed in specifically preimmunized mice and Marchant (29) showed that if such an immunized mouse were challenged simultaneously with both a large and a very small inoculum, often only the smaller challenge would grow. Thus, sneaking through is apparently produced not only by a failure of immunization, as in the Merwin-Hill allografts, but also by a failure of any established immune reaction to "see" a tumor that grows from a very small inoculum. The difference between the two phenomena may be caused simply by a difference in antigenic strength, the tumor system probably being much weaker. Be that as it
may, it appears that the untransplanted nascent tumor may not only fail to immunize effectively but might not even be inhibited by any immunity it did induce.

To recapitulate, I have suggested several possibly interrelated phenomena that might be involved in the apparent lack of immunizing activity by the nascent tumor in the primary host: the possible induction, for unknown reasons, of tolerance rather than immunity; the possible effect of the orthotopic site; the sneaking-through phenomenon; and/or a paucity of immunizing transplantation antigens.

Up to this point, the data I have cited, namely the lack of a consistent effect of immunodepression on tumor incidence and the apparent failure of the untransplanted tumor to immunize, suggest that tumor antigens may have little if any role to play in the modulation of the growths of untransplanted tumors, regardless of the subsequent immunogenicity of the tumor when transplanted. However, there are other possibilities which I will now present.

The Case in Favor of a Role for Immunogenicity in Modulating the Growth of Untransplanted Tumors

It is widely recognized that a low level immune reaction may stimulate rather than inhibit tumor growth, an action probably dependent upon the activities of a variety of T-cell cytokines (34) and perhaps, in some cases, upon the concentration of an antibody (35). A low dosage stimulatory phenomenon has also been observed in cases in which resistance to tumor cell growth is mediated by macrophages or NK cells (11, 36). Although the mechanisms underlying the stimulation of tumor growth are largely unknown, recent work has shown that a variety of cytokines has the capacity either to promote or to inhibit growth of target cells directly and/or to stimulate angiogenesis. Thus, growth of Kaposi’s sarcoma is probably dependent upon lymphokines (37). Epidermal growth factor has been shown to stimulate tumor growth at picomolar concentrations but to cause inhibition at nanomolar concentrations (38). The role of lymphokines in growth promotion is currently one of the most rapidly burgeoning fields of biological investigation (34).

The theory of immunostimulation and the data that support it have been reviewed a number of times and need not be presented in detail here (23, 39–41). Suffice it to reiterate that, both in vivo and in vitro, low concentrations of immune reactants may tend to stimulate tumor growth whereas larger concentrations are often inhibitory to growth. Thus, it follows that a tumor of low immunogenicity, i.e., a tumor that induces a relatively small quantity of immune reactants, may be stimulated rather than inhibited by the “immune” reaction it induces. If changes in the cellular composition of the immune reactants are involved in determining whether inhibition or stimulation of growth occurs (42), the arguments presented in this paper would not be significantly altered.

The relationship between the concentration of immune reactants and the stimulation or inhibition of tumor growth must necessarily be similar to that shown in Fig. 1. The detailed shape of the curve is unknown but, as shown, is probably sufficiently accurate in its essential features to permit some deductions. The scales are arbitrary and intended only to indicate the direction of change.

The first question I wish to raise about the arguments I presented in the first half of this paper concerns the apparent lack of immunogenicity of transplanted spontaneous tumors. Lack of immunogenicity has generally been defined as a lack of an effect of attempted immunization with tumor upon the ability of subsequent implants of that tumor to grow in the putatively immunized syngeneic animal. However, it is obvious that there are two parts to this process: the ability of the tumor to immunize, i.e., to induce an accumulation of immune reactants, and the susceptibility of the tumor to the effects of those reactants. Usually these two parts are not experimentally distinguished, but there are a number of observations, obtained by using variant lines of a single tumor, that show clearly that the two are, at least to a large extent, independent variables. If the various sublines of a tumor are examined, it will often be found that some are good immunizers but poor responders whereas others may be poor immunizers but be, nonetheless, sensitive responders (2, 43–48). Thus, a tumor may be deemed nonimmunogenic because of a lack of immunizing capacity and/or because it is unaffected by immunity. For the purposes of this paper, where the concern is ultimately with the role of immunity in the behavior of untransplanted tumors, both of these elements that contribute to immunogenicity are essential; if either were completely lacking there could be no effect on the growth of the tumor. The relationship of the level of immune reactants to the growth of the tumor, as depicted in Fig. 1, assumes that a given level of reactants produces a corresponding effect on growth; this assumption, despite the independence of the immunizing capacity and the sensitivity to the effects thereof, is probably valid if averaged over many tumors.

Looking at Fig. 1, it is apparent that, with spontaneous tumors, there are two possibilities. The tumors could truly lack immunizing ability; such tumors would be at point “a” on the curve. Alternatively, if the tumors were actually weakly immunogenic, an immunizing implant might approach point “b”; immunization might then move the challenge inoculum to the general vicinity of “d”. Under these circumstances there might be little difference between the growth of the challenge tumor in the immunized animal and the growth of the control implants in nonimmunized mice; “b” and “d” are at much the same growth level despite different concentrations of immune reactants. Given the inaccuracies of the in vivo immunization-challenge test, the tumor would probably be scored incorrectly as nonimmunogenic.

The above argument, suggesting that weakly immunogenic tumors might be scored as nonimmunogenic because of the shape of the curve in Fig. 1, may have little heuristic appeal, but there are data to support its probable frequent applicability. The paper, among the many that could be cited, that is most often invoked to show that spontaneous rodent tumors are usually nonimmunogenic when transplanted is that of Hewitt et al. (16). Twenty-seven different spontaneous tumors were examined for immunogenicity by a variety of means and the authors found nothing they could interpret as immunogenicity in any one of them. However, in only 7 cases was actual immunization attempted; the test in these cases was to immunize with irradiated tumor cells and then compare the growths of challenge implants of the tumor in the immunized versus the nonimmunized controls. In 7 of the 7 tumors tested, the challenge implants grew significantly better in the immunized as compared to the nonimmunized controls, a result that the authors dismissed as some type of artifact. To me, the most likely
interpretation of these data is that immunization with irradiation-killed cells moved the implant of the weakly immunogenic spontaneous tumors from a point near "b" on the curve in Fig. 1 to the vicinity of point "c". Now it so happens that immunization with irradiated killed cells is probably less effective than is the classical immunization with live cells followed by excision of the immunizing tumor. Had the usually more effective immunization with live cells been performed, more and/or more effective immune reactants might have been elicited and the tumor might have been moved further to point "d". Thus, with more effective immunization, the results would probably have been in accord with the usually negative results of attempts by others to immunize against spontaneous tumors (15). The important point is that in all 7 cases reported by Hewitt et al., the spontaneous tumors would have been deemed weakly immunogenic had the possibility of immunostimulation of tumor growth been entertained.

I believe that the results obtained by Hewitt et al. concerning immunization with irradiated cells were most likely due to the presence on or in the tumor cells of tumor transplantation type antigens; this possibility is supported by the work of Van Pel and Boon (47) who have succeeded in producing immunity to apparently nonimmunogenic tumors, including one of the very tumors used by Hewett et al., by using mutagenized tumor cells to immunize against the unaltered parental lines. This would seem to demonstrate the presence of antigens in or on the spontaneous tumors. The presence on spontaneous tumors, as shown by Van Pel and Boon, of antigens that can respond to an immunity does not, as I have already discussed, necessarily mean that these antigens can also induce immunity as indeed the Van Pel study itself shows (47); the spontaneous tumors might, despite the presence of target antigens, still be nonimmunogenic and such antigens might play no role in modulating the growth of nascent, untransplanted tumors. However, the demonstration by Van Pel and Boon that some apparently nonimmunogenic tumors do contain antigens that are potential targets for an immune reaction certainly increases the probability that such tumors can, if only to a small degree, also immunize.

On the basis of the above, I suggest the probability, and I think it is a probability rather than a mere possibility, that most and perhaps all transplanted tumors, spontaneous as well as induced, are immunogenic, albeit to differing degrees. The presence of weak antigens capable of immunization can apparently be detected, even with transplanted spontaneous tumors, by titrating the immunization of the hosts, as was inadvertently done by Hewitt et al., but only if immunostimulation of tumor growth is accorded its due status along with immunoinhibition. Unfortunately, the only direct evidence I can cite to support my contention that transplanted spontaneous tumors are capable of immunization is that provided by the paper of Hewitt et al. (16), so the issue cannot be considered settled.

The question of whether the presence of immunogenicity, as subsequently demonstrated by the transplantation of the tumor, affects the growth of the untransplanted tumor in the primary host remains to be answered.

The evidence, as presented by Stutman (7), that immunosuppression is unable to consistently alter the tumor incidence seems, at first consideration, difficult to reconcile with any postulated effect of tumor antigens upon the growth of untransplanted tumors; nonetheless, I shall try to do so. The first evidence that I will cite in support of the hypothesis that transplantation antigens on nascent tumors do influence the growths of such untransplanted tumors is found in a study of 154 sarcomas. The relationship of the latencies of the tumors (the period between carcinogen application and tumor detection) to the immunogenicities, as determined by immunization-challenge tests in vivo, was examined (49). Although each tumor had been induced by the same dosage of the carcinogen 3-methylcholanthrene, the resultant tumors exhibited a range of immunogenicities. It was found that tumors that were subsequently shown to be of low-intermediate immunogenicity had had the shortest induction times after carcinogen administration. The simplest interpretation of these data seems to be that a level of and/or quality of tumor antigen that produced an intermediate level of immune reactants in the immunization-challenge transplantation test also produced, around the untransplanted nascent tumor, a lower but an optimal level of immune reactants for the stimulation of the growth of that tumor; either a greater or a lesser reaction produced a longer latency.

The second paper suggesting an immunogenic role for the antigens of the untransplanted tumor involved a study of the carcinogen 3-methylcholanthrene, at various concentrations, in animals of varying immune capacities (50). Tumors appeared fastest, in response to the higher concentrations of carcinogen, in animals that possessed an intermediate level of immune capacity. Presumably, at the higher concentrations of carcinogen the nascent tumors, despite the effects of the sneaking-through phenomenon, elicited, in more highly immunocompetent hosts, a respectable immune response and might therefore appear in the neighborhood of "d" on the curve in Fig. 1. In hosts of intermediate immune capacities they would be at an intermediate point near "c". In the most immunodeficient animals the tumors would approach "b" or even "a". At low levels of carcinogen, when the resulting tumors presumably induced only a weak immune reaction (more than a spontaneous tumor but less than a tumor induced by a high concentration of carcinogen), no effect of the titration of the immune capacity was detectable. Thus, these experiments suggest that the antigens of the nascent untransplanted tumor did influence tumor growth when the immunogenicities of the tumors were presumably high but had no detectable influence when the immunogenicities were presumably low. Again, in order to show the effect of the antigens of the untransplanted tumors on the growths of those tumors, it was necessary to titrate, in this case the immune capacities of the hosts rather than the immunogenicities of the tumors. The failure to show an effect when the tumors were presumably of low immunogenicity may have resulted from insufficient data, but the result does suggest that the antigens of weakly immunogenic tumors, including spontaneous tumors, may indeed arouse very little immune response and may have little or no influence upon the growth of nascent untransplanted lesions.

A third group of papers showing an apparent effect of the antigens of the nascent tumor upon its growth again involved a titration of the immune capacities of the hosts. In these cases, carcinogen-treated skin was grafted to syngeneic hosts of varied immune capacities. It was shown that a hyperreactive immune capacity in the host could lower the incidence and shorten the time before regression of the papillomas that the grafting, serving as a promoter, had produced (51). Other studies had suggested that papillomas thus induced were immunogenic (52), although a delayed regression of most of them would occur even in the absence of a detectable immune reaction (53). In another study, papillomas appeared most rapidly in hosts of intermediate immune competencies, suggesting once again that the antigens of the nascent tumor were influencing the growth of that tumor and, incidentally, once again supporting the immunostimulation hypothesis (42).

In all of these cases, nascent tumors were presumably transplanted along with the skin grafts so it may be difficult to know whether to consider the tumors as transplanted or not. In fact, Andrews (54) presented data showing that disturbing a nascent tumor by a procedure such as skin transplantation helped to alert the immune system to the presence of tumors; however, careful examination of this study shows that the immune competence of the host was a significant determinant of tumor growth even in the absence of a tumor-disturbing transplantation procedure (54). In support of this conclusion, the nude mouse...
seems to be relatively resistant to the induction of skin tumors using a classical chemical rather than transplantation as a promoter, a resistance that can be overcome to some extent by increasing the immunocompetency of the nude. The intricacies of these and other related skin carcinogenesis experiments are reviewed in the paper by Outz (42).

Reconciliation

Two problems remain: (a) how to reconcile these results showing that the immunogenicity of the untransplanted tumor does influence its own growth, at least when the tumor is highly immunogenic, with the vast literature cited by Stutman (7) that, in aggregate, suggested that the immune capacity of the host is usually without influence on the incidence of such tumors; (b) how to explain that the untransplanted tumor, even if influenced by host immunity, seems not to immunize the primary host against subsequent challenge implants of that tumor (24, 25).

Many of the studies cited by Stutman (7) concerned carcinogen-induced tumors. In these cases, I suggest that most of the nascent tumors would, in Fig. 1, have fallen at about "d." A severe but not complete immunodeficiency, as in the nude mouse, might lower the concentration of immunoreactants around the nascent tumor from "d" to the vicinity of "b." Thus, little or no effect on tumor incidence would be observed. Seemingly, the only reliable way to observe the possible effects of immunogenicity on the untransplanted tumor is by titrating the immune capacities of the hosts or the immunogenicities of the tumors. However, it appears that spontaneous tumors and tumors induced with low levels of carcinogen are of such low immunogenic effectiveness in the nascent untransplanted state that altering the immune capacity of the host has little or no influence upon their growths. Furthermore, in the case of weakly immunogenic tumors, lowering the immune capacities of the hosts would be expected to decrease rather than increase an already low tumor incidence and any effect of the immunodepression would be of small magnitude and difficult to detect.

The second problem, how the incidence of a potentially highly immunogenic nascent tumor can be altered by an immune reaction but nonetheless fail to produce a significant alteration of the growth of subsequent challenge implants, is easily solved. A number of possible, not mutually exclusive, solutions can be envisaged. One would be that, as the immune response evolves with time after immunization, it may gradually lose its effectiveness, perhaps because of the appearance of suppressor cells (13, 55). If immunization by the nascent tumor were, because of the sneaking-through phenomenon, partial tolerance, or other mechanisms, weak to begin with, the reaction might die away rapidly and not be able to alter the growth of a challenge tumor that was implanted sometime later. A second solution might be that the challenge implant, by producing its own strong immune reaction, might swamp any effect that the weak reaction to the nascent tumor may have evoked. This could happen if the precaution of irradiating both experimental and control animals before challenge, as was suggested by Globerson and Feldman (2), were not taken. A third possible solution, and the one most appealing to me, is that the immunity induced by the untransplanted tumor may always be in the stimulatory range; thus, the usual implantation-challenge type test, in which the control implants in normal mice usually grow well, may not detect a stimulatory effect that was produced by the growth of the untransplanted tumor. In support of this explanation is the observation, by at least three separate observers, that challenge implants of tumor into the primary autochthonous host, rather than being inhibited by host immunity, tended to grow better than in naive control animals (24, 25, 56); it should be noted that this type of observation could equally well be the consequence of tolerance production in the autochthonous host rather than a result of immunostimulation (56) or both mechanisms might be at work simultaneously. A fourth observer found that the autochthonous host sometimes supported a tumor implant better or, in other cases, worse than did naive control mice (57), a result that is easily explicable in terms of the curve in Fig. 1; probably the added immunization produced by the challenge implant was insufficient to move a weakly immunogenic tumor out of the immunostimulatory range but was able to do so when the tumor happened to be sufficiently immunogenic.

Clinically Relevant Conclusions

The analysis presented in this paper permits one to entertain the hypothesis that most or even all tumors contain transplantation type antigens as was discussed by Forni and Santoni (58). The analysis also suggests that even the untransplanted tumor, at least when the tumor can be shown by subsequent transplantation tests to be highly immunogenic, may immunize the primary host but be stimulated by the reaction thus produced. By analogy, this should appear to human tumors that were induced by a strong exogenous oncogenic stimulus, but in the absence of the possibility of doing transplantation tests in the human, this hypothesis may be essentially untestable; however, some very suggestive clinical data are available (59).

In cases in which an augmented immune reaction caused by immunotherapy may seem, in vivo, to have an inhibitory effect on a tumor, the probability should be considered that the effect may be produced by a diminished immunostimulation rather than by an absolute inhibition. Conversely, when immunosuppression augments tumor growth, the effect may result from increased stimulation, i.e., moving the reaction from point "d" toward point "c" on the curve in Fig. 1. From a clinical standpoint, these differences are probably academic, but they do suggest that instances of apparent immune surveillance may be an illusion.

Immunogenicity, with resultant immunostimulation, may be a necessary condition that enables a tumor to overcome a variety of non-immunological surveillance mechanisms, especially during early progression (36, 40). Perhaps a postulated but undetectably small effect of immunity on the growth of even spontaneous tumors is effective in this regard and may explain why immunogenicity is so widespread among tumors regardless of etiology. The possibilities of successful immunotherapy with vaccines or other methods of increasing the immune response seem promising inasmuch as even spontaneous tumors apparently possess tumor-associated antigens the effectiveness of which might be augmented by a wide variety of devices; I have referenced a small sample of this rapidly burgeoning literature (46, 60–72).

However, the pitfalls are also evident. The analysis suggests that with weakly immunogenic tumors, such as those induced by a weak carcinogenic stimulus or tumors that occur spontaneously, the immune reaction might sometimes be increased substantially, beyond the range that would maximally stimulate growth, without noticeably inhibiting the growth of the tumor; the increased reaction might simply move the tumor from "b" to "d" on the curve in Fig. 1. This may not necessarily indicate that the effort should be abandoned but simply that the increased quantity of the immune reactants remained inadequate for effective therapy.

Apparently, in order to obtain a therapeutic response, the increase in the immune reaction will need to be massive, especially as concerns weakly immunogenic tumors, i.e., especially as concerns, in all probability, most human tumors. Too small an increment of the immune response might stimulate rather than inhibit the growths of weakly immunogenic tumors, as I believe the work of Hewitt et al. (16) directly demonstrates; they might sometimes be more easily inhibited by immunosuppression than by immunoaugmentation. It may not be
unreasonable to suggest that the immunodepression that often accompanies tumor growth (13, 73) may be a defensive reaction on the part of the host. It follows that, in many cases, immunodepression is an unrecognized benefit of chemotherapy (74).

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EFFECT OF IMMUNOGENICITY

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