A Conception of Tumor Autonomy Based on Transplantation Studies: A Review

HARRY S. N. GREENE

(Department of Pathology, Yale University School of Medicine, New Haven, Conn.)

The definition of a tumor as an autonomous growth has enjoyed persistent popularity in textbooks of pathology. In such definitions the adjective "autonomous" is employed to express the idea of independence with respect to two different particulars. One of these relates to freedom from the laws restraining and co-ordinating normal tissue growth, and the other concerns release from the necessity of a continued stimulus. The results of a long series of transplantation studies suggest that the concept of autonomy has a broader application to the field of cancer than is indicated by these attributes, and accordingly a brief review of the experience is presented.

It was observed early in the work of this laboratory that the transplantability of spontaneous rabbit tumors varied in relation to their duration (7, 19, 21, 23). Early tumors could not be transferred to normal animals, whereas tumors obtained after metastasis were readily transplantable. The occurrence of a large number of spontaneous tumors, particularly of the uterus and breast, made investigation of this relationship possible (4-6, 10, 22, 24). Biopsy specimens obtained at monthly intervals throughout the course of disease were subjected to morphological study and to various types of transplantation. In general, four types of transplantation were attempted: autologous, or transfer back elsewhere in the same individual; homologous, or transfer to an unrelated animal of the same species; transfer to other tumor-bearing animals; and heterologous, or transfer to normal animals of a different species.

Autologous transfer was almost always successful, even in the case of the very earliest tumors. In distinction, homologous transfer was only successful late in the course of the tumor and was followed by rapid decline of the primary host and death from metastasis. The results of heterologous transfer paralleled those of homologous transfer, and all tumors that grew in normal unrelated rabbits also grew when transplanted to guinea pigs.

The results of transplantation of early tumors to rabbits bearing spontaneous tumors of the same type were in sharp contrast to those obtained in normal unrelated animals, for takes invariably occurred. The growth rate was generally slow at first but increased in tempo, closely paralleling that of the spontaneous tumor of the new host. Further, the ability to grow in normal animals was attained simultaneously by both spontaneous and transplanted tumors.

It is inferred from these experiments that the ability to survive in the environment of a normal animal is a developmental acquisition and not a property of the tumor from its inception. Prior to the attainment of this property, however, the tumor does possess the ability to survive in the primary host or in other animals bearing similar tumors. Thus, at this stage, survival appears to be dependent on the special constitutional status of the spontaneous tumor-bearing animal. The factors concerned in this status are not operative in normal animals, and, accordingly, the tumors cannot be transferred to normal animals. Later in the course of development, the tumor becomes independent of these factors, or autonomous, and will survive in their absence in normal animals.

Such a conception of cancer autonomy differs from that implied by the usual definition. It predetermines independence of the factors concerned in the development of a tumor as well as those concerned
in its genesis and thus applies only to the fully evolved cancer and not to growths in the process of development. Such growths are not autonomous in this sense, but on the contrary are dependent—dependent for their continued existence and development on factors peculiar to the tumor-bearing individual.

Studies of mouse and human tumors give added evidence of the developmental nature of the property of autonomy (13). A series of transplantation experiments similar to those described in the rabbit have been carried out during the course of spontaneous mammary tumors in C3H mice. Transfer of early tumors to unrelated mice or to alien species gave rise to no takes, but, after the occurrence of metastasis, both homologous and heterologous transplantation were successful. In sharp contrast to the results obtained in unrelated mice, transfer to other C3H mice frequently resulted in growth. It should be emphasized, however, that in view of the intimate relationship between the highly inbred members of the C3H strain, transfers of this type are not comparable to homologous transfers in rabbits and possess no more significance from the viewpoint of autonomy than an autologous transfer in this species. Further, the majority of C3H mice eventually develop mammary tumors and, therefore, must carry the factors necessary for the genesis and development of the tumors. Transfer from one C3H mouse to another is, accordingly, not a test of tumor autonomy. Conceivably, the continued influence of the factors carried by apparently normal C3H mice may account for the conversion of a dependent to an autonomous mammary tumor as is occasionally observed after long serial passage in this strain. The specific relation of the factors to mammary tumors is indicated by the fact that despite extended serial passage of several dependent methylcholanthrene-induced tumors in this strain, autonomy did not develop. In other respects, transplantation studies involving methylcholanthrene-induced tumors gave results similar to those obtained with mammary tumors—that is, early growths could be transferred to C3H mice but not to other strains or species, and such transfer only became possible after the induced tumor had resided in the primary host for a considerable length of time.

Autologous and homologous transplantation experiments are obviously not permissible in man, and an investigation of human tumors from the viewpoint of autonomy has been limited to heterologous studies (3, 8, 9, 12, 15, 16, 18, 20). Guinea pigs have been used as the recipient host and the anterior chamber of the eye as a transplantation site. The incidence of spontaneous tumors in the guinea pig is extremely low, and the possibility of the factors concerned in the development of a human tumor influencing a transplant in this species is sufficiently remote that growth may be interpreted as evidence that the tumor has attained independence of such factors. In a series of 123 human tumors subjected to heterologous transplantation, 65 grew and 58 failed to grow.

A determination of the developmental relationships of autonomy in human tumors is less direct than in the case of animal tumors where immediate autopsy can be performed and accurate records of the duration of the tumor are available. Some information can be obtained, however, by a comparison of the biological status of the tumor at the time of transfer (dependent or autonomous) with its anatomical status in the patient with reference to metastasis, the ultimate fate of the patient, and the survival period (17). In the series noted above, all the tumors known to have metastasized were found to be autonomous. When only local nodes were known to be involved and organic metastasis could not be demonstrated by clinical or x-ray examination, 59 per cent were autonomous. In contrast, transplantation was successful in only 29 per cent of cases without lymph node involvement or recognizable metastases. The relationship between autonomy and metastasis suggests that autonomy, like metastasizability, is a late stage in tumor development. The fate and survival periods of the patients yield further evidence in this direction. Sixty-one, or 93.8 per cent, of the patients whose tumors proved to be autonomous are now dead, and only 4, or 6.1 per cent, are still living. In contrast, 46, or 79.3 per cent, of the patients whose tumors were dependent at the time of transfer are alive, and only 12, or 20.7 per cent are dead. The interval between transfer and death averaged 5.5 months when the tumor proved to be autonomous and was increased to 9.4 months when the tumor proved to be dependent. In the group of patients bearing autonomous tumors and still living, a period of 20 months has elapsed since transfer, while living patients with dependent tumors have survived for an average period of 41 months.

In several instances, consecutive biopsies have been obtained at intervals during the course of a human tumor, and the results of transplantation confirm the relationships noted above. The tumors would not grow in normal animals during the greater part of their observed course, and transplantability, or autonomy, was a late development associated with the occurrence of metastasis and a rapidly fatal termination.
It is concluded from these experiments that, with reference to biological properties, cancers of rabbits, of mice, and of man are not sudden transformations in normal cells but, on the contrary, represent the final step in a developmental process. During the greater part of their course, the tumors are dependent in nature, their continued existence being conditioned by factors peculiar to the tumor-bearing individual. Autonomy, or the ability to survive in the absence of such factors, is a late development and is followed by a rapid acceleration in the fatal course of the disease.

Such an interpretation renders information of immediate importance concerning the factors on which the development of a tumor depends. An experimental approach is difficult, few investigations have been pertinent, and little is known. Experimentation with the mammary and uterine tumors of rabbits suggests that in these cases, at least, the factors are endocrinological in nature. Animals bearing such tumors show widespread endocrine changes suggestive of the continued action of estrogenic hormone. Such changes are not found in normal rabbits, and the possibility arose that they might be concerned in the development of the tumor. Accordingly, a group of rabbits was subjected to the long-continued administration of estrogenic hormone in small doses, and, following this treatment, a mammary tumor found to be dependent by transfer to normal animals was transplanted to their eyes. A comparable experiment utilizing a dependent uterine tumor was also carried out. In both cases, the transplanted tumors survived and grew. It seems probable, therefore, that in these special cases the constitutional state incident to the long action of estrogenic hormone supplied the factors essential to the continued existence of the tumors.

It should be emphasized that these are special cases, and there has been no evidence of the operation of estrogenic hormone in the development of tumors of other organs. The effect of castration or of the administration of estrogenic hormone in patients with prostatic tumors is highly suggestive that such tumors may be dependent on androgenic hormone. Further, the results of the treatment of human mammary tumors with estrogen or testosterone may be based on the neutralization of dependent factors.

Unfortunately, cancer has been studied predominantly as a local lesion, and the constitutional status of the tumor-bearing animal has received relatively little attention. The existence of an altered constitution is readily demonstrable in the changed susceptibility to the transfer of heterologous tumors. The Brown-Pearce rabbit tumor grows poorly, if at all, in normal C3H mice, but, when transplanted to C3H mice bearing spontaneous tumors, takes invariably occur, and growth is rapid (14). In like manner, the Rous chicken sarcoma grows on subcutaneous transfer to tumor-bearing C3H mice, but takes have not been obtained in normal C3H mice. The growth of homologous tumors is enhanced, and passage of a transplantable mouse tumor to tumor-bearing mice is also associated with the more rapid occurrence of metastasis. A definitive basis for the differing behavior of the tumor-bearing animal is not known. A pronounced variation in ascorbic acid metabolism has been observed in this laboratory, but experiments undertaken to determine its pertinence are not complete.

It has been found that the factors concerned in tumor development are constitutional in distribution and are not localized at the site of the primary growth (21). Fragments of early dependent uterine tumors have been transferred to various parts of the rabbit's body, and serial biopsies with transplantation studies of the resulting growths have been carried out at intervals throughout the remainder of the animal's life. Autonomy was attained at all sites of autologous transfer, and no significant variations in the time of attainment distinguished the uterus from other regions.

It is of interest in passing to note that in the experiment cited in the previous paragraph a considerable variation in growth rate characterized the behavior of the different autologous transplants when transferred to normal animals. This variation was sometimes extreme. In one case, transplants from the uterus grew to fill the anterior chamber of a normal animal in 3 weeks, whereas fragments obtained from an anterior chamber transplant in the primary host required 3 months to reach a comparable size in normal animals. The absence of a relationship between autonomy and growth rate has also been suggested by other experiments, and a determination of the mitotic index of a tumor has been found to be of no value in assessing its ability to grow in normal animals. In like manner, the morphology of the tumor has not been helpful in this respect. The degree of differentiation or organization appears to bear some relationship to the growth rate, but it is of little pertinence as an indication of autonomy.

It is significant that early embryonic tissues, like cancer, possess the ability to grow in alien species (11). Unlike cancer, however, such tissues lose their autonomy with continued development, and by mid-gestation their transplantation reactions are those of normal adult tissue. A shift from
a state of autonomy to one of dependency has not been observed during the course of the tumors studied in this laboratory, but inasmuch as the attainment of autonomy and metastasis are coincidental occurrences, the interval of time available for such a development is sharply limited. In Earle’s tissue culture studies, the period of observation is not restricted to the duration of a tumor-bearing individual’s life, and extended investigations are possible. He noted that cells subjected to the action of methylcolanthrene in tissue culture became autonomous, but, after continued culture in the same environment, the ability to grow on animal transfer was lost (1, 2). The inferences contained in these observations invite investigation, but, aside from the possibility that the autonomous state may be reversible, there is special significance in the fact that an attribute of such singular and distinctive nature as autonomy characterizes embryonic tissue as well as cancer. The sharing of this property in addition to a close resemblance in morphological, immunological, and biochemical constitution focuses attention on one outstanding dissimilarity in behavior. In both primary and experimental hosts, embryonic tissue undergoes differentiation, whereas cancer does not. The implied suggestion that the step from embryonic tissue to cancer may be relatively short and concerned with the process of differentiation is not new but remains only partially explored.

Normal adult tissues survive and grow on anterior chamber transfer to other animals of the same species, but always fail to survive heterologous transfer. Apparently, factors essential to their continued existence are common to the species of origin but are not shared by other species. (Inflammatory or foreign body reactions do not always follow transfer of adult tissues to alien species, and the failure of growth would sometimes appear to depend on other than immunological differences.) The more stringent qualifications of tumors in developmental phases are met only by the tumor-bearing animal, but, in an autonomous phase, the independence of antecedent requirements is such that the conditions necessary for survival and growth can be supplied by an alien species. In fact, cancer autonomy transcends zoological orders, for the growth requirements of the Rous chicken sarcoma are provided by the rabbit, guinea pig, and mouse (16, 25).

Although the word “autonomy” aptly describes the independent status of cancer, it should be clearly recognized that it serves nothing more than a descriptive purpose and requires translation in terms of biological cell changes as well as a causal explanation. Investigation of the mechanism of autonomy has taken a variety of forms. The possibilities are manifold and may concern either the acquisition or loss of properties. A modification in the former direction, relating simply to the ability of the tumor cell to induce a stromal reaction, might supply the necessary conditions. In the animal body, the tumor cell is completely dependent on its stroma for the essentials of existence, and the success of transfer depends on the ability of the transplanted cells to invoke a stromal reaction in the new host. Accordingly, the dependent nature of early tumors may arise from an incomplete development of this ability, the induction of stroma in a normal animal requiring a greater capacity than is necessitated by the altered responsiveness of the connective tissue of a tumor-bearing animal. Experimentation along such lines has been suggestive, and, in this connection, it should be noted that dependent tumors are transplantable to tumor-bearing animals and, further, that tumor-bearing animals provide a stroma for certain heterologous tumors that fail to survive transfer to normal animals.

On the other hand, there is experimental evidence to indicate that, during its developmental course, the tumor cell loses specificity and, concomitantly, its ability to invoke antibodies. It is conceivable, therefore, that the dependency of an early tumor is no more than a reflection of a destructive antibody reaction following the introduction of its cells into a normal animal and that the autonomy of an older tumor depends on the loss of ability to induce such a reaction.

These and other speculations are the subjects of present study, but whether autonomy represents an enhanced stroma-inducing ability, a loss of specificity, or some other modification in the tumor cell, the fact remains that it is a developmental acquisition and that the primary neoplastic focus and the fully evolved cancer differ with respect to this property. The differentiation of tumors or of tumor stages on the basis of a fundamental biological attribute suggests the existence of comparable differences in metabolic and biochemical constitution. From this point of view, it would appear highly important to characterize tumors with reference to dependency or autonomy in order to insure uniformity of materials in chemical or metabolic investigations. In the field of experimental therapy, a distinction would seem essential, for a variation in the influence of chemical, radioactive, hormonal, or other agents would be in line with the known differences in biological properties. Further, in the general field of cancer research, an interpretation and correlation of re-
suits would be facilitated if the tumors utilized were so defined as to allow a valid comparison with experiments based on different material. In view of the widespread use of mouse tumors and inbred mouse strains in cancer research, it should be re-emphasized that transplantability within a strain is no proof of autonomy.

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