The occasional spontaneous regression of autochthonous tumors is a reasonable basis for raising the possibility that immunologic responses by a tumor-bearing host might affect growth and survival of neoplastic cells. The most interesting implication underlying this possibility is that the tumor possesses one or more antigenic determinants which are lacking in its host.

What kinds of analyses can be visualized as establishing the validity of this possibility? If the host who is rejecting an autochthonous tumor is doing so by virtue of an immune response, one ought to find evidence for the response by either of two general means: (a) antibody from host serum should react with soluble or particulate components of the autochthonous tumor; (b) components of the tumor injected into host skin should produce a specific inflammatory response, either of immediate or delayed type.

Whereas a wide variety of methods for detecting antibody-antigen reactions exist, if antibodies relevant for autochthonous tumor rejection exist, it is probable that they will be found at low concentrations; hence, the justification for seeking them with the most sensitive assays now available—e.g., passive cutaneous anaphylaxis, hemagglutination, and complement fixation. Novel methods to deal with special antigens, e.g., those which may be unfunctional, may have to be improvised; e.g., using T125-labeled or fluorescein-labeled \( \gamma \)-globulin. When serological analyses are negative, analyses of immunologic phenomena are frustrating. Yet we know that significant immunologic responses can occur when antibodies are not detectable in serum, even with the most sensitive assays now available (e.g., in wheal-and-erythema reactions to pollens; sometimes in anaphylaxis; and in delayed-type hypersensitivity—see below).

What if the "immune response" is of the sort now designated as delayed-type hypersensitivity? In this case, the only means now available for recognizing this possibility is through observing slowly evolving, specific, inflammatory reactions in the skin of the rejecting host who is inoculated intradermally with tumor cells or extracts of such cells. By specific we mean here: (a) that the same cells or extracts inoculated in the skin of a tumor-free host, or of the tumor-bearing host who is not rejecting the tumor, will produce no inflammatory response; and (b) that viable lymphoid cells derived from either lymph nodes, spleen, or blood of the rejecting host will convey to a normal recipient of the same species skin reactivity which mimics in time-course and specificity the skin reaction of the donor animal. The advantages of using isogenic strains of animals are generally appreciated and are especially noteworthy in the case of analyses of putative delayed-type hypersensitivity responses. Transfer of lymphoid cells between isogenic donor-recipient pairs is more likely to give clear-cut and more durable results than between genetically dissimilar pairs with histoincompatibility. A high incidence of an autochthonous tumor in an isogenic strain would certainly provide inviting opportunities to determine the influence of "immunization" with tumor homogenates in Freund's adjuvant on the natural history of the tumor.

If autochthonous tumors bear antigenic determinants not present in the host, it is, of course, probable that host antibody to tumor antigens will be found, by either serologic or skin testing. However, the significance of such antibodies for the growth and survival of the tumor would then remain to be established. One would imagine that if the distinctive determinants were on the tumor cell surface the possibility for in vivo interaction of antibody with cell would be great and could well have an effect on tumor behavior (stimulate proliferation or initiate regression?). If, on the other hand, the distinctive tumor antigens were situated inside the neoplastic cell, the liberation of antigen (say by spontaneous cell death) would be likely to occur and to induce antibody formation. However, such antibody would be expected then to have little or no access to the antigens of the robust, viable tumor cell and so be without biologic significance for tumor regression or progression (unless in the tumor mass there existed sufficient extracellular products of cell lysis to allow...
for more-or-less conventional allergic reactions to take place within the tumor mass).

For investigators of "cancer immunology" it is especially important to consider the meaning and implications of a negative serologic test for antitumor antibodies. For example, when a tumor-bearing host rejects an autochthonous tumor, failure to detect in the host's serum antibody which reacts with extracts of the rejected tumor may be interpreted in one of several ways; e.g., (a) the test extract contains little or none of the relevant antigenic determinants, or (b) the serum actually contains no antibodies at all, or (c) the antigens in the extract are present and relevant, and serum antibodies are also relevant and present—but at concentrations below the limit of detection by the most sensitive assays available; i.e., < 0.01 μg to 30 μg antibody/ml serum.

The last mentioned possibility (viz., c above) deserves particular attention and is the basis for a theory of delayed hypersensitivity now being elaborated by F. Karush and myself. According to this theory, conventional serum antibodies may exhibit biologic activity even though their concentrations in serum are so low as to be not detectable by the most sensitive assays available. This situation becomes possible if 2 conditions exist: (a) that the affinity of antibody for its homologous antigen be so great (association constant > 10^{19}) that these two reactants will form stable complexes at steady-state concentrations of antibody that are so small as not to be detectable (i.e., < 10^{-19} moles/l); and (b) that antibody be generated and secreted at a rate that compensates for the rate at which antibody forms complexes with antigen—i.e., at a rate great enough to maintain at steady state the specified low antibody concentration. In view of the broad range of affinities of antibodies for antigens, and the very high affinities recently found for certain antibody-antigen systems, this speculation does not extrapolate much beyond actual experimental findings.

In connection with the possible immune basis for rejection of autochthonous tumors, it should be noted, according to the foregoing speculation, that, for passive transfer of the rejection phenomenon to be successful—under the circumstances specified above—viable antibody-secreting cells would have to be transferred; serum would be inadequate on account of the enormous unphysiologic volumes needed to compensate for its low antibody concentration.

In the final analysis, the ultimate demonstration that a host immune response is responsible for regression of an autochthonous tumor is likely to require transfer of serum and/or lymphoid cells from the host that exhibits tumor regression to another member of the same isogenetic strain who carries the same autochthonous tumor, with subsequent tumor regression in the recipient.

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Immune Responses and Regression of Autochthonous Tumors

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